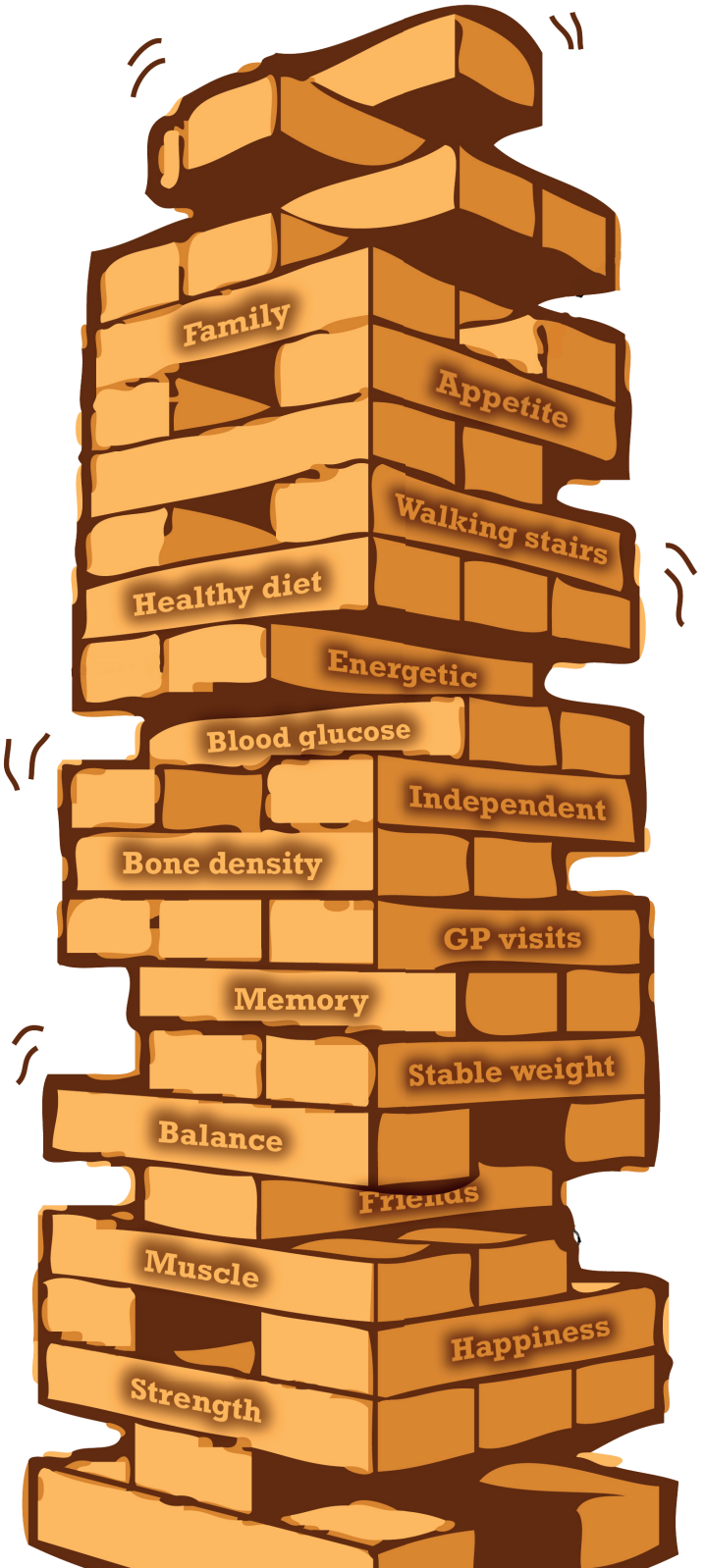

Frailty in People with Intellectual Disabilities: frequency, determinants and consequences

Josje Schoufour

FRAILTY IN PEOPLE WITH INTELLECTUAL DISABILITIES: FREQUENCY, DETERMINANTS AND CONSEQUENCES

Josje Schoufour

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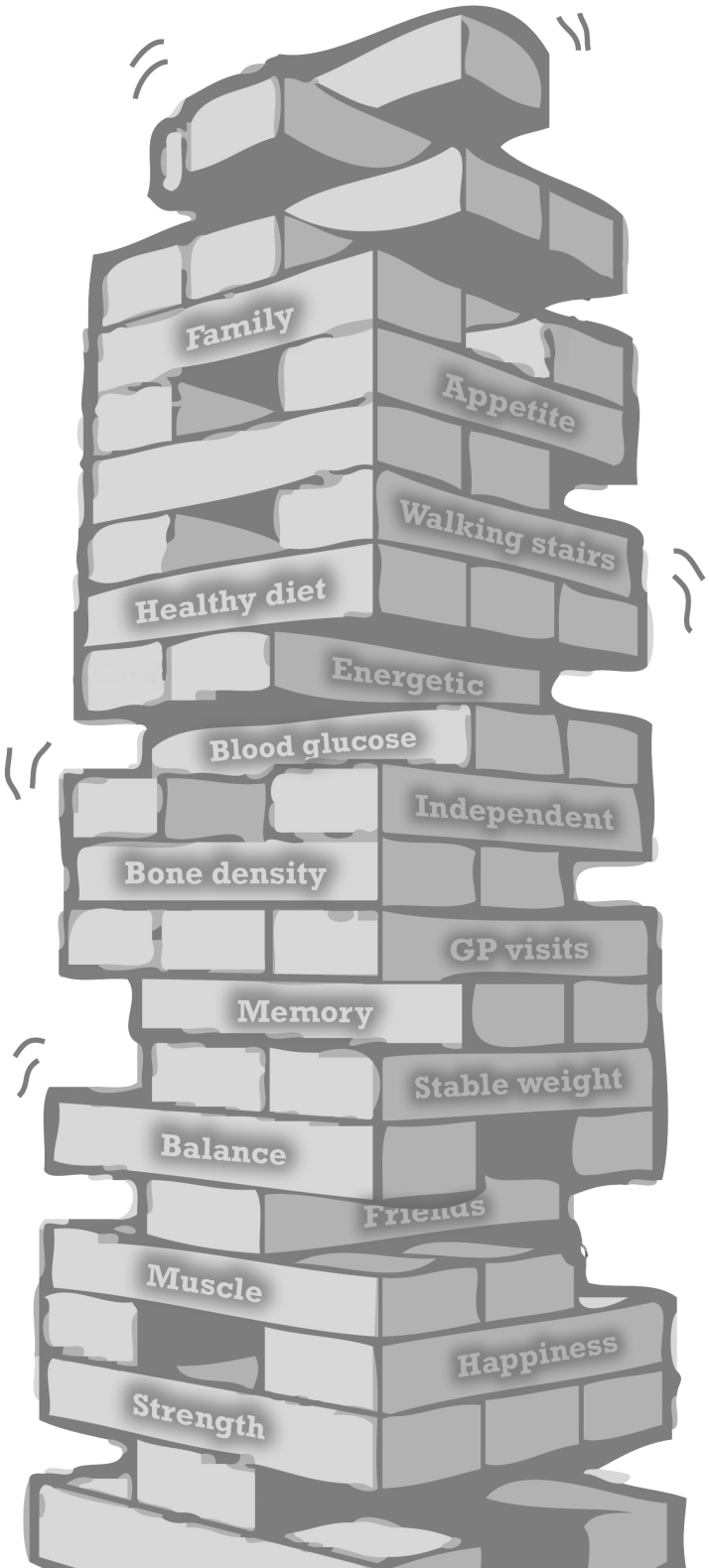
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Healthy diet
Energetic
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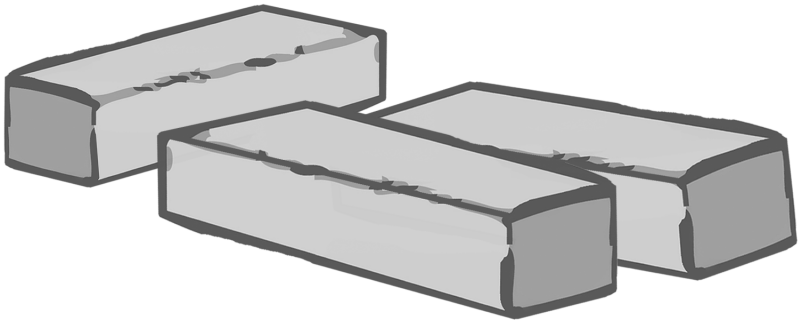
Chapter 1

General introduction



The last two centuries, the increased life expectancy has led to a shift in the age distribution towards higher ages, in high-income countries [1, 2]. Although the total number of older people is increasing and people reach a higher age, the additional life years are not always healthy years. As a consequence, both individuals and society have to deal with age-related health problems including chronic diseases, cognitive decline, social isolation and disabilities in daily functioning. As Clegg and coauthors recently stressed in the Lancet, eventually, the accumulation of such problems may lead to the onset of frailty, a phenomenon receiving increased attention in both science and health care [3]. Frail individuals are more likely to deteriorate in their daily functioning, develop mobility limitations, are more often hospitalized, develop more often chronic diseases and have shorter survival probabilities [3]. With increased longevity, the number of frail older persons is increasing, making frailty one of the major health care problems in high-income countries [3-5].

There are reasons to believe that frailty may be more notable in people with intellectual disabilities (ID), who are characterized by limitations in both intellectual functioning (IQ below 70) and in adaptive behavior, that have started before the age of 18. In addition to general aging problems, people with ID have, from a young age forwards, an increased risk of motor and sensory disabilities, chronic diseases, mental health problems and syndrome-specific complications, which could make them extra vulnerable to develop frailty [6-9]. The improved quality of residential and healthcare has also increased the life expectancy of people with ID [10-12] which could possibly result in a disproportionally high number of age-related problems. Even so, there was very little known about frailty in people with ID.

People with ID are more and more living and participating in the community. This trend is further stimulated by the transition of long-term care that will take place in the Netherlands. Until 2014, specialized long-term care was financed under the Dutch Act on Exceptional Medical Expenses (AWBZ). In 2014 a transition took place from the AWBZ to the Social Support Act (Wmo). With this transition the Dutch government wants to achieve affordable, good and accessible care that allows people to live in their own homes for as long as possible. This transition also applies to people with mild and moderate levels of ID. In order to stimulate healthy aging and to provide information to parties responsible for their care, solid epidemiological research is required. Therefore, this thesis focuses on the measurement, frequency, determinants, and consequences of frailty in older people with ID.

OPERATIONALIZATION OF FRAILTY

A frail individual will have difficulties recovering from a stressor event, for example a bone fracture. A non-frail individual may, e.g. temporarily lose some independency, become a little frustrated and lose (or gain) some weight, after which he or she makes a full recovery. In contrast, a frail individual, has a high risk of losing considerable muscle mass, getting depressed, remain dependent and get cognitive problems, and, although he or she will partly recover, there may be a permanent deterioration in function. Although, experts agree that frailty is a condition in which older people are more vulnerable to adverse health outcomes as a result of age-related decline in many physiological systems, there is no agreed-upon definition nor a broadly accepted measurement strategy [3, 5]. There are several operational definitions and measurement methods that identify the frail individual.

The two most frequently used operational definitions of frailty are the 'frailty phenotype'[13] and the 'frailty index' [14], both introduced during the first decade of this century. The frailty phenotype, introduced by Fried and colleagues in the Cardiovascular Health Study, is based on five core clinical features that are used to identify frailty (unintentional weight loss, weakness, slow walking speed, self-reported exhaustion, and low physical activity). The fundamental basis of the frailty phenotype is a cycle, representing a downward spiral of age-associated physiologic factors that eventually lead to the onset of the five core clinical elements of frailty. The frailty phenotype has been validated, in terms of predicting adverse health outcomes, in several older populations (nursing home, hospitalized, and living in the community) [15]. The major advantage of this operationalization is its applicability in clinical practice, because the five core elements can be measured in a short physical assessment. However, disabilities (e.g mobility limitations, cognitive impairments) can affect the reliability of the frailty phenotype. It has therefore been suggested that the frailty phenotype produces meaningful results for non-disabled older people only [16].

The second approach, the frailty index, defines frailty as the accumulation of a broad spectrum of non-specific age-related impairments (deficits), including symptoms, signs, diseases, disabilities or laboratory measurements [14, 17]. The frailty index was developed and validated in the Canadian Study of Health and Aging, by Rockwood and Mitnitski [14]. In contrast to the frailty phenotype, the frailty index does not consist of a fixed set of variables, has a continuous nature (no strict categorization), identifies frailty using different health domains, and has meaningful results in disabled and non-disabled individuals [16]. Frailty indices have been calculated for large older populations from different countries. Although these frailty indices were constructed using different da-

tasets, different deficits, and different numbers of deficits (20-130), all predicted adverse health outcome [18-20]. Since the frailty index does not require a fixed set of variables, it is possible to compose a frailty index from an existing health data set [21]. In addition to the frailty phenotype and the frailty index, there are many more instruments [22]. Several frailty instruments use self-report questionnaires addressing multiple health domains, e.g. in the Netherlands, the Tilburg Frailty Indicator [23] and the Groningen Frailty Indicator [24].

FRAILTY IN PEOPLE WITH ID

People with Down syndrome have an increased risk for age-related disorders such as thyroid dysfunction, Alzheimer disease, musculoskeletal disorders, hearing loss, and visual impairment [25, 26]. Consequently, although the life expectancy of people with Down syndrome has increased, there seems to be an early onset of functional decline that can be considered as early aging on a genetic basis. With the exception of Down syndrome, there are no clear indications for 'early aging' in people with other causes of ID. Even so, it has long been a common understanding that people with ID are old from the age of 50 years onwards [27, 28]. This understanding may influence support and intervention. For example, a 60 year-old lady with mobility limitations might be offered a wheelchair because she is already 'old', whereas with adequate treatment this could have been postponed. We wondered whether, the observed early aging or functional decline might be an early onset of frailty. If so, this would offer possibilities for prevention or delay of functional deterioration. Indeed, studies in the general population show that frailty is a dynamic process that is reversible by interventions [3, 29-32]. Information about the frequency, determinants and consequences of frailty can help to understand and influence the observed early aging in people with ID.

As stated before, there are many different operationalizations of frailty. It was unknown whether they are applicable and valid in people with ID. Brehmer and Weber were the first to investigate frailty in this population. They developed an experience-based questionnaire that classified over a quarter (27%) of 50 included adults aged 50 years and over as frail [33]. This scale has not yet been validated in terms of predictive value for adverse health outcomes, and the uniqueness of the questionnaire makes direct comparison with the general population impossible. Evenhuis et al. applied the frailty phenotype to people with ID aged 50 years and over (n = 848) [34]. They showed that frailty is more common in people with ID than in the general population. Also, they found a high correlation between mobility impairment and frailty. Since mobility im-

pairment in this population can be lifelong or develop early in life, this could limit the validity of this frailty operationalization.

For several reasons we have chosen to measure frailty with a frailty index. First of all, it can cover a broad range of domains considered important for health and dependence (e.g. nutritional status, physical activity, energy, cognition) [22, 35]. Second, as a frailty index does not require the use of a pre-defined set of variables, we were able to include problems that are often prevalent in people with ID (e.g. dysphagia, chronic obstipation, epilepsy), as well as use diagnostic questionnaires that have been validated in people with ID. Third, a frailty index is designed using a well-evaluated standardized procedure, which enables comparison with other groups [21]. Fourth, self-report, which would be problematic for those with limited understanding or communication problems, can be avoided. Last, a frailty index can be composed from a (pre-existing) comprehensive assessment. The Dutch Healthy Ageing and Intellectual Disability study provided an opportunity to design a frailty index.

THE HEALTHY AGEING AND INTELLECTUAL DISABILITY STUDY

There are very few large epidemiological studies on the health of people with an ID. Therefore, the Healthy Aging and Intellectual Disability study (HA-ID) was initiated in 2007 to gain more knowledge about the health of older people with ID. Three large Dutch care organizations (Abrona, Ipse de Bruggen and Amarant) and two university departments (the department of Intellectual Disability Medicine of Erasmus Medical Center Rotterdam and Movement Sciences of Groningen University) participated in this study. The aims of the HA-ID study were to perform baseline assessments of health conditions relevant to prevention, to identify risk groups and to select and evaluate diagnostic tools. The HA-ID study was based on of three sub-themes: physical activity and fitness, nutrition and nutritional state, and depression and anxiety.

Participants were recruited from the three care organizations, that provided a broad spectrum of care, ranging from ambulatory support to intensive residential care. At the start of the study, in 2008 the three care provider services together offered care to 2322 people with ID aged 50 years and over, which was 10% of the total Dutch population with ID receiving formal care. Eventually 1050 participants were included who constituted a near-representative sample of people with ID who use formal care in the Netherlands. Within the three subthemes of the HA-ID study, a comprehensive set of measurements was selected, including physical assessments, a fitness test battery, actigraphy, pedometer measurements, mealtime observations of swallowing,

nutritional diaries, screening questionnaires and standardized psychiatric interviews for depression and anxiety, questionnaires on life events, quality of life, IADL, ADL, mobility, dementia, social circumstances, somatic complaints, and laboratory tests as well as the collection of data from the medical and location files. We wondered whether the frailty index would show the same predictive value as observed in the general population. The lifelong impairments (e.g. neurological problems, musculoskeletal problems, visual and hearing impairments), observed in people with ID, could have led to early rehabilitation and, possibly, to habituation. For example, people with cerebral palsy are likely to use walking aids or a wheelchair. It was unknown how such early limitations might influence frailty. In the general population, disabilities in daily living (e.g. going to the toilet, meal preparation, grooming) are considered a consequence of frailty [36-38]. On the contrary, in people with ID, limitations in activities of daily living can be life-long and might contribute to frailty rather than the other way around. Therefore, to study the relation between frailty and adverse health outcomes, a longitudinal follow-up study of the HA-ID population was established, evaluating aspects of health, dependence and mobility of the participants three years after the baseline measurements.

The extensive dataset of the HA-ID study was used to answer the main research questions in this thesis: how is frailty distributed in the ID population, what are its correlates and to what extent does it predict adverse health outcomes? This general research question was broken down in the sub-studies outlined in the next section.

AIMS AND OUTLINES

Chapter 2 provides an overview of the different frailty measurements and their potential applicability to the ID population. Chapter 3 describes the design of a frailty index for people with ID using data from the HA-ID study. The distribution of frailty in this sample is presented. Furthermore, differences between subgroups (age, level of ID, gender and Down syndrome) are described. These results were compared to results from the general population. In chapter 4, the characteristics are examined of participants with the lowest frailty index score named the 'least frail'. The least frail participants give insight into possible intervention strategies. To understand why people with ID show signs of early frailty, we had a closer look at possible physiological pathways towards frailty. Therefore we examined the association between inflammation, renal functioning, micronutrient status and metabolic factors, and frailty, as described in chapter 5. Using follow-up data from the HA-ID study, we examined whether high frailty index scores at baseline predicted negative health outcomes three years later. First, the relation was studied between frailty and the risk to develop (more severe) disabilities in daily functioning and mobility (chapter 6). To further study the consequences of frailty we evaluated its

relation with falls, fractures, hospital admission, medication use, and chronic diseases (chapter 7). If frailty leads to a deterioration of health and dependence it will eventually also influence health care costs. To approach this, we studied the relation between frailty and (increased) care intensity (chapter 8). In chapter 9, we show the relation between frailty and all-cause mortality. As previously mentioned, we hypothesized that the frailty index would be a more suitable measure for an early-handicapped population than the frailty phenotype. To test this hypothesis we compared the applicability and the relation with adverse health outcomes of the frailty index with those from the frailty phenotype (chapter 10). The general discussion (chapter 11) reflects on the main results and findings of this thesis and provides recommendations for the implications for clinical practice and future research.

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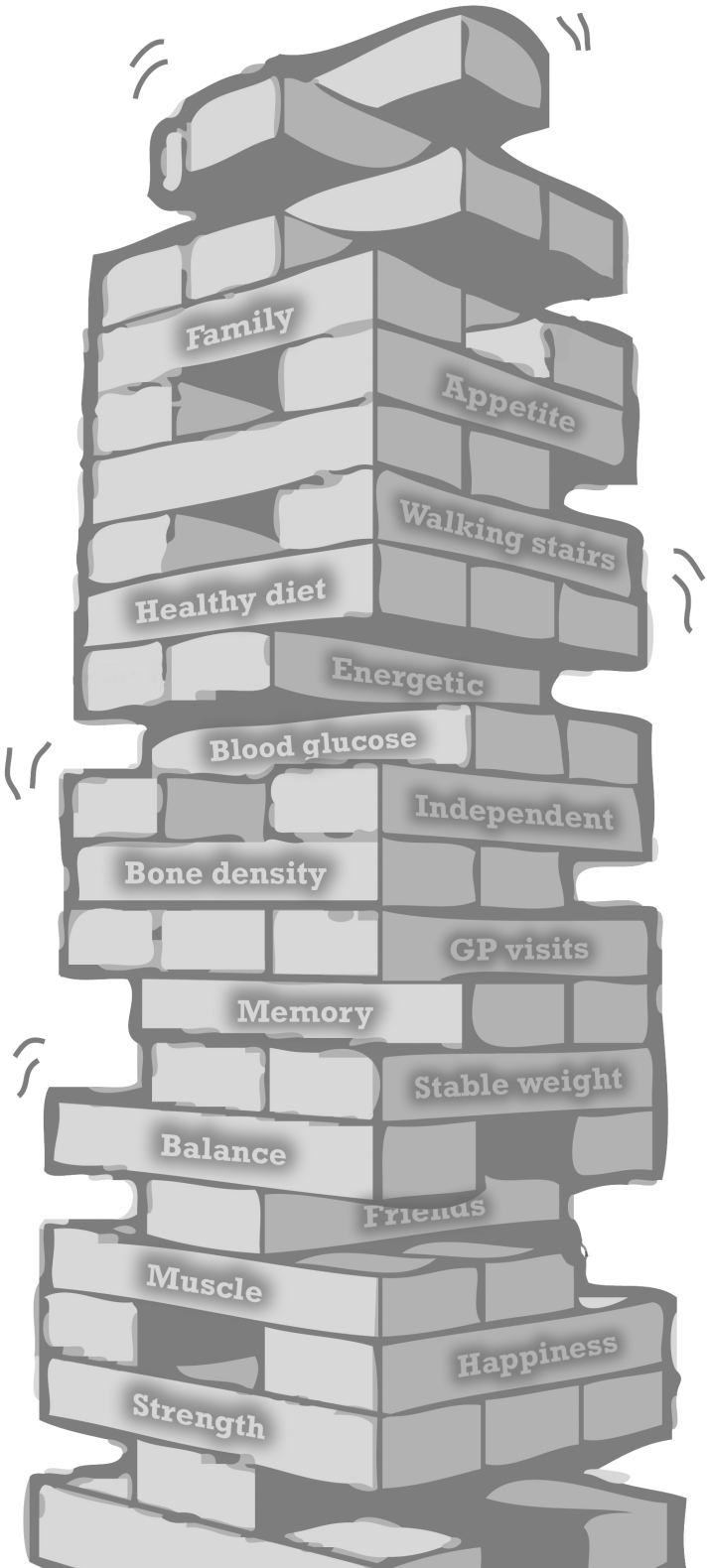
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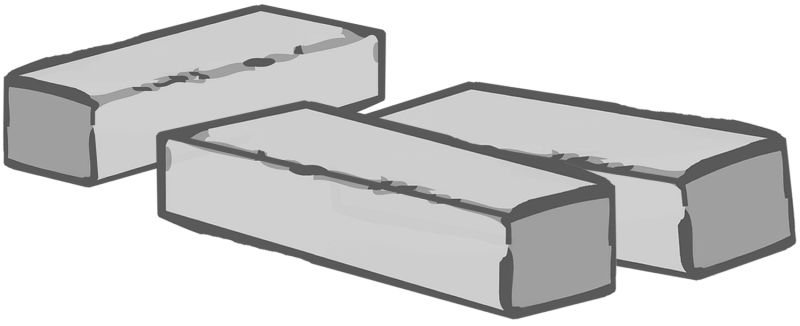
Bone density
GP visits
Memory
Stable weight
Balance
Friends
Muscle
Happiness
Strength

Chapter 2

Frailty and intellectual disability: a different operationalization?

Heleen M. Evenhuis, Josje D. Schoufour, Michael A. Echteld

Developmental Disabilities Research Reviews, 2013. 18(1): p. 17-21



ABSTRACT

Frailty is increasingly being recognized as a relevant health measure in older populations, associated with an increased risk of adverse health outcomes and care dependency. Because it is generally received that people with intellectual disabilities are "old" from age 50 onwards, frailty research in this group might lead to an understanding of factors, contributing to this perception. The development since the 1990s of conceptual and operational definitions of frailty has resulted in different approaches: biological (phenotype), multidimensional, and non-specific deficit accumulation. All approaches consider disability a consequence rather than a cause of frailty. This may be different for long-disabled populations, which would have consequences for validity of frailty measures. First research shows that the different approaches are applicable to study populations with intellectual disabilities as well. Frailty as defined by both the phenotypic and deficit accumulation approach appears to develop considerably earlier and is more severe in people with intellectual disabilities than in the general older population, supporting the notion of early aging. Before any clinical implications can be outlined, health outcomes (validity), causes, and prevention of frailty should be investigated.

Key words: Intellectual disability, frailty, frailty phenotype, frailty index

INTRODUCTION

In public health research as well as geriatric clinical practice, frailty is increasingly being recognized as a relevant health measure in older people, associated with an increased risk of adverse health outcomes (falls, acute and chronic disease, complicated hospital stay), functional decline and care dependency, declining quality of life, and early death [1-6]. As in the general population, the proportion of aging individuals is steadily increasing in the population with intellectual disabilities. However until recently, frailty in this population has not been investigated. Insight into its frequency, distribution, determinants, and consequences would be of paramount importance for prevention and treatment policies, as well as for healthcare policy in general for this vulnerable and high cost population group. We will give an overview of the most relevant conceptual definitions of frailty and their operationalizations in the general population, and present outcomes of first application of the different approaches to adults with intellectual disabilities.

CONCEPTUAL DEFINITIONS

Buchner and Wagner (1992) were the first to formulate a conceptual definition of frailty: "A state of reduced physiological reserve associated with increased susceptibility to disability." This and following definitions [7, 8] were exclusively based on biological functions. Other researchers support an integral, multidimensional concept of frailty, addressing, apart from biological functions, also cognitive, psychological, social, and environmental aspects [9-12]. Since 2008, several international expert consensus meetings have addressed the definition and assessment of frailty [13-15], showing that the multidimensional nature of frailty was increasingly accepted, as was the necessity to include multiple domains in its assessment. These different conceptual definitions of frailty have resulted in a range of operationalizations for clinical and scientific use.

PHYSICALLY ORIENTED OPERATIONALIZATION

The theoretical model developed by Fried and co-authors for the American Cardiovascular Health Study (CHS) [1] is an example of a physically oriented operationalization, designed around conditions that were considered markers of frailty in the scientific literature (Figure 1). It has resulted in a "frailty phenotype" which includes measures of decreased muscle function and endurance (Table 1). This frailty phenotype has been validated against adverse health outcomes at a population level [1, 16]. Although its

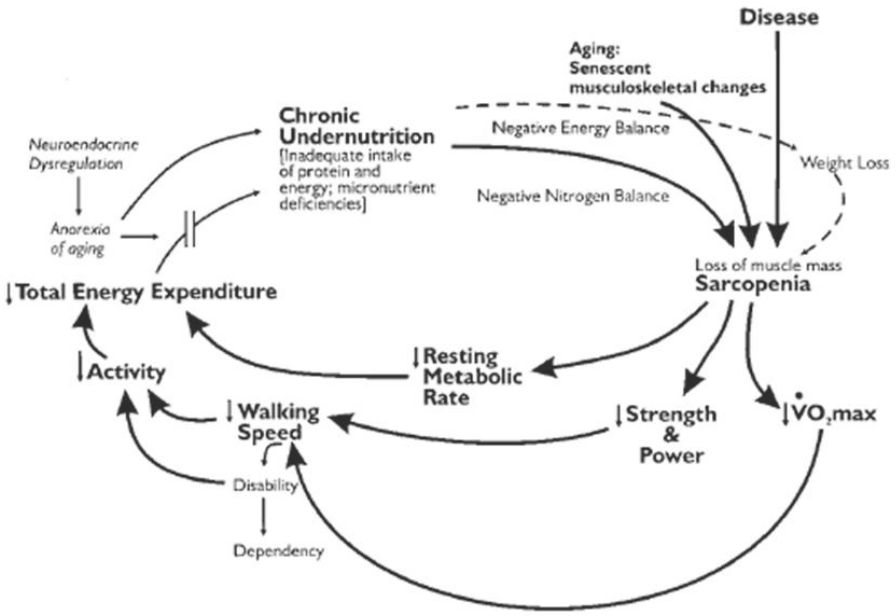


Figure 1. Cycle of frailty hypothesized as consistent with demonstrated pairwise associations and clinical signs and symptoms of frailty [1].

sensitivity and specificity as a diagnostic measure have not been evaluated, it is now widely used in geriatric clinical care. Table 1 shows, that muscle function and mobility play a central role in this approach, and it has been argued that phenotypic frailty represents in fact disability. There is now a growing consensus in the general geriatric literature that, although there is an overlap of frailty with disability, these are distinct clinical entities that are causally related [1, 17]. In late life, physical disability, resulting in mobility loss, or impaired (instrumental) activities of daily life [(i)ADL], is considered an outcome of diseases and physiologic alterations with aging. It may develop progressively or acutely, e.g., after a fracture or stroke [18]. So for the general older population, disability is considered a consequence rather than a cause of frailty [13, 18].

This may be completely different for long-disabled populations, such as the population with intellectual disabilities addressed in this article. No experimental research of frailty in long-disabled groups had been published, but it was to be expected that in such groups, disability can be a consequence of, but also, a contributing factor to frailty. Therefore, we have assessed phenotypic frailty in older people with intellectual disabilities, using data collected during 2009 and 2010 in the Dutch study "Healthy Ageing and Intellectual Disabilities" (HA-ID) [19]. The study cohort of 1050 clients of formal service providers for people with intellectual disabilities, aged 50 years and over, is nearly representative

Tabel 1.

A	Characteristics of frailty
1	Shrinking: weight loss; sarcopenia (loss of muscle mass)
2	Weakness
3	Poor endurance; exhaustion
4	Slowness
5	Low activity
B	Cardiovascular Health Study measure
1	Baseline: > 10 lbs loss unintentionally in prior year
2	Grip strength: lowest 20% (by gender, body mass index)
3	"Exhaustion" (self-report)
4	Walking time/15 feet: slowest 20% (by gender, height)
5	Kcals/week: lowest 20%: males: < 383 Kcals/week; females: < 270 kcal/week
C	Presence of frailty
	Positive for frailty phenotype: ≥3 criteria
	Intermediate or pre-frail: 1 or 2 criteria present

for all clients of Dutch formal specialized care, consisting of people with borderline to profound disabilities whom are provided sheltered living in more or less centralized settings, community-based living in group homes, daycare only, or independent living with specific outreaching support. We hypothesized that frailty would strongly overlap with and might even be identical to motor and severe cognitive disability. It was established that in the age group 50–64 years, prevalence of phenotypic frailty (11%) [20] was as high as in the general population aged 65 years and over (7–9%) [1, 21-24], with a further increase after the age of 65. Age, Down syndrome, dementia, motor disability, and severe or profound intellectual disability were significantly associated with frailty, but in a multivariate analysis, only motor disability had a unique association with frailty. Indeed, people using walking aids or a wheelchair were 10 times more likely to be frail as those who walked independently. In a regression model with the above variables, 25% of the variance of frailty was explained, implying that motor or severe intellectual disability only partially explain frailty. We were critical towards application of the narrow frailty phenotype to people with intellectual disabilities, because apart from longstanding disability, this group is subject to multiple comorbidity and medication use, negative life events and other damaging psychological and environmental factors during their whole life, which all might contribute to higher frailty in old age. Therefore, we were more interested in the broader operationalizations of frailty.

MULTIDIMENSIONAL OPERATIONAL DEFINITIONS

The multidimensional approach has resulted in a range of operationalizations that are in fact clusters of items, considered relevant on a basis of shared experience of gerontologists, and not always supported by explicit theory. In a systematic review, Levers et al [25]. identified physical, cognitive/psychological, nutritional, and social factors, as well as the variables "aging" and "disease," in both the theoretical and experimental literature. The authors concluded that confusion existed about the relational direction between frailty and such factors. More recently, Gobbens et al. [12] have published an integral model of frailty, based on hypothesized relations between variables in time (Figure 2). A pathway is shown from possible determinants of frailty (life course, disease, age-related decline in physiologic reserve) to frailty (presenting with markers of physical, psychological, and social decline) to adverse outcomes. Each stage may offer opportunities for interventions. It appeared that the predictive validity of a multidimensional self-report questionnaire, based on the model (Tilburg Frailty Indicator, TFI), appeared moderate to good for disability, most aspects of healthcare utilization, and quality of life after 1 and 2 years [4]. Addition of the Timed Up and Go test improved predictive validity for disability [26]. We have judged applicability of the TFI items to the population with intellectual disabilities, concluding that 17 out of 25 items can be answered by people with borderline and mild intellectual disabilities, of which one by independently living persons only. However, four of these items should be objectively assessed for a reliable result (questions on sensory impairments, memory problems, and weight loss). For persons with moderate or severe intellectual disabilities, only 10 items can be completed by their caregivers. Some of the items are insufficiently discriminative in subgroups (e.g., being married, highest education level, two or more chronic conditions). Therefore, the TFI might be applied to and evaluated in adults with borderline or mild disabilities. The multidimensional model has been applied by Brehmer and Weber to Austrian adults with intellectual disabilities [27]. The authors developed a multidimensional self-report and observation-based questionnaire, based on published determinants in the general population as well as consensus of experts, in this case in intellectual disability care. A first evaluation was performed in a group of 190 adults (18–76 years) of whom 60% lived in a residential setting and the others lived alone or with family. The outcomes showed a satisfying internal consistency for the total questionnaire, but not for all individual items. With provisional frailty criteria, 17 participants (9%) were identified as frail, of which a majority had mild or moderate intellectual disabilities and lived in an institutional setting. The authors are planning further evaluation of the reliability and validity of the instrument.

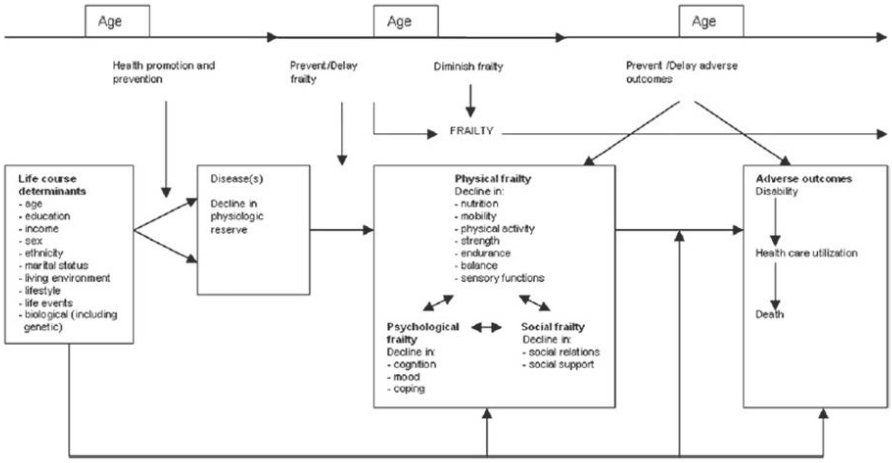


Figure 2. An integral conceptual model of frailty [17].

ACCUMULATION OF DEFICITS

A different approach was taken by Rockwood and Mitnitski [3], who abandoned the search for specific determinants or markers of frailty, based on theoretical models and empirical accounts, after realizing that "combining traditional foci of gerontologists left much variance unexplained and did not consider relative fitness." They aimed for a model that was "conceptually simple, could evaluate impairments in many systems, accommodate change, and grade severity of frailty." An approach was proposed in which health- and age-related deficits present in individuals are simply counted, and relative frailty is inferred on that basis, without specifying deficits or combinations of deficits. Deficits are included that are readily available in survey or clinical data, including symptoms, signs, disabilities, diseases, and laboratory measurements. If a sufficiently large number (at least 30) of variables are considered, the variables can be selected at random and still yield comparable results of the risks of adverse outcomes, as long as they adhere to a number of basic principles [28, 29]. A frailty index score is calculated as the proportion of potential deficits that are present in an individual, resulting in a value between 0 (no deficits present) and 1 (all deficits present) [29]. The validity of this approach has been demonstrated in 65+ and 70+ population studies, examining average accumulation of deficits between countries, relationship with mortality, and differences between population-based and institutional or clinical cohorts [3, 30]. In different community-based populations, the distribution of index scores is always as shown in Figure 3, independent of specific deficits included in the index, with most scores around 0.15, a skewed distribution to the right with a limited prevalence of score 0 (zero state), and maximal scores around 0.7 [29]. Recently, the distribution in a large 50+ European

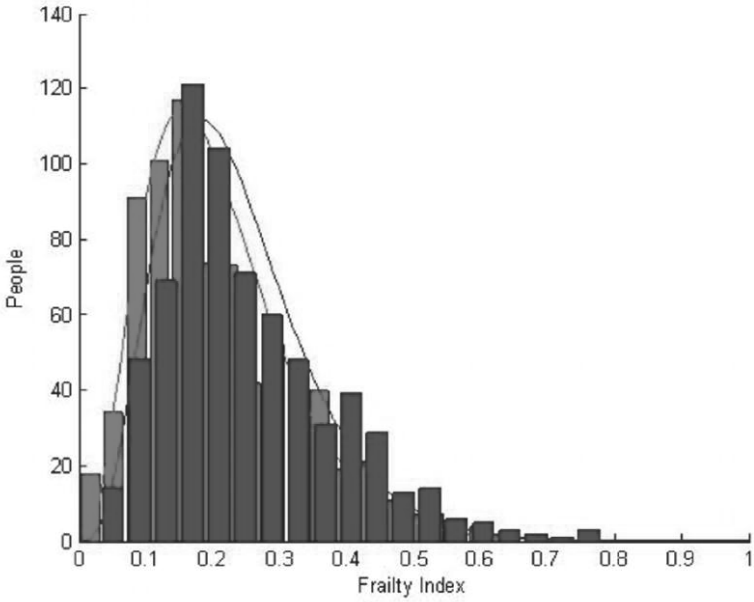


Figure 3. Frailty index distribution. Gamma distribution fit (lines) of the observed distribution of the frailty index (bar) in the baseline (gray) and 18 month follow-up (black) sample [29].

population sample has been published, showing a different picture with a majority of scores below 0.2 (Figure 4) [5].

We were specifically interested in the frailty index approach, because the conceptual model of frailty, published by Gobbens et al. [14], may apply to aging persons with intellectual disabilities as well, but its operationalization is problematic. People with intellectual disabilities often experience early multimorbidity and may, apart from a cognitive disability, have motor and/or sensory problems from a young age onwards [31-33]. Further, their living conditions often differ from those of other people. In addition, we feared that focusing too much on published and consensus data for the general population might lead to a failure to identify variables that are specifically relevant to development of frailty in this population. Therefore, we decided to test the applicability and outcomes of the deficit accumulation approach, too. The collection of over 400 variables in the HA-ID study enabled us, in a collaboration with Rockwood and Mitnitski, to develop a frailty index consisting of 51 health- and age-related physical, mental, and social items, and to perform a cross-sectional evaluation of the distribution of frailty index scores in this population, as well as of their relationship with age. It appeared that the distribution of frailty index scores in the 50+ population with intellectual disabilities is more similar to that in general 70+ populations than to that in the general 50+ Euro-

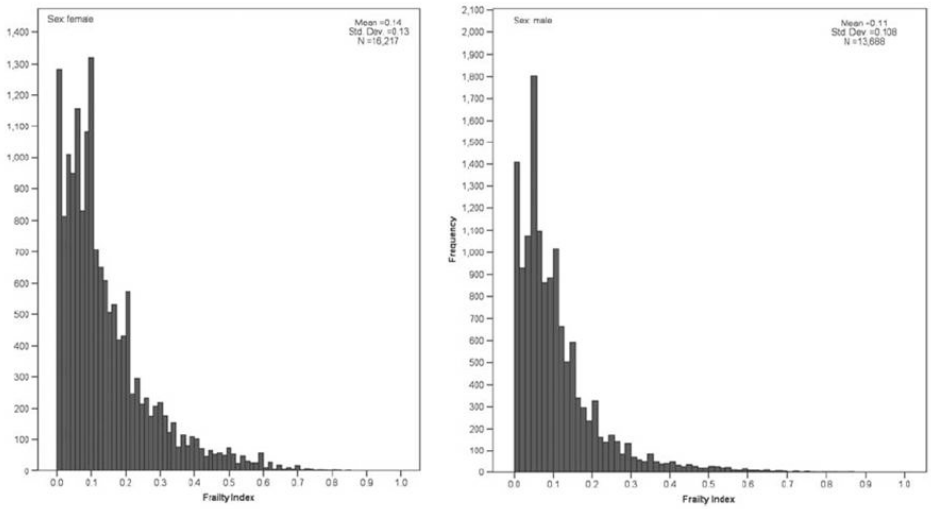


Figure 4. Distribution of the frailty index in a 50+ European study population [5].

pean population. The group aged 50–59 years had a mean frailty index score similar to that of individuals aged 80–89 years in the general European population [5], after which the scores increase in further age groups. No participants had zero deficits.

CONCLUSION AND NEXT STEPS

We conclude that the phenotypic, multidimensional, and deficit accumulation approaches of frailty principally can all be applied to people with intellectual disabilities. Frailty seems to be more prevalent and more severe in relatively young individuals, as compared to the general population. This may explain the notion of "early aging" in this group. However, an outline of clinical implications for prevention and treatment cannot yet be made as long as health outcomes (validity), causes, and prevention of frailty have not been evaluated in this population. Therefore, our research group is now collecting 3-year follow-up data in the above HA-ID cohort. Our aims are to evaluate predictive validity of the phenotypic and frailty index outcomes for adverse health outcomes and daily functioning, and to analyze the relative contribution of positive and negative determinants, leading to a valid operational definition of frailty for this group.

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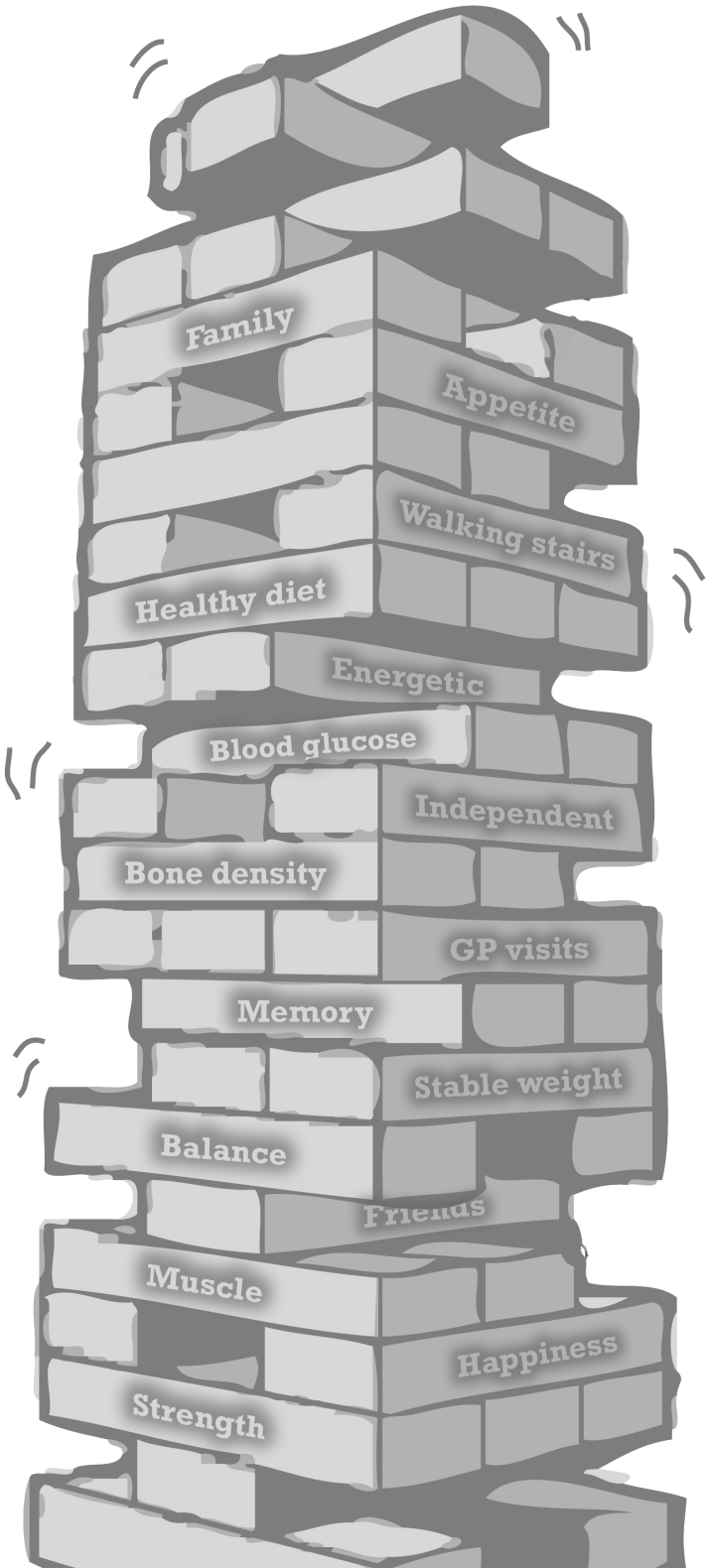
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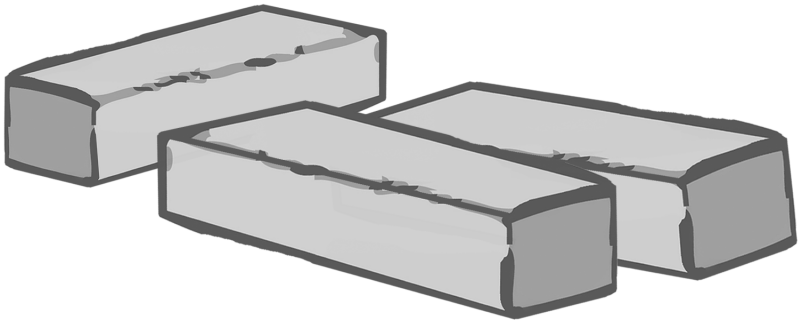
Appetite
Walking stairs
Healthy diet
Energetic
Blood glucose
Independent
Bone density
GP visits
Memory
Stable weight
Balance
Friends
Muscle
Happiness
Strength

Chapter 3

Development of a frailty index for older people with intellectual disabilities: results from the HA-ID study

Josje D. Schoufour, Arnold Mitnitski, Kenneth Rockwood, Heleen M. Evenhuis, Michael A. Echteld

Research in Developmental Disabilities, 2013. 34(5): p. 1541-1555



ABSTRACT

Background: Although there is no strict definition of frailty, it is generally accepted as a state of high vulnerability for adverse health outcomes at older age. Associations between frailty and mortality, dependence, and hospitalization have been shown. We measured the frailty level of older people with intellectual disabilities (ID). Furthermore variation in gender, age, and level of ID were identified. Results were compared to a frailty study in the general European population. **Methods:** This research elaborates on a large cross-sectional study: Healthy Ageing with Intellectual Disability (HA-ID). Nine hundred-eighty-two men and women (≥50yr) with ID were included. Based on the collected data, we developed a frailty index with 51 health-related deficits, and calculated a frailty index score between 0 and 1 for each individual. Deficits included physical, social and psychological problems. **Results:** The mean frailty index score was 0.27 (standard deviation.13). Frailty was positively correlated with age ($r = .297$, $p < .001$). More severe ID was associated with higher frailty scores ($\beta = .044$, $p < .001$). The upper limit of the frailty index was 0.69, which was consistent for all age categories. **Conclusion:** As people with ID are getting older, the question whether additional years are spent in good health becomes salient. Here, people with ID over age 50 had frailty scores similar to most elderly people over 75y. Future research is needed to confirm if frail elderly people with ID have an increased risk of adverse health outcomes.

Key words: Older people, intellectual disability, health, frailty, frailty index, aging

INTRODUCTION

Although frailty, a state in which older persons are more vulnerable to negative health outcomes, has been extensively studied in the general population, little is known about frailty in people with intellectual disabilities (ID). Frailty in this population might be of major importance, given that people with ID have, in addition to general aging problems, an increased risk of motor and sensory disabilities, chronic diseases (e.g. epilepsy), and mental health problems [1-3]. It is therefore plausible that there is an early onset of frailty in this population compared to the general population. Furthermore, life expectancy of people with ID is approaching the general public's life expectancy [4, 5]. To be able to prevent or delay frailty in this population, research on frailty in this population is urgently required.

The underlying mechanisms behind frailty are not yet fully understood. While it is well accepted that frailty is a useful construct, there is yet no consensus on how it should be operationalized, nor is there complete consensus on the definition, or on how it should be diagnosed [6]. The essential feature is that it is a state of increased risk for adverse health outcomes [7]. Gobbens et al described frailty as "a dynamic state affecting an individual who experiences losses in one or more domains of human functioning (physical, psychological, social), which is caused by the influence of a range of variables and which increases the risk of adverse outcomes" [8] which is in line with prior conceptualizations [9, 10]. Associations between frailty and mortality, institutionalization, and dependence have been shown [11]. Since frailty is a highly age-associated phenomenon [11, 12] and the number of older adults increases across the globe [13], frailty becomes one of the major challenges for health care professionals [14].

Despite lacking complete consensus, two approaches are broadly accepted in the operational definition of frailty. The first defines frailty as a syndrome, with specific features; the second defines frailty from a multidimensional perspective. The frailty phenotype [11] proposes five features, using elements operationalized in the Cardiovascular Health Study (CHS). It classifies people as frail if 3 or more of the following features are present: slow walking speed, impaired grip strength, low activity levels, unintended weight loss, or exhaustion. The phenotypic approach has shown to correlate with adverse health outcomes in wide range of studies in different settings [15]. Our research group investigated frailty status of 848 clients of formal ID care, aged 50 years and over, according to these criteria and found that 13% was frail. Among the subgroup aged 50-64 years, the prevalence of frailty (11%) is comparable to that in the general population aged 65 years and over. Frailty in the subgroup aged 65 years and over was 18%, compared to 7-9% in the general population [16]. It has been suggested that frailty measured according to the

CHS criteria is highly influenced by low mobility [17], which was also found in our study group with ID. Due to the exclusively physical orientation of the criteria, longstanding motor disability may be misclassified as frailty. It could be that the second perspective to measure frailty, the multidimensional one, is more suitable for this population. This broader concept includes in addition to physiological health also social circumstances and mental health. There are several methods using such a multidimensional perspective, e.g. in the Netherlands, the Tilburg Frailty Indicator [18] and the Groningen Frailty Indicator [19]. However such methods based on self-report may be difficult to apply in this population because of limited understanding and communication problems, as well as unidentified health problems [20].

Another multidimensional measure for frailty is the frailty index which is explicit in characterizing frailty not as a syndrome, but as a state. A frailty index is a quantitative measure based on a concept of non-specific accumulation of a broad spectrum of age-related impairments (deficits), including symptoms, signs, diseases, disabilities or laboratory measurements [12, 21]. A main advantage of the frailty index is the wide range of deficits which are not merely focused on physical health but also include social circumstances and mental health [22]. A systematic review taking into account 20 different frailty instruments concluded that the only instrument taking all frailty factors (nutritional status, physical activity, energy, strength, cognition, mood, social relations/social support) into account is the frailty index [23]. Frailty indices have been calculated for large older populations in Canada, Australia, Sweden [24], China [25, 26], Wales [27], Mexico [28], United Kingdom [29, 30], Europe [31], and the United States [32, 33]. Although these frailty indices were constructed using different datasets, different deficits, and different numbers of deficits (20-130), all were highly associated with early mortality [24, 34, 35]. High frailty index scores are related to institutionalization [36, 37] and to cognitive decline [38]. Frailty indices, designed for different countries, show the same characteristics: a skewed distribution concentrated to the right, a high correlation with age, and a consistent upper limit of the frailty index Score. Furthermore, Rockwood et al., showed that a random selection of deficits, within any given frailty index, yields comparable frailty estimates [37]. Several researchers showed that frailty index-defined frailty predicts adverse health outcomes more precisely than phenotypic-defined frailty [38-40]. These results indicate a robust relation between deficit accumulation and frailty [34].

For us, an advantage of this method is the relatively free choice of deficits, so a frailty index can be specified for older adults with ID. Furthermore, the broader approach might be a more valid perspective for this population. Constructing a frailty index for older people with ID may therefore help to provide insight into the onset and character of

frailty and its associated factors in this group. The main aim of this study was to provide first insight into the accumulation of deficits among older persons with ID. To achieve this objective the following questions needed to be answered.

- Is it feasible to create a frailty index for older people with ID from an existing set of health data?
- What are the properties of the frailty index (distribution, correlation with age and the slope of the 99th percentile score of each age group, minimum and maximum score)?
- What are the differences in mean frailty index scores in subgroups (according to gender, age, and level of ID)?
- What are the differences in mean frailty index score per age decade in older people with ID compared to the general population?

METHODS

Design

Data from the HA-ID study, a cross-sectional observational study in 1050 clients of ID care provider services, were employed for these analyses. The main goal of the HA-ID study was to establish the health status of older persons with ID using formal care for people with ID in the Netherlands. Inclusion criteria and data collection have been described elsewhere [41]. In short, participants were recruited through three Dutch care provider services offering a broad spectrum of care, ranging from ambulatory support to residential care. The three care organizations are located in different parts of the Netherlands. The Medical Ethics Committee of the Erasmus Medical Center Rotterdam (MEC- 2008-234) and the ethics committees of the participating care organizations approved this study. This study adheres to the Declaration of Helsinki for research involving human subjects.

Participants

All 2322 clients of 50 years and older receiving care or support by one of the participating care organisations were invited to participate in the study. The total number of clients who participated in the study was 1050. Those capable of understanding the available information signed the consent form themselves. Legal representatives were approached for those not able to make this decision. The level of intellectual disability ranged from borderline to profound. The HA-ID population is nearly representative for all Dutch older people with ID using formal services. There is a slight underrepresentation of men $X^2(1, N = 2322) = 0.53, p = .028$, people aged 80 and above $X^2(8, N = 2322) = 27.41, p = .001$, and people living independently $X^2(3, N = 2237) = 50.55, p < .001$.

Data collection

The HA-ID study consisted of three main themes: (1) physical activity and fitness, (2) nutrition and nutritional state, and (3) mood and anxiety. Within these themes a broad diagnostic assessment was performed in addition to the collection of file data. These assessments included: physical assessments, a fitness test battery, actigraphy, pedometer measurements, mealtime observations of swallowing, nutritional questionnaires (gastroesophageal reflux and undernutrition), screening questionnaires and standardized psychiatric interviews for depression and anxiety, questionnaires on life events, quality of life, (instrumental) activities of daily living, mobility, dementia, social circumstances, somatic complaints, as well as laboratory tests. All used instruments were carefully selected for this study and population and if necessary and applicable, psychometric properties were tested and reported [41-43]. The physical fitness assessments were performed by physiotherapists, physical activity instructors or occupational therapists, who were all experienced with people with ID and trained during a two-day course. Questionnaires were completed by self-report or if not applicable, through observation-based reports completed by professional caregivers. All test administrators were trained by the researchers themselves or external experts; their test assessments and scoring were tested regularly during the entire duration of the study. Level of ID was obtained from the scores of psychologists or test assistants, who determined level of ID from available IQ tests, Vineland scores and social emotional development. Data were collected between February 2009 and July 2010.

Inclusion criteria for health deficits into the frailty index

During the HA-ID study, 409 different variables (including single items from questionnaires) were collected. The frailty index employed here was based on a selection of these variables. An overview of criteria for selecting a variable for inclusion is shown in Table 1. We used the selection criteria published by Searle at al. [44]: 1) The deficit must be associated with health status, 2) The prevalence of the deficit must generally increase with age, 3) Only deficits that do not 'saturate too early' should be selected, which means that ceiling effects should not occur within the sample population, 4) The deficits should cover all basic dimensions of health. To meet these requirements, all deficits without a significant correlation with age within this study population ($p > .1$) were excluded (e.g. communication problems, sadness, trying to eat inedible things, dealing with money, severe behavioural problems, and hyperthyroidism). To exclude deficits that saturate too early, deficits with prevalences over 80% were excluded (not doing laundry and ironing). To cover a broad variety of health aspects, variables about mental wellbeing, blood values, chronic diseases, fitness, nutritional status, level of independence ((instrumental) activities of daily living), physical and mental risk factors, and social aspects were included. Additional inclusion criteria were developed for this specific population

by consensus of our research group. Deficits were excluded if outcome values were missing in over 30% of the participants (e.g. experiencing dizziness, sit and reach test, 30 seconds chair test, and information about dental health). Furthermore, single items of questionnaires were used as individual deficits rather than using subscale or total scores of the questionnaire, in order to increase the number of deficits. However, several items of questionnaires may refer to the same topic and will therefore be highly correlated ($r > .7$). To limit the influence of specific topics in such cases, only the item with the highest correlation with age was included. For example from the variables 'fatigue' & 'lack of energy' and 'dressing' & 'grooming' only two of the four (fatigue and dressing) were chosen. Similarly, if multiple items were designed to measure the same concept, the item with the most objective measure or with the highest correlation with age was chosen. For this reason variables such as 'able to walk 50 meters', and metabolic syndrome were excluded, while general mobility and the individual factors of metabolic syndrome were included. Last, deficits with prevalences below 5% were not included (for example sleep apnea and Parkinson's disease). If possible, related variables with low prevalences were combined to multi-item deficits (including: chronic obstructive pulmonary disease & asthma, diabetes mellitus type 1 & 2 and/or high serum glucose levels, coronary heart disease & heart failure & cardiac dysrhythmia & having a pacemaker). Only variables fulfilling all inclusion criteria were included as a deficit. The list of excluded variables was screened for variables that were excluded beyond expectations. Questions regarding dementia showed no relation with age, which was surprising. Further research revealed Down syndrome as a confounder. It is a well-known fact that people with Down syndrome are more likely to develop early Alzheimer dementia and other dementia problems [45, 46] and have a decreased life expectancy [33]. When adjusted for Down syndrome four dementia variables did correlate with age ($\beta = .059\text{-}0.09$, $p < .1$) and were therefore included in the frailty index as well.

Table 1. criteria that need to be fulfilled before a variable was included into the frailty index

A maximum of 30% of the cases is missing
The deficit should be present in > 5% of the participants
If items are designed to measure the same concept, the item that best fits the criteria is chosen.
If questionnaires are used, single items of that questionnaire can be used as deficits as long as they fulfil all criteria and do not correlate too strong with each other (r > 0.7).
The deficit is associated with health status.
The deficit is positively associated with age (*p*-value < 0.1).
The deficit does not saturate too early (in over 80% of the participants the deficit was present).
The deficits together must cover different health aspects.

Scoring of deficits

All deficits were scored between '0' and '1', '0' indicating the absence of the deficit and '1' the complete presence of the deficit. Pragmatic cut-off values were used that are congruent with previous publications. If available, valid cut-off values for people with ID were used, and otherwise cut-off values for the general older population were applied. Diseases were scored dichotomously: 1 = disease present, 0 = disease absent. For variables with intermediate response, values between 0 and 1 were used. Variable scores derived from blood samples were scored according to cut-off values as stated in the laboratory guide of the Erasmus Medical Center, Rotterdam. Cut-off values for fitness tests were derived from literature (general older population), with the exception of the Box and block test. Reference values [47] for this test were not suitable for the ID population and therefore quartiles obtained in the HA-ID population were used for score calculations. Diabetes mellitus was scored 1 for participants with the diagnosis diabetes mellitus according to their medical record, participants taking drugs for diabetes (ATC-code A10), or participants with serum glucose levels above 7 mmol/l. If applicable, scores were stratified for gender (walking speed, grip strength, high-density lipoprotein, haemoglobin), for body mass index (grip strength), or height (walking speed). If, due to physical problems, participants were unable to perform the walking speed test, grip strength test or box and block test, a score of 1 was given. The cut-off values were not stratified for age categories. No weighting of individual variables was applied, consequently all chosen deficits contributed equally to the final frailty score.

Calculation of the frailty index

A frailty index score was calculated for each individual by dividing his/her sum of deficit scores by the total number of deficits measured, resulting in a score between 0 (no deficits present) and 1 (all deficits present). If for example an individual scored twelve points out of 51, the frailty index score was 12/51 = 0.24. In general, the frailty index becomes more precise if more variables are included [44], but it has been shown that with an index of 30-40 deficits it is possible to predict adverse health outcomes [24]. Therefore participants with less than 30 deficits measured were excluded from further analyses. Missing deficits were coded as missing values and were not included in the frailty index score calculation. Therefore, a difference in total deficit count between participants was possible, but no one with fewer than 30 deficits in the denominator was included.

Analyses

Frequencies for all possible variables were calculated to identify floor effects (deficit present in < 5% of the participants), ceiling effects (deficit present in > 80% of the participants), and missing values (unknown in > 30% of the participants). To assess the association between age and potential deficits, a scatter plot was generated for each

deficit and the correlation coefficient and *p*-value were calculated. A $p < .1$ was required in order to be included.

Pearson Chi-square tests were used to compare the group of clients for whom a frailty index could not be calculated, because less than 30 variables were known, with the group with a frailty index score on baseline characteristics: age, gender, level of ID, and presence of Down syndrome. If the criteria for the expected cell frequency were not met (maximum of 20% of the cells with an expected count less than five) variables were recoded into combined variables. If dichotomous variables did not meet the criteria, the Fisher's exact test was used as an alternative.

Properties of the frailty index were analysed. First, mean and standard deviation of the frailty score were calculated for the total study population. A histogram was plotted to examine the distribution of the frailty index. The regression coefficient B was calculated to estimate the increase in mean frailty index score per year. The minimum and maximum score of the frailty index was calculated. Age-specific trajectories of the frailty index were calculated as the mean frailty index score across 10-year age groups. To obtain insight into a potential relationship of maximum frailty index scores with age, we calculated 99th percentile scores per 10-year age group, and subsequently calculated the slope of these 99th percentile scores.

The extent to which the frailty index was sensitive for individual included deficits was evaluated using a random re-sampling procedure. Fifty subsets of 75% of the total number of included deficits were repetitively used to calculate frailty indices and the best fit regression line with age.

Mean and standard deviation of the frailty score were calculated for different subgroups: gender, age group (per 10 year), level of ID (borderline, mild, moderate, severe, profound), and the presence of Down syndrome. Differences in frailty score between subgroups were tested with an independent samples *t*-test (presence of Down syndrome and gender), or univariate regression analysis (level of ID and age). All tests were two-sided and a *p*-value of less than .05 was considered to be statistically significant. In order to compare our results with the general population, data from a European 50+ study were used to plot the mean frailty index score of the general population against age.

The random re-sampling procedure was performed using Matlab (version 7.9). All other statistical analyses were performed using SPSS statistics 17.0 for Windows (SPSS, Inc, Chicago, IL, USA).

RESULTS

Deficits included in a frailty index for older people with intellectual disabilities

Data from the HA-ID study included 409 variables for evaluation to construct a frailty index for older people with ID. Of the 409, 162 were excluded due to insufficient responses or were a duplicate of similar variables (Figure 1). An additional 204 variables did not meet the pre-specified criteria. After which 11 variables were combined to 4 deficits. After adjusting for Down syndrome four questions about short-term memory did correlate with age and were retained. Finally, 51 variables were included in the frailty index (Figure 1). Detailed information about included deficits and cut-off values is shown in Table 2.

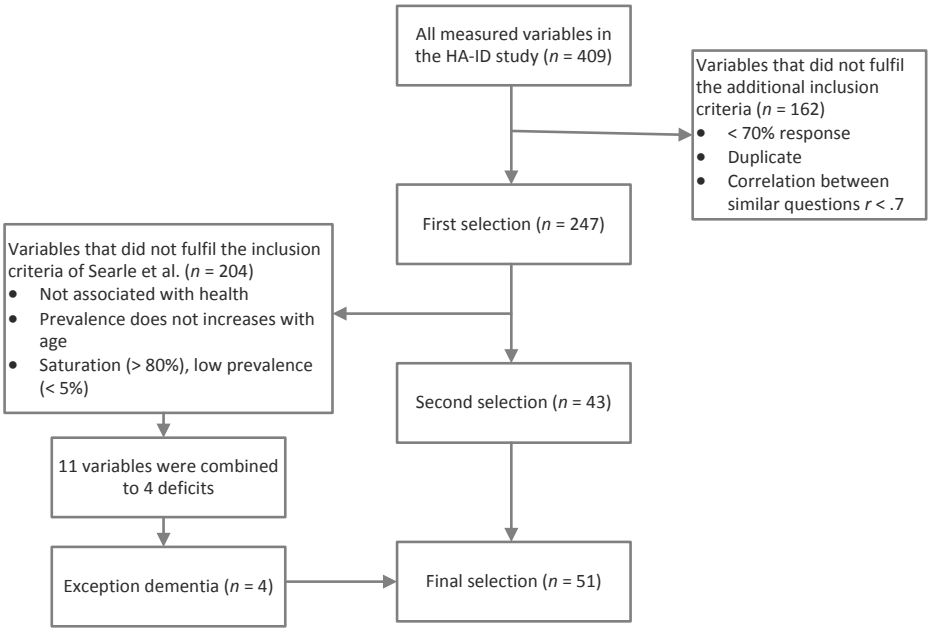


Figure 1. Flow chart of deficit selection.

Participant selection

Only participants with at least 30 known deficits were included, consequently all participants with 21 or more missing values were excluded from further analyses. Of the 1050 participants, 68 had too many missing values and were not included in further calculations. Main reasons for many missing values were incomplete questionnaires or missing file information for community-dwelling participants who received medical care from general practitioners. No significant differences were found between the 982 participants with a calculated frailty index and the 68 excluded participants with respect to gender $X^2(1, N = 1050) = 0.532$, $p = .466$, level of ID $X^2(4, N = 923) = 3.92$, $p = .417$, age

Table 2. Overview of deficits included in the frailty index

#	Deficit	Additional information	Cut-off values and FI scores	Ref
1	Bladder control	ADL, Completed by professional caregivers of the participants	Incontinent = 1 Sometimes continent = 0.5 Continent = 0	[59]
2	Dressing	ADL, Completed by professional caregivers of the participants	Needs help = 1 Partly with help = 0.5 No help = 0	[59]
3	Walking stairs	ADL, Completed by professional caregivers of the participants	Needs help = 1 Partly with help = 0.5 No help = 0	[59]
4	Bathing	ADL, Completed by professional caregivers of the participants	With help = 1 No help = 0	[59]
5	Transfer bed to chair	ADL, Completed by professional caregivers of the participants	Unable, no sitting balance = 1 Major help = 0.66 Minor help = 0.33 No help = 0	[59]
6	Groceries	IADL, completed by professional caregivers of the participants	Not independently = 1 With help = 0.5 Can do groceries = 0	[60]
7	Housekeeping	IADL, completed by professional caregivers of the participants	Not independently = 1 With help = 0.5 Can do housekeeping = 0	[60]
8	Falling	Number of falls in the last three months. Information gathered via the professional care giver	> 11 falls = 1 6-10 falls = 0.75 3-5 falls = 0.5 1-2 falls = 0.25 0 falls = 0	
9	Present at the care centre (max 10 shifts per week)	Information gathered via the professional care giver	≥3 visits a week = 0 < 3 visits a week = 1	
10	Fatigued	ADESS (Dutch translation of the Anxiety, Depression And Mood Scale) over the past six months. Completed by professional caregivers	Very often = 1 Often = 0.66 Sometimes = 0.33 Never = 0	[42, 61]
11	Listless	ADESS (Dutch translation of the Anxiety, Depression And Mood Scale) over the past six months. Completed by professional caregivers	Very often = 1 Often = 0.66 Sometimes = 0.33 Never = 0	[42, 61]
12	Panic attacks	ADESS (Dutch translation of the Anxiety, Depression And Mood Scale) over the past six months. Completed by professional caregivers	Very often = 1 Often = 0.66 Sometimes = 0.33 Never = 0	[42, 61]
13	Decreased food intake, due to loss of appetite, digestive problems, chewing of swallowing difficulties	Mini Nutritional Assessment (MNA) over the past three months. Completed by professional caregivers.	Severe decrease in food intake = 1 Moderate decrease in food intake = 0.5 No decrease in food intake = 0	[62]
14	Weight loss	Mini Nutritional Assessment (MNA) over the past three months. Completed by professional caregivers.	Weight loss greater than 3kg = 1 Does not know = 0.5 Weight loss 1-3kg = 0.5 No weight loss = 0	[62]
15	Fluid intake per day (water, juice, coffee, tea, milk)	Mini Nutritional Assessment (MNA) over the past three months. Completed by professional caregivers.	Less than 3 cups = 1 1 to 5 cups = 0.5 > 5 cups = 0	[62]

Table 2. Overview of deficits included in the frailty index (Continued)

#	Deficit	Additional information	Cut-off values and FI scores	Ref
16	Calf circumference (CC) in cm	Mini Nutritional Assessment (MNA) Completed by professional caregivers.	CC < 31 = 1 CC ≥ 31 = 0	[62]
17	Only eats selected types of food (e.g. pudding, rice)	Screening Tool of Eating Problems (STEP) over the last month. Completed by professional caregivers	> 10 times = 1 Between 1-10 times = 0.5 Not at all/not a problem = 0	[63]
18	Only eats small amounts of the presented food	Screening Tool of Eating Problems (STEP) over the last month. Completed by professional caregivers	> 10 times = 1 Between 1-10 times = 0.5 Not at all/not a problem = 0	[63]
19	Only eats foods of certain textures.	Screening Tool of Eating Problems (STEP) over the last month. Completed by professional caregivers	> 10 times = 1 Between 1-10 times = 0.5 Not at all/not a problem = 0	[63]
20	Mobility	Provided by professional caregivers	Wheelchair = 1 Walks with support = 0.5 Walks independently = 0	
21	CVA	Medical file, last 24 months	Yes = 1 No = 0	
22	Coronary heart diseases/ heart failure/cardiac dysrhythmia/ pacemaker	Medical file, last 24 months	Yes = 1 No = 0	
23	Cancer	Medical file, entire life	Yes = 1 No = 0	
24	Asthma/COPD	Medical file, last 24 months, mediation	Yes = 1 No = 0	
25	GERD	Medical file, last 24 months	Yes = 1 No = 0	
26	Obstipation	Medical file, last 24 months, medication	Yes = 1 No = 0	
27	Risk for Diabetes Mellitus (DM) or known DM	Medical file, blood glucose levels, medication	DM according to medical file or taking drugs for DM and/or serum glucose ≥7 mmol/l = 1 No DM according to medial file, no DM drugs and blood glucose 6.1-6.9 = 0.5 No DM according to medial file, no DM drugs and blood glucose < 6.1 = 0	[64]
28	Scoliosis	Medical file	Yes = 1 No = 0	
29	Visual /Hearing impairments (V/H impairment)	Medical file	At least one severe V/H impairment = 1 Two moderate V/H impairment = 1 One moderate V/H impairment = 0.5 No V/H impairment = 0	
30	Medication use (polypharmacy)	Medical file	≥ 7 drugs = 1 4-6 drugs = 0.5 0-3 drugs = 0	[65, 66]
31	Over or under weight	Medical examination	BMI < 18.5 OR > 30 = 1 BMI 18.5-20 OR 25-30 = 0.5 BMI 20-25 = 0	[67, 68]
32	High blood pressure	Medical file	Yes = 1 No = 0	

Table 2. Overview of deficits included in the frailty index (Continued)

#	Deficit	Additional information	Cut-off values and FI scores	Ref
33	Peripheral atherosclerosis	Medical examination	Ankle Arm index > 0.9 = 0 0.8-0.9 = 0.5 < 0.8 = 1	[69, 70]
34	Osteoporosis (t-score)	Medical examination	< 2.5 = 1 -1 till -2.5 = 0.5 > -1 = 0	[71]
35	Manual Dexterity (BBT)	Fitness assessment The participants were asked to move as many coloured blocks as possible in one minute. The blocks were 2.5cm^3 and needed to be moved from one side of a wooden box to the other side.	lowest quartile = 1 second quartile = 0.66 third quartile = 0.33 Highest quartile = 0	
36	Walking speed	Fitness assessment Comfortable walking speed was measured by the average of three records of the time needed to complete 5 meters after 3 meters for acceleration.	Slow walking speed was Stratified for height and gender. Male height ≤173cm ≥7 sec = 1 Male height > 173cm ≥6 sec = 1 Females height ≤ 159cm ≥7 sec = 1 Females > 159 cm ≥6 sec = 1 Faster = 0 Participant who were not able to succeed the walking speed assessment due to physical limitations were scored positive (score 1) as well.	[11]
37	Grip strength	Fitness assessment Measured with a Jamar Hand Dynamometer (#5030J1, Sammons Preston Rolyan, USA)	Grip strength was stratified for gender and BMI. *Male* BMI ≤ 24: ≥29kg = 0 BMI 24.1–26: ≥30 kg = 0 BMI 26.1–28: ≥30 kg = 0 BMI > 28: ≥32 kg = 0 *Female* BMI ≤ 23: ≥17 kg = 0 BMI 23.1–26: ≥17.3 kg = 0 BMI 26.1–29: ≥18 kg = 0 BMI > 29: ≥21 kg = 0 Below cut-off values = 1 Participant who were not able to succeed the grip strength assessment due to physical limitations were scored positive (score 1) as well.	[11]
38	Hypercholesterolemia	Medical dossier	Yes = 1 No = 0	
39	HDL	Blood examination	HDL was stratified for gender *Male* 0-0.9 mmol/l = 1 0.9-1.55 mmol/L = 0.5 > 1.55 mmol/L = 0 *Female* 0-1.1 mmol/l = 1 1.1-1.55 mmol/L = 0.5 > 1.55 mmol/L = 0	

Table 2. Overview of deficits included in the frailty index (Continued)

#	Deficit	Additional information	Cut-off values and FI scores	Ref
40	Haemoglobin	Blood examination	Stratified for gender *Male* 8.6-10.5 mmol/L = 0 < 8.6 OR > 10.5 mmol/L = 1 *Female* 7.5-9.5 mmol/L = 0 < 7.5 OR > 9.5 mmol/L = 1	[64]
41	Dysphagia	Diagnosis via DDS questionnaire	Severe dysphagia = 1 Moderate dysphagia = 0.5 No Dysphagia = 0	[72]
42	Hospitalization	Asked in informed consent form. Hospitalization is the past 12 months	> 2 = 1 1-2 = 0.5 No = 0	
43	Makes a sad/ depressing impression	SDZ, completed by professional caregivers Last three months	Often = 1 Several times = 0.66 Sometimes = 0.33 Never/very rare = 0	[73]
44	Has fun and interest in daily activities	SDZ, completed by professional caregivers Last three months	Never/very rare = 1 Sometimes = 0.66 Several times = 0.33 Often = 0	[73]
45	Sleeps more than regularly (trouble getting out of bed, falls asleep during the day)	SDZ, completed by professional caregivers Last three months	Often = 1 Several times = 0.66 Sometimes = 0.33 Never/very rare = 0	[73]
46	Fast fatigue easily fatigued/listless	SDZ, completed by professional caregivers Last three months	Often = 1 Several times = 0.66 Sometimes = 0.33 Never/very rare = 0	[73]
47	Is slow or passive in his/her movements	SDZ, completed by professional caregivers Last three months	Never/very rare = 0 Sometimes = 0.33 Several times = 0.66 Often = 1	[73]
48	Knows which year it is	The Dementia Questionnaire for Mentally Retarded Persons (DMR)	Normally No = 1 Sometimes = 0.5 Normally Yes = 0	[74]
49	Knows the way to familiar places	The Dementia Questionnaire for Mentally Retarded Persons (DMR)	Normally No = 1 Sometimes = 0.5 Normally Yes = 0	[74]
50	Is seeing group mates	The Dementia Questionnaire for Mentally Retarded Persons (DMR)	Normally No = 1 Sometimes = 0.5 Normally Yes = 0	[74]
51	Knows that today is a weekend or a week day	The Dementia Questionnaire for Mentally Retarded Persons (DMR)	Normally No = 1 Sometimes = 0.5 Normally Yes = 0	[74]

($M_{excluded}$ = 60.19, $SD_{excluded}$ = 6.78 $M_{included}$ = 61.64, $SD_{included}$ = 8.09), $t(1047) = 1.43$, $p = .098$ (two-tailed) and the presence of Down syndrome $X^2(1, N = 920) = 0.034$, $p = .853$.

Properties of the frailty index and differences in subgroups

The mean score of the frailty index was 0.27 with a standard deviation of 0.13 (Table 3). The range of frailty index scores was between 0.02 and 0.69. The distribution of the frailty index was slightly skewed (skewness value = 0.53, *SD* = 0.08) to the right (Figure 2). The average frailty index score showed a .005 (.018 taking the natural log of the frailty index) per year increase with age $r = .297$, $t\ (980) = 9.74$, $p < .001$ (Figure 3). There was no significant slope of the 99th percentile slope, showing the same maximum frailty index score among all age groups. When a frailty index based on a random selection of 75% of the used deficits is plotted against age 50 times, the intercept changes, while the slopes of the regression lines are virtually the same (Figure 4). Table 3 shows that there were no significant differences in frailty index scores by gender (M_{male} = 0.27, SD_{male} = 0.13 M_{female} = 0.28, SD_{female} = 0.13), $t(980) = 1.41$, $p = .159$ (two-tailed). However, if the difference between genders is adjusted for severity of ID, women show significantly higher frailty index scores compared to men $\beta = .088$, $t(878) = 2.91$, $p = .004$. Frailty increased significantly with more severe ID $\beta = .440$, $t(879) = 14.54$, $p < .001$. Participants with Down syndrome show significantly higher frailty scores compared to those with ID by other

Table 3. Participant characteristics and associations with the frailty index

Characteristic	*n*	Mean FI	*SD*	*p*-value
Total	982	0.27	0.13	-
Gender				.159[a]
Male	507	0.27	0.13	
Female	475	0.28	0.13	
Level of ID				< .001[b]
Borderline	29	0.19	0.11	
Mild	191	0.21	0.12	
Moderate	432	0.26	0.12	
Severe	147	0.33	0.12	
Profound	82	0.41	0.10	
Age categories				< .001[b]
50-59 years	458	0.25	0.12	
60-69 years	344	0.28	0.12	
70-79 years	156	0.34	0.12	
80-89 years	21	0.41	0.14	
90 years and above	3	0.42	0.03	
Down syndrome				.007[a]
No	732	0.27	0.13	
Yes	142	0.31	0.13	

[a]Differences between groups calculated with independent sample *t*-test
[b]Differences between groups calculated with univariate linear regression analysis
Note, FI = frailty index

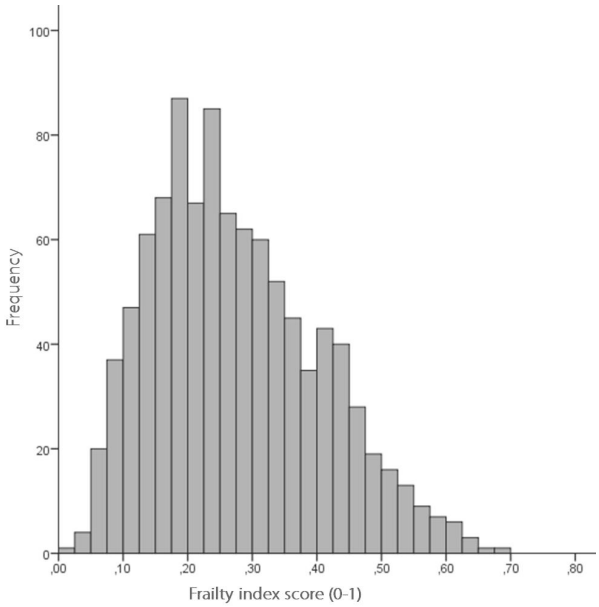


Figure 2. Frailty index distribution: Observed distribution of the Frailty index for older persons with intellectual disabilities.

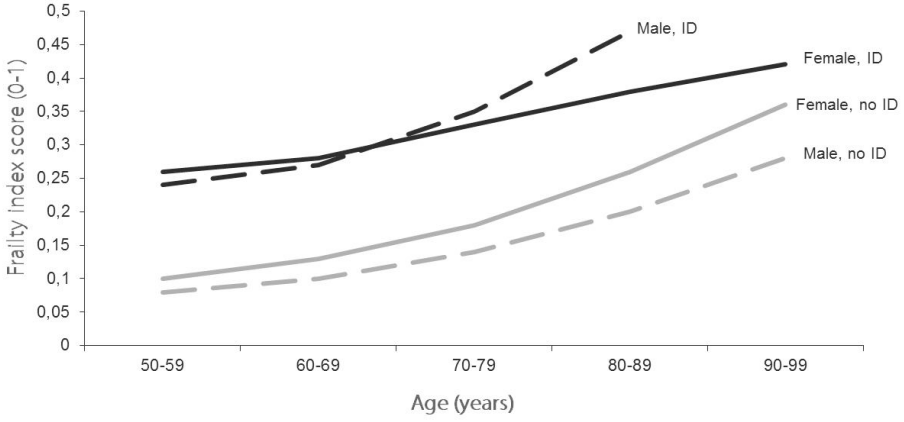


Figure 3. Frailty index and age. Upper lines represent the average frailty index per age category and the corresponding trend line with a slope of .005 for older people with ID. The lower lines represent the average frailty index per age category and the corresponding trend line from a large 50+ general European population [31].

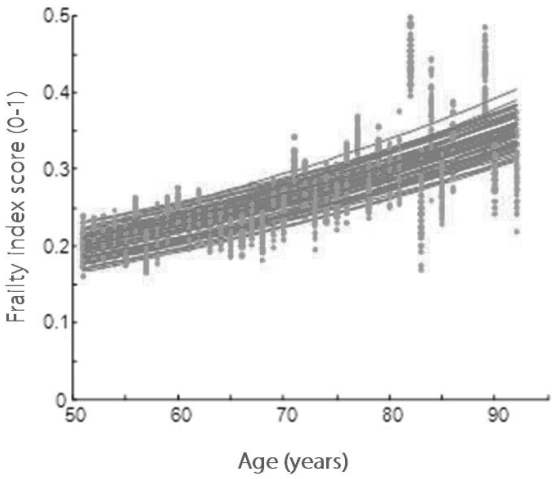


Figure 4. Robustness of the frailty index in respect to the composition of variables. 50 times 75% of the deficits were randomly selected to create and plot a frailty index against age. Each line represents the best fit regression line of the average frailty index score. While the intercept changes, the slopes of the regression lines are virtually the same.

causes ($M_{no\ \text{Down syndrome}} = 0.27$, $SD_{no\ \text{Down syndrome}} = 0.13$ $M_{\text{Down syndrome}} = 0.31$, $SD_{\text{Down syndrome}} = 0.13$), $t(872) = 2.72$, $p = .007$ (two-tailed). At each age increment older people with ID showed higher mean frailty index scores than the general population (Figure 3).

DISCUSSION

For the first time, a frailty index was successfully constructed for older people with intellectual disabilities receiving formal care. We showed that it is possible to construct a frailty index for this specific population and provided a list of all included deficits, their diagnostic method, and applied cut-off values. The frailty index calculated for this study includes social, physical, and psychological aspects of health. For 982 people with intellectual disabilities aged 50 years and over, a frailty index score was calculated based on 51 deficits. The mean score was 0.27. Per year increase in age, the frailty index increased on average with .005 points (or .018 taking the natural log of the frailty index). The upper limit of the frailty index was 0.69 and this limit was consistent over all age categories. As was to be expected, more severe levels of ID were clearly associated with higher frailty index scores ($p < .001$). Comparing our results to previous studies among non-disabled populations, it appears that the mean frailty index score is higher and that frailty in our population, on average, starts at a much younger age compared to the general public (Figure 3).

The large number of the included deficits, the objective measurement of most deficits, and the critical selection of the deficits provide a robust measure of frailty. Other strong points of this study are the large and near-representative study population, providing results applicable to all Dutch older people (50+) with ID receiving specialized care. Note, however, that older people with borderline or mild intellectual disabilities, not using formal ID care, were not included in the study. Nevertheless, our data must be interpreted with caution. Although the population was near-representative, older people with ID living independently or with relatives using formal care were slightly underrepresented in the HA-ID study. Because of the high correlation between the frailty index score and more severe ID this underrepresentation might have caused a slightly higher mean frailty index. The applicability of a number of cut-off values across a sample that covers many ages is problematic (e.g. osteoporosis and grip strength). In addition, most cut-off points have not been validated for this specific population.

Weighting of deficits can improve the area under the curve of a receiver operating characteristic curve analysis [48], which is often interpreted as improving the predictive ability of the index. Weighting is commonly done in index variables in other epidemiological studies because some items might have more influence on the frailty status of an individual than other items. However, here we did not weight the deficits, because the arguments against weighting appear to be stronger, which is likely why none of the published frailty indices weighted their variables. First, although weighting improves prediction, this is only narrowly construed, "retrospective prediction" – i.e. it improves the fit in an existing database, but limits generalizability to other databases. Second, most importantly, statistical techniques to weight variables rely on the assumption of independence between the items, which typically does not hold in complex biological systems in which the components interact. Indeed, it is this reason – the redundancy of information of items – which means that the items in a frailty index are "auto-weighted". In other words, items that are more important to frailty status in a given individual will be seen in the presence of other deficits. For example, consider two individuals each of whom reports a skin condition. Many skin conditions are benign – an individual with such a skin condition would show little impact on frailty status. In a 51 item frailty index, for example, such a skin condition would contribute only one deficit (a score of about 0.02). But if in the second individual the skin condition would reflect a disabling disorder (an autoimmune disease, for example) it would be associated with disability items, with feelings of fatigue, with slowing and with other immune disorders – easily contributing 10 other deficits, or an increase in score by about 0.2. In this way, indirectly, serious conditions put more weight on the frailty score; in this sense, it is "auto-weighted". Last, this approach also allows the cumulative impact of small items, which might individually

not be associated with an adverse outcome to be considered jointly, which sometimes will demonstrate a strong effect [49].

Little research has been conducted on frailty in people with ID. Brehmer and Weber were the first to investigate frailty in people with ID, showing that, according to their frailty questionnaire, over a quarter of adults aged 50 years and over with ID was frail [50]. However the small sample size (n = 50) and different format make it impossible to compare the results with studies conducted in the general population and with our study. According to the phenotypic approach, frailty was more often seen in older people with ID than in the general population [16]. However as mentioned before, frailty measured according to the phenotypic approach might be influenced by longstanding motor disability, often seen in this population. Therefore we measured frailty from a multidimensional perspective, according to a standardized method and with a large study population, which means that our results could be compared to the general population.

Frailty indices constructed and calculated for non-disabled older populations usually show a mean score between 0.08 and 0.17 with a skewed gamma distribution, a deficit accumulation rate of .03 (log scale) per year, and a maximum score around 0.70 [12, 39, 51]. Recently, a European frailty index study was published showing properties consistent with earlier results [31]. In this study among 29,905 non-institutionalized older people aged 50 years and above, a frailty index was established of 40 items, mostly overlapping with deficits used by us [31]. From these results we can conclude that older people with ID have much more deficits compared to the general non-disabled (50+) population, but accumulate fewer deficits per increased year of age (β = .297). Furthermore, studies conducted among older populations (65 or 70 years and over) showed a frailty index score distribution similar to ours, indicating that older people with ID accumulate as many deficits as seen in the general population 20 years later. This raises the question what the frailty levels are in younger age groups. Lifelong comorbidity in many persons with ID might cause an early onset of frailty. In the general population (15-79 years old), there are already some deficits present in the earliest age categories, exponentially increasing with age [52]. This indicates an ongoing decline of health, starting at relatively young age, eventually leading to frailty. It could be that in older people with ID, lifelong cognitive, sensory, motor disabilities and chronic comorbidity cause a very early onset of deficit accumulation, leading to early frailty. However, our frailty index should be validated against decreasing health and independence before further conclusions can be drawn.

The distribution of the frailty index in our study is similar to frailty indices in other populations with impairments. Mitnitski et al. showed that the frailty index in people

without ID but with cognitive impairments caused by Alzheimer, Parkinson, or other forms of dementia has a rather normal distribution and a much higher mean compared to the non-disabled population [12]. Institutionalized elderly people without ID also show higher means compared to community-dwelling people without ID. However, as opposed to the population with ID, the correlation between the frailty index and age is close to 0 among these impaired groups [24, 27]. In fact, the distribution and mean frailty score in older people with ID are comparable to frailty indices seen in the general population in those with a mild form of dementia, with much lower mean scores than in those with severe dementia, but clearly higher than in people without cognitive impairments [12]. It has been shown that frail elderly people have an increased risk of subsequent cognitive decline [38, 53] whereas conversely, low cognition might lead to frailty [54]. Such relationships can be explained by low cognition resulting from beginning dementia. Although as opposed to dementia, intellectual disability is usually not a progressive condition, we found an association between frailty and more severe ID. This might be explained by measurement conditions: items from the (instrumental) activities of daily living ((I)ADL) questionnaire and the DMR are related to cognition [55, 56]. Older people with more severe levels of ID are therefore more likely to have high frailty scores compared to those with borderline or mild levels of ID.

Most frailty indices show that on average women have more deficits than men. However, women seem to tolerate the deficits better, as evidenced in a lower correlation with mortality [34]. If adjusted for level of ID, we also found a significant higher mean frailty index score for woman compared to men. A remarkable result of our study was the lack of the so-called 'zero state', i.e., participants with no deficits. Previous studies show that roughly 3% (70 years and above) [44] and 9% (50 years and above) [31] of the older people without disabilities have no deficits. Although the population in this study was on average younger, none of the participants scored "0" deficits. This, again, can partly be explained by (I)ADL and DMR items in the frailty index, which are influenced by cognition. However, other problems such as chronic comorbidity, low physical activity and nutritional deficiencies might also cause the lack of a zero state.

More research is necessary to investigate which deficits mostly contribute to the frailty status of older people with ID. The cross-sectional nature of the data makes it impossible to examine the predictive value of the used frailty index, with regard to deteriorating health, independence, and mortality. Longitudinal research is necessary to validate the frailty index. Since no gold standard is available, predictive validation should be used to investigate whether our frailty index is able to predict adverse health outcomes such as falls, hospital admission, decrease of (I)ADL, the onset of diseases and mortality. Although the complete frailty index would be too time consuming, burdensome and expensive to

use for clinicians and caregivers in routine practise, there are several applications of the frailty index in clinical settings. For example, a shorter version of the frailty index can be used as a screening tool to identify individuals at risk [57]. Furthermore, in research settings the frailty index can be used as a tool to evaluate the effect of interventions [58].

This study shows that older people with ID aged 50 years and over already accumulate as much deficits as older people without ID aged 70 and above. In the field of ID care, persons with ID are already classified as "old" at the age of 50. It could be possible that this phenomenon of "early aging" is partly explained by the early onset of frailty. If older people with ID are indeed frail at an earlier age and "biologically old", in spite of an increased life expectancy, one can question the quality of life in the later years. In order to prevent early aging and loss of quality of life it is essential to study possible explanations for the high mean frailty index score and early onset of frailty.

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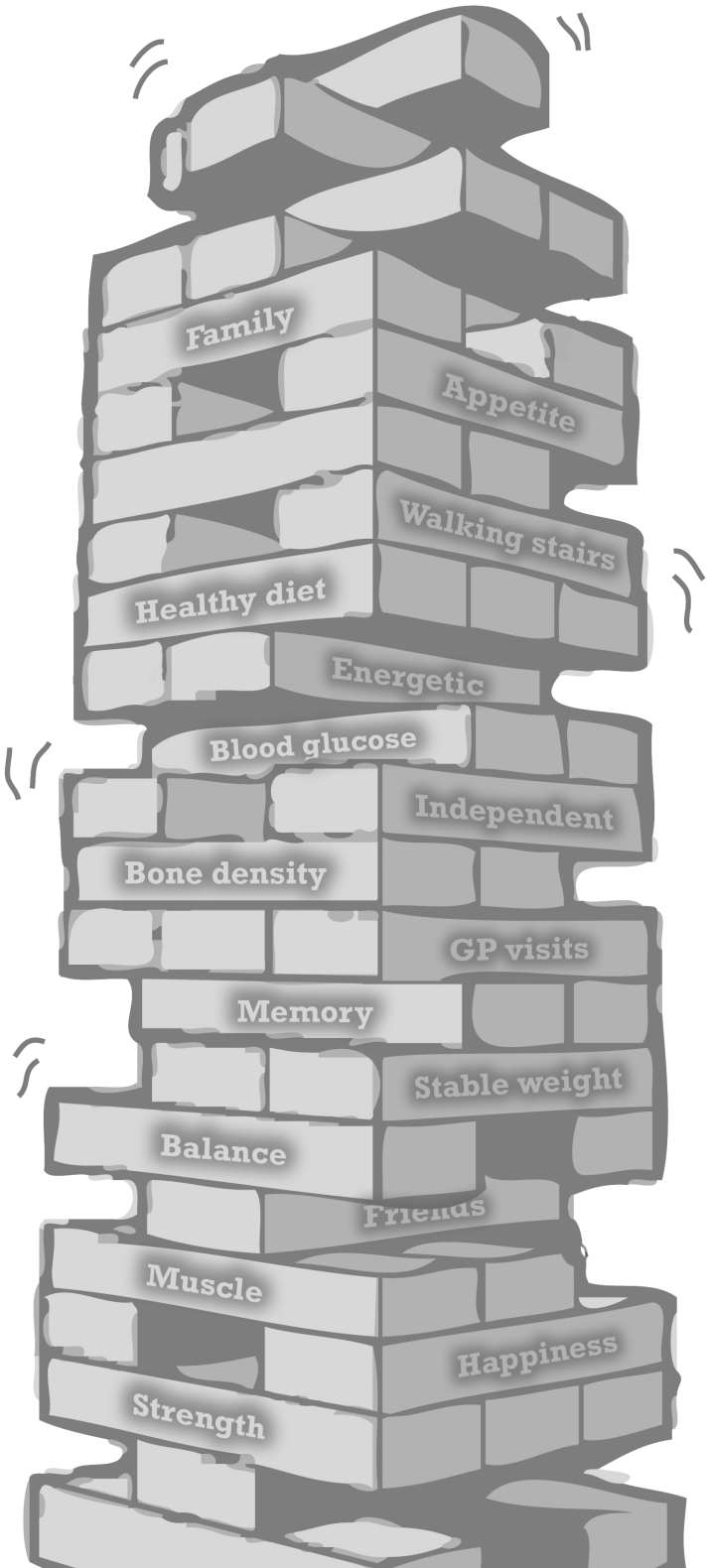
Family
Appetite
Walking stairs
Healthy diet
Energetic
Blood glucose
Independent
Bone density
GP visits
Memory
Stable weight
Balance
Friends
Muscle
Happiness
Strength

Chapter 4

Characteristics of the least frail adults with intellectual disabilities: a positive biology perspective

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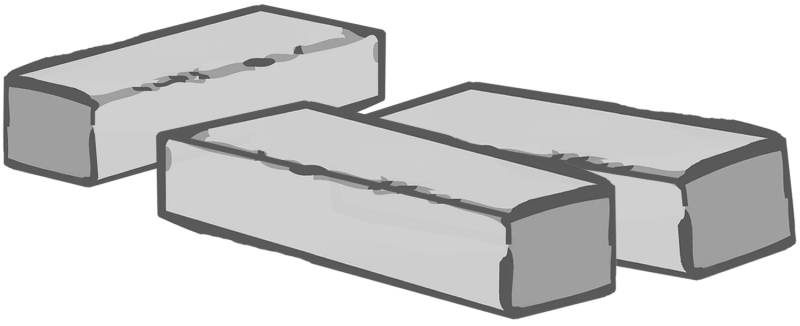

ABSTRACT

The current study focuses on the characteristics of older people with intellectual disabilities with the lowest frailty levels. Frailty is an increased risk of adverse health outcomes and dependency. Older adults with intellectual disabilities (ID) show more signs of early frailty than the general population. Knowledge of the least frail group characteristics may provide insight into possibilities to prevent early frailty in older people with intellectual disabilities. This study was part of the Healthy Aging and Intellectual Disability study (HA-ID) which incorporated 1050 adults aged 50 years and over with all levels of ID. Frailty was measured with a frailty index. The least frail group was selected based on a frailty index score ≤ 0.10. Odds ratios were used to compare the occurrence of health deficits in the least frail group to the remaining group. The least frail group consisted of 65 participants, corresponding with 6.6% of the study population. The least frail group was significantly younger, had less severe levels of ID, and less often Down syndrome than the remaining group. The lack of mobility and physical fitness limitations, dependence, no signs of depression/dementia, and little medical problems characterized the least frail group. The percentage of 50+ adults with intellectual disabilities within the least frail group is very low compared to that in the general aging population (> 43%). Interventions to prevent or delay frailty in this population are highly recommended and can focus on health characteristics of the least frail group.

Key words: Frailty index, Healthy aging, Intellectual disabilities, Older adults

INTRODUCTION

Most of today's medical research is concentrated on the question: "What causes pathology?" Focusing on the understanding of disease causes and the invention of new therapies is considered the so-called 'negative biology'. Controversially, 'positive biology' aims at understanding why some people age without the diseases and problems that many others suffer from. This perspective receives far less attention, although it could offer more insight in successful aging and generate a greater health benefit for the older adults than would eliminating one specific disease [1]. A useful method for understanding the process of aging and healthy aging is frailty. Frailty is a state of increased risk of adverse health outcomes, which reflects multisystem physiological changes and is highly associated with age [2]. A recent study showed that very high levels of frailty (deficit accumulation) were present in older people with intellectual disabilities (ID) [3]. The current paper adopts a positive biology perspective by analysing the characteristics of older people with ID with the lowest frailty levels. There are several methods for measuring frailty. One widely used approach is the frailty index [4].The frailty index is based on a non-specific accumulation of deficits in several health domains. Deficits are defined as diseases, symptoms, disabilities, laboratory results or health related questionnaires and must cover a range of systems. A frailty index score is calculated by dividing the sum of deficits present by the total number of deficits measured, resulting in a score between 0 and 1 [5]. The frailty index score is highly associated with the risk of deterioration of health, dependence, and hospital admission, and frail people have decreased life expectancies [6].

Recently, we developed a frailty index for older adults with ID based on data collected in the Healthy Ageing and Intellectual Disability study (HA-ID), a cross-sectional study performed in 1050 participants aged 50 years and over in The Netherlands [3, 7]. In addition to general aging problems adults with ID have an increased risk of motor and sensory disabilities, chronic diseases (e.g. epilepsy), and mental health problems [8-10]. These factors could lead to increased frailty across the lifespan, and in this way to early frailty in older adults with ID. Although the frailty index developed for older adults with ID has not yet shown to be related to negative health outcomes, preliminary data show that average frailty levels are high, and that frailty levels in older adults with ID aged 50 are comparable to frailty levels of older people without ID aged 70 and above. Furthermore it was shown that more severe ID and higher age were associated with an increased frailty score. Frailty in this population is of growing interest, since life expectancy of adults with ID is approaching the general public's life expectancy [11, 12]. The increased life expectancy and the high number of frail people make interventions to prevent or delay frailty urgently required.

In the perspective of positive biology, it would be interesting to know why some adults maintain very low frailty levels at high ages and remain in the so called zero-state -having no measured deficits- for a long time. Previous studies show that roughly 3% (70 years and above) [5] and 9% (50 years and above) [13] of the general population can be classified in the zero state. Across the lifespan, these "fit" adults are far less likely to die within 12 years and stay relatively fit over time [14]. Positive biology would promote the use of health information of these fit older people for the prevention of future frailty [1]. Among participants of the HA-ID study no one was classified in the zero state [3]. However, there are older adults with ID who are relatively fit compared to others in the population. Therefore, in this study we investigated characteristics of the adults scoring lowest on the frailty index. More specifically: Which deficits are found significantly less often in older adults with ID with low frailty index scores than in the remaining group?

METHOD

Design and setting

In 2008, three Dutch care organizations and two academic departments (Intellectual Disability Medicine, Erasmus MC Rotterdam; Center for Human Movement Sciences, UMCG Groningen) started a large cross-sectional study titled 'Healthy Ageing and Intellectual Disability' (HA-ID), to establish the general health status in older adults (50 years and over) with ID in the Netherlands. Three themes were chosen: physical activity and fitness, nutrition and nutritional state, and mood and anxiety. Within these themes a broad diagnostic assessment was conducted including physical fitness tests which were performed by physiotherapists, physical activity instructors or occupational therapists who were trained during a two-day course and all experienced in working with people with ID, and questionnaires, which were completed by the professional care givers or if applicable by self-report. IQ scores, Vineland scores and social emotional development was used to determine the level of ID by psychologists or test assistants. Data were collected between February 2009 and July 2010. Detailed information has been published elsewhere [7]. The Medical Ethics Committee of the Erasmus Medical Center Rotterdam (MEC- 2008-234) and the ethics committees of the participating care organizations approved this study.

Participants

The participating care organisations are located in the middle, southern and western part of the Netherlands. The three care organizations together had 2322 clients with borderline to profound ID aged 50 years and over, who were all invited to participate. The total number of people that actually participated was 1050. The study population

is nearly representative for the Dutch population using formal care for adults with ID aged 50 and above, with a slight underrepresentation of men ($X^2(1, N = 2322) = 0.53$, $p = .03$), people aged 80 and above ($X^2(8, N = 2322) = 27.41$, $p = .001$), and people living independently ($X^2(3, N = 2237) = 50.55$, $p < .001$) [7].

Frailty index

A frailty index was created according to the procedure described by Searle et al. [5]. The deficits were defined as symptoms, laboratory results, health status, disabilities, and diseases. Deficits were included in the frailty index if they met all the following criteria: (1) the deficit is associated with health status, (2) the deficits' prevalence increases with age, (3) the deficit must not saturate too early, (4) the frailty index must cover a range of domains. Four additional criteria were applied: (1) a maximum of 30% of the cases is missing, (2) if items are designed to measure the same concept, the item that best fits the other criteria is chosen, (3) single items of a questionnaire can be used as deficits as long as they fulfil all criteria and do not correlate too strongly ($r > 0.7$) with each other, (4) the deficit should be present in > 5% of the participants. In total, 51 variables fulfilled all criteria and were used to construct a frailty index. All variables were recoded into values between 0 (deficit not present) and 1 (deficit completely present). Cut-off values were derived from the literature or the laboratory guide from Erasmus Medical Center Rotterdam (2009). An overview of deficits included in the frailty index together with their cut-off values is described in elsewhere [3]. Missing values remained unscored. No weighting of variables was applied, so each deficit contributed equally to the frailty index score. The frailty index score was calculated by the sum of all deficit-scores divided by the total amount of deficits. Previous studies showed that at least 30 deficits are necessary to reliably predict adverse health outcomes [15]. Therefore all participants with less than 30 deficits assessed were excluded from further analyses. The excluded participants ($n = 68$) were not significantly different from the included participants ($n = 982$) regarding to gender ($X^2(1, N = 1050) = 0.532$, $p = .47$), level of ID ($X^2(4, N = 923) = 3.92$, $p = .42$), age ($M_{excluded} = 60.19$, $SD_{excluded} = 6.78$, $M_{included} = 61.64$, $SD_{included} = 8.09$), ($t(1047) = 1.43$, $p = .10$) and the presence of Down syndrome ($X^2(1, N = 920) = 0.034$, $p = .85$ [3].

Definition of the least frail group

Investigating the characteristics of zero-state participants was not possible, because none of the participants had a frailty index score of zero. Rockwood et al. designed subgroups for different frailty scores: the relatively fit (frailty index score ≤0.03), less fit (0.03 < frailty index score ≤ 0.10), least fit (0.10 < frailty index score ≤ 0.21), and frail (frailty index score > 0.21) [14]. The fittest group of our study was selected by combining the "relatively fit" and "less fit" groups. Consequently all older adults with a frailty index

score of 0.10 or below were selected and will be further referred to as "the least frail". The least frail group was compared to the participants with a frailty index score above 0.10, referred to as the remaining group.

Statistical procedure

All statistical analyses were performed using SPSS statistics 20.0 for Windows (SPSS, Inc, Chicago, IL, USA). Independent samples *t*-tests and Pearson Chi-Square tests were used to calculate the differences of the basic characteristics (age, gender, level of ID, and Down syndrome) between the least frail group and the remaining participants.

In order to make all outcomes comparable, all deficits were dichotomised as follows, 0 if the deficit was absent and 1 if the deficit was partly or completely present. Percentages of the presence of the deficits were calculated for the least frail group and the remaining participants. Pearson Chi-Square tests were used to assess differences in frequencies between the groups. Univariate logistic regression analysis was used to calculate the chance that the absence of a deficit predicts classification to the least frail group. Multivariate logistic regression models were used to determine the magnitude of the independent contributions (in terms of odds ratios) of deficits for classification into the least frail group. Significant differences at baseline characteristics ($p < .05$) between the two groups and characteristics known from literature were included in the multivariate model. Per definition, each deficit and the index are correlated, because 1/51 of the dependent variable corresponds with the independent variable. To eliminate this correlation the index was recomposed without the item of interest for each deficit. All tests were two-sided and a *p*-value of less than .05 was considered to be statistically significant. For the calculated Pearson Chi-Square tests and *OR*s Bonferroni correction was applied and a p-value $< .05/51 = .001$ was considered to be significant. *OR*s for deficits that significantly influenced the outcome (belonging to the least frail group) or deficits that were completely absent in the least frail group were combined to clusters. These clusters were made by grouping deficits from the same overall domains together.

RESULTS

Basic characteristics

The distribution of frailty index scores, with a mean frailty index score of 0.27 ($SD = 0.13$) was slightly skewed with a longer right tail (skewness = .53, $SE = 0.08$; Figure 1). Sixty-five participants had a frailty index score ≤ 0.10 and were classified as the least frail group, corresponding with 6.6% of the study population, so 918 participants were classified as the remaining group. The average frailty index score of the least frail group was 0.08 versus 0.29 in the remaining group. Significant differences were found for age, level

of ID, and Down syndrome (Table 1). Although the least frail group was significantly younger than the remaining participants, older participants were included as well, 15.4% was 65 years or over (Figure 2). No significant difference for gender was found. However, because previous results showed a significant influence of gender on frailty when adjusted for level of ID, gender was included in the multivariate model as well [3].

Table 1. Basic characteristics of the least frail group compared to the remaining participants

	Least frail FI ≤ 10	Remaining group FI > 0.10	*p*-value
N (%)	65 (6.6%)	917 (93.4%)	
Mean FI score (*sd*)	0.08 (0.02)	0.29 (0.12)	< .001[a]
Age in years	58 (5.4)	62 (8.2)	< .001[a]
Gender: *n* female (%)	25 (38%)	450 (49%)	.098[b]
Level of ID *n* (%)			< .001[b]
borderline	6 (11%)	23 (2.8%)	
mild	31 (54%)	160 (19%)	
moderate	20 (35%)	412 (50%)	
severe	0 (0.0%)	147 (18%)	
profound	0 (0.0%)	82 (10%)	
Down syndrome *n* (%)	3 (5.6%)	139 (17%)	.028[b]

[a] Differences between groups calculated with independent sample *t*-test
[b] Differences between groups calculated with Pearson Chi-Square test
Note, FI = frailty index

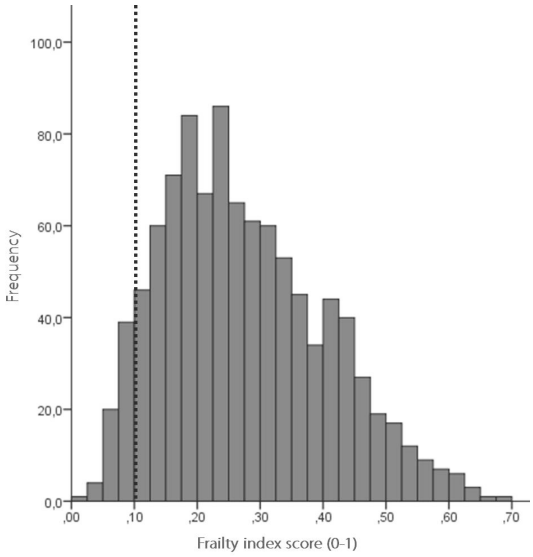

Figure 1. Distribution of frailty index scores (*n* = 982). The dotted line marks the cut-off value (frailty index score ≤ 0.10) for the least frail group, corresponding with 6.6% of the study population.

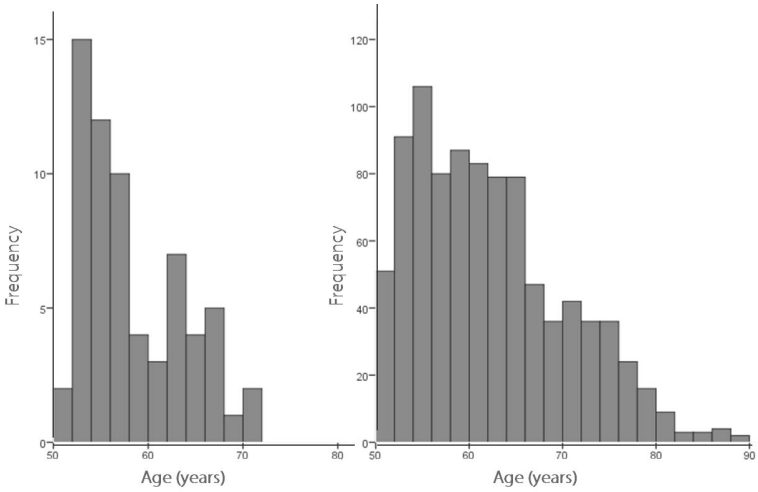

Figure 2. Distribution of age for the least frail (frailty index score ≤0.10; left figure) and the remaining group (frailty index score > 0.10; right figure).

Prevalence of the deficits

A significant difference in prevalence between the least frail and the remaining group was found for 39 of the 51 deficits. After Bonferroni correction (.05/51), 24 deficits remained significantly less prevalent in the least frail group (Table 2). Nine deficits were completely absent (dressing impairment, only eats food of certain textures, mobility limitations, coronary heart disease/heart failure/cardiac dysrhythmia/pacemaker, gastroesophageal reflux disease, hypercholesterolemia, sleeps more than regularly, does not know the way to familiar places, and does not know that today is a weekend or a week day). For these deficits no *OR* could be calculated. The unadjusted *OR*s ranged between 65.8 (walking stairs) and 0.85 (fluid intake per day). The *OR*s, adjusted for age, gender, level of ID, and Down syndrome, ranged between 21.9 (walking stairs) and 0.68 (fluid intake; Table 2). Deficits with significant or no calculated *OR* could be clustered in five groups: mobility and physical fitness, independence, signs of depression/dementia, medical, and other (Figure 3).

DISCUSSION

This study identified the characteristics of the least frail older adults with ID, based on a frailty index. There were no participants with a frailty index score of zero. Sixty-five participants had a frailty index score of 0.10 or lower and were classified as the least frail group, corresponding with only 6.6% of the study population. As was to be expected, the least frail participants were younger, had less severe ID, and less often Down syn-

Table 2. Deficits included in the frailty index. Differences in the occurrence of deficits in the least frail group (frailty index score ≤ 0.10) and the remaining group (> 0.10) in percentages. Odds Ratios show the odds to be classified as "least frail" if a deficit is present in an individual. The magnitude of the independent contribution of the deficit on classification towards the remaining group is provided in adjusted Odds Ratio's.

#	Deficit	*N total*	Least frail (F I ≤10) % (*n*)	Remaining group (FI > 0.10) % (*n*)	*p-value*	Odds ratio (*CI*)	*n* (adj *OR*)	Adjusted odds (*CI*)
1.	Bladder control	982	14.1% (9)	49.6% (455)	< .001**	6.01** (2.93-12.3)	790	2.56* (1.08-6.08)
2.	Dressing	982	0.0% (0)	47.9% (440)	< .001**	∞ -	790	∞
3.	Walking stairs	982	1.6% (1)	51.5% (473)	< .001**	65.8** (9.08-476)	790	21.9* (2.95-163)
4.	Bathing	982	11.6% (8)	68.2% (623)	< .001**	16.4** (7.74-34.7)	790	8.39** (3.37-20.9)
5.	Transfer bed to chair	982	3.2% (2)	27.1% (249)	< .001**	11.3** (2.75-46.7)	790	8.77* (1.17-65.6)
6.	Groceries	982	25.0% (18)	75.8% (690)	< .001**	9.41** (5.40-16.4)	790	4.60** (2.21-9.55)
7.	Housekeeping	982	59.3% (48)	92.6% (834)	< .001**	8.56** (5.15-14.2)	790	3.92** (2.00-7.70)
8.	No falling	972	12.5% (8)	24.3% (221)	.031*	2.25* (1.06-4.80)	783	3.31 (0.99-11.1)
9.	Present at the daycare centre	934	11.3% (7)	16.1% (140)	.320	1.50 0.67-3.37	758	1.07 (0.352-3.26)
10.	Not fatigued	967	25.0% (16)	56.3% (508)	< .001**	3.86** (2.16-6.90)	775	5.18** (2.37-11.3)
11.	Not listless	967	21.0% (13)	36.5% (330)	.014*	2.16* (1.16-4.05)	775	2.09 (0.95-4.57)
12.	No panic attacks	967	18.8% (12)	24.3% (219)	.318	1.39 (0.73-2.65)	775	1.84 (0.79-4.28)
13.	No decreased food intake, due to loss of appetite, digestive problems, chewing or swallowing difficulties	970	3.1% (2)	14.6% (132)	.010*	5.29* (1.28-21.9)	781	5.51 (0.73-41.7)
14.	No weight loss	970	27.7% (18)	29.1% (263)	.814	1.07 (0.61-1.88)	781	0.90 (0.42-1.81)
15.	Sufficient fluid intake per day	970	17.5% (11)	15.2% (138)	.633	0.85 (0.43-1.67)	781	0.68 (0.28-1.66)
16.	Calf circumference (CC) in cm	886	6.9% (4)	22.3% (185)	.006*	3.88* (1.39-10.9)	774	2.28 (0.67-7.74)
17.	Does not only eat selected types of food	977	1.6% (1)	8.9% (81)	.041*	6.13 (0.84-44.8)	787	3.08 (0.37-25.4)
18.	Does not only eat small amounts of the presented food	977	1.6% (1)	17.4% (159)	.001*	13.1* (1.80-94.9)	787	7.33 (0.98-55.1)
19.	Does not only eat foods of certain textures	977	0.0% (0)	8.4% (77)	.016*	∞	787	∞
20.	Mobility	982	0.0% (0)	28.0% (257)	< .001**	∞	790	∞
21.	No stroke	857	2.0% (1)	6.2% (50)	.234	3.24 (0.44-23.9)	773	2.10 (0.24-18.0)
22.	No coronary heart diseases (heart failure/cardiac dysrhythmia/pacemaker)	860	0.0% (0)	9.7% (79)	.022*	∞	775	∞
23.	No cancer	858	4.1% (2)	4.9% (40)	.786	1.22 (0.29-5.21)	775	1.03 (0.23-4.66)
24.	No asthma/chronic obstructive pulmonary disease	877	7.1% (4)	13.6% (112)	.165	2.05 (0.73-5.79)	790	2.69 (0.75-9.70)
25.	No gastroesophageal reflux disease	854	0.0% (0)	21.2% (171)	< .001**	∞	770	∞
26.	No chronic constipation	876	7.4% (4)	41.8% (344)	< .001**	9.00** (3.22-25.14)	789	4.13* (1.43-12.0)

Table 2. (Continued)

#	Deficit	*N total*	Least frail (FI ≤10) % (*n*)	Remaining group (FI > 0.10) % (*n*)	*p-value*	Odds ratio (*CI*)	*n* (adj *OR*)	Adjusted odds (*CI*)
27.	No risk for diabetes mellitus (DM) or known DM	884	14.0%(8)	15.2% (126)	.807	1.10 (0.51-2.38)	790	1.60 (0.58-4.39)
28.	No scoliosis	850	2.0% (1)	11.1% (89)	.045*	6.00 (0.82-44.0)	768	2.49 (0.32-19.6)
29.	No visual / hearing impairments	853	28.8% (15)	56.2% (450)	< .001**	3.16** (1.71-5.86)	769	1.58 (0.76-3.31)
30.	No polypharmacy	877	10.7% (6)	53.8% (442)	< .001**	9.72** (4.21-22.9)	790	7.74** (3.10-19.3)
31.	No over or under weight	851	71.2% (52)	68.5% (533)	.631	0.88 (0.52-1.49)	741	0.96 (0.48-1.93)
32.	No high blood pressure	851	13.5% (7)	22.1% (176)	.129	1.86 (0.83-4.19)	769	2.85 (1.05-7.74)
33.	No peripheral atherosclerosis	740	9.3% (5)	23.0% (158)	.019*	2.93* (1.15-7.49)	646	2.84 (0.94-8.59)
34.	Bone density (t-score)	738	52.5% (32)	73.1% (495)	< .001**	2.47** (1.45-4.19)	647	1.65 (0.87-3.13)
35.	Manual dexterity (Box & Block Test)	717	39.0% (23)	77.5% (510)	< .001**	5.39** (3.10-9.39)	605	3.25* (1.58-6.69)
36.	Walking speed	804	1.8% (1)	37.8% (283)	< .001**	33.5** (4.61-243)	683	12.0* (1.60-89.4)
37.	Grip strength	684	25.0% (16)	55.8% (336)	< .001**	3.79** (2.10-6.82)	558	2.47* (1.22-4.98)
38.	No hyper-cholesterolemia	844	0.0% (0)	10.6% (84)	.016*	∞	763	∞
39.	High-density lipoprotein (HDL)	700	86.0% (37)	83.4% (548)	.651	0.82 (0.34-1.98)	599	0.99 (0.31-3.18)
40.	Haemoglobin	705	9.1% (3)	24.6% (165)	.042*	3.25 (0.98-10.8)	608	1.26 (0.35-4.61)
41.	No dysphagia	888	62.0% (44)	79.5% (650)	.001**	2.39** (1.44-3.97)	747	1.73 (0.93-3.24)
42.	No hospitalization	828	6.0% (3)	12.0% (93)	.202	2.13 (0.65-6.97)	691	3.49 (0.71-17.2)
43.	Does not make a sad/depressed impression	785	33.3% (11)	55.3% (416)	.013*	2.48* (1.18-5.18)	638	3.37* (1.26-9.02)
44.	Has fun and interest in daily activities	785	45.5% (15)	63.8% (480)	.032*	2.12* (1.05-4.27)	638	1.79 (0.72-4.43)
45.	Does not sleep more than regularly	785	0.0% (0)	38.6% (291)	< .001**	∞	638	∞
46.	Is not fast fatigue/listless	785	27.3% (9)	56.4% (424)	.001*	3.45* (1.58-7.52)	638	2.81* (1.10-7.21)
47.	Is not slow or passive in movements	785	3.1% (1)	46.9% (353)	< .001**	27.4* (3.72-201)	638	15.1* (1.98-115)
48.	Knows which year it is	975	22.2 (16)	66.0% (596)	< .001**	6.80** (3.83-12.0)	783	2.08 (0.94-4.38)
49.	Knows the way to familiar places	975	0.0% (0)	21.6% (197)	< .001**	∞	783	∞
50.	Is seeing group mates	975	45.9% (34)	74.9% (675)	< .001**	3.51** (2.17-5.69)	783	2.00* (1.10-3.69)
51.	Knows that today is a weekend or a week day	975	0.0% (0)	35.5% (324)	< .001**	∞	783	∞

* *p*-value < .005, ** *p*-value < .001 (.005/51)
Note, FI = frailty index

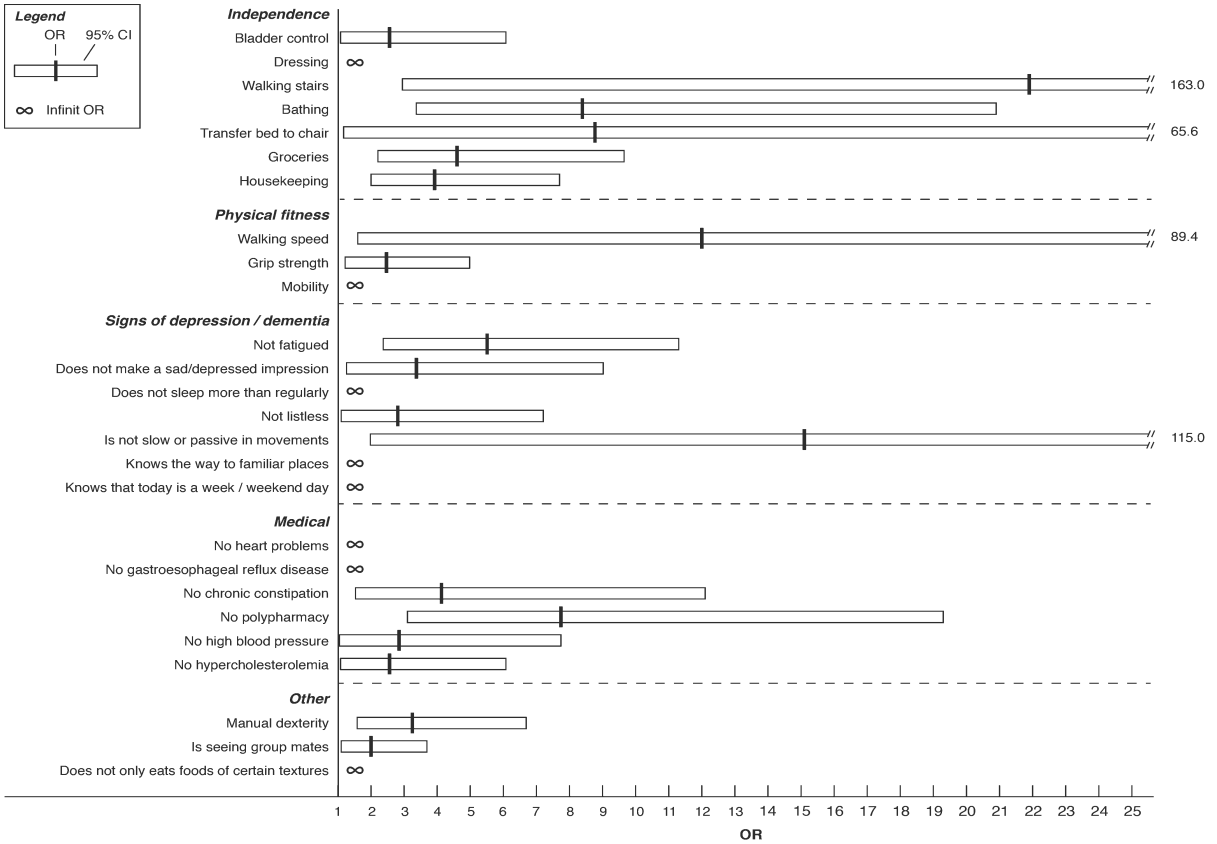

Figure 3. The independent (adjusted for age, gender, level of ID, and presence of Down syndrome) contribution to the variance of the least frail group using multivariate logistic regression analysis, resulting in odds ratios (*OR*). *OR*s are presented for deficits that significantly influence the outcome or were completely absent in the least frail group. Results are clustered in five groups: independence, mobility and physical fitness, aspects of depression/dementia, medical and other.

drome than the remaining group. This group also included participants above the age of 65 (Figure 2). Nine deficits were completely absent in the least frail group. Twenty-four deficits were less commonly found in the least frail group than in the remaining group after Bonferroni correction. After adjustments for baseline characteristics, the least frail were characterized by the absence of mobility and physical fitness limitations, relative independence, less signs of depression/dementia and less specific medical problems (heart problems, gastroesophageal reflux disease, chronic constipation, polypharmacy, high blood pressure, and hypercholesterolemia).

There are only a few published studies addressing the zero-state or least frail in the general population. A Canadian study showed that 76% of 40-69-year-old Canadians would have been classified as least frail (frailty index score ≤ 0.10), and 53% of the Canadians aged 70 years and over [14]. In a European study, the frailty index score distribution showed that around 43% of female and 60% of male participants aged 50 years and over had a frailty index score ≤ 0.10 [13]. So, the 6.6% of the ID population classified as least frail is very small compared to the general population. In the general population it has been shown that relatively fit individuals stay fit over time (follow-up period of 12 years), whereas individuals who are frail are less likely to become fit. Similarly, as age increases it becomes less likely to improve frailty scores [14]. This emphasizes the importance of early identification and prevention of frailty.

Our results show a wide range of deficits that are associated with classification in the least frail group. Variables with the most significant values were ability to bath independently, do groceries and housekeeping independently, not being fatigued, absence of polypharmacy and a normal blood pressure. Older adults who scored well on these variables were more likely to belong to the least frail group. Because of the cross-sectional design of the study, no causal inference can be made between deficits and being in the least frail group. Nevertheless, knowing which deficits are present in the least frail may be helpful for the design of interventions for the prevention of early frailty. Deficits with the highest value could be clustered into the following groups:

1. Mobility and physical fitness. In the general population, frailty is associated with low mobility, low grip strength, low balance, and low physical activity [16-19]. Likewise, the higher the frailty index, the more likely it will include mobility disability [20]. That is likely because mobility is an integrative variable, which means that many health problems will affect mobility [21]. These results from the general population show a very important correlation between frailty and physical activity and mobility. Since it has been shown that physical limitations are very common in older adults with ID [22] and predicts classification towards the least frail group, interventions aiming to increase physical activity and maintaining mobility seem very important for the prevention of frailty in older

adults with ID. However, this might not always be possible due to childhood mobility impairments (e.g. cerebral palsy).

2. Independence. In our study, items from the IADL and ADL scales [23, 24] were shown to be good predictors for classification into the least frail group. In the general population, physical frailty predicts ADL limitations [25]. In addition, the higher the level of deficit accumulation, the more likely that there will be future disability [26]. In older adults with ID it is important to know the underlying mechanism whereby decreased dependence is related to frailty before preventive measures can be started. For example it has been shown that ADL and IADL limitations are mainly caused by severe ID and mobility limitations [27]. Maintaining or improving mobility might therefore be a better intervention than improving specific ADL or IADL activities.

3. Signs of depression/dementia. Several signs of dementia and depression had very low prevalence in the least frail group. In the general population, elderly people who are frail are more likely to report signs of depression and anxiety than non-frail people [28]. Hermans, Beekman, & Evenhuis found that in older adults with ID, depressive symptoms are often unknown to the participants' behavioural therapist or psychologist [29]. They argued that pro-active detection by use of screening instruments and interventions are recommended in this population. Prospective studies should show whether such interventions contribute to the prevention of frailty in older adults with ID.

4. Medical problems. Most medical conditions, included in the frailty index, are rare or completely absent in the least frail group. This result was expected since conditions such as hypercholesterolemia, heart problems and gastroesophageal reflux disease are related to other health problems, that are also included in the index, making it very unlikely for people with serious medical conditions to have a frailty index score ≤ 0.10. Since frailty and the presence of diseases are correlated it is important to integrate proactive diagnostics to detect subjective signs. It has been shown, for example, that early detection of hearing impairment [30] and cardiovascular risk factors [31, 32] are very important in adults with ID.

In addition to possible options and ideas to delay frailty in older adults with ID the outcomes of adults with the lowest level of frailty can also be used as a mean of understanding the outcomes for the group as a whole [33]. Particularly, the outcomes of the least frail group can offer an estimate of the background or ambient risk for the whole group. The risk of a negative health outcome in a person with *N* deficits at baseline is the sum of the risk associated with *N*, plus the risks associated with the least frail group [34]. With these results the additional risk for a negative health outcome (e.g. death and hospital admission) can be calculated for a person or group.

Our study has two main strengths. First, our large and near-representative study population provided results that are applicable to all older Dutch adults (50+) with ID receiving specialized care or support. Second, frailty was measured from a multifactorial perspective with a method that is robust and widely used [5]. The frailty index has been used frequently in the general population and has proven to be a valid instrument that is highly predictive of deterioration of health, including hospital admission, falls, diseases, reduced independence, and early death [21, 35, 36]. Furthermore, most of the frailty indices developed for the general population include all eight frailty factors (nutritional status, physical activity, mobility, strength and energy, cognition and mood, lack of social contacts and social support) that Vries de et al. identified as important to the concept of frailty after careful consideration of multiple frailty concepts [37]. An additional advantage of this method for this new population is the relatively free choice of deficits, which enabled us to specify an index applicable to older adults with ID. Although our frailty index needs to be validated against negative health outcomes, we confirmed the robustness of our frailty index in the older ID population by randomly selecting 75% of the deficits to create and plot a frailty index against age. This showed that the index's relationship with age was not influenced by the deficits in the index [3]. An alternative method to measure frailty is the frailty phenotype [38]. But because this exclusively physically oriented measure may misclassify longstanding motor disability as frailty in this population, the multidimensional perspective seems more appropriate [39]. Existing frailty questionnaires using a multidimensional approach are often based on self-report but are difficult to apply in this population due to problems of limited understanding and communication [40].

Our results nevertheless need to be interpreted with caution. First of all, older adults with borderline or mild ID who did not use formal care were not included in the study. Secondly, the frailty index developed for older adults with ID has not yet demonstrated relationship with adverse health outcomes. Due to the cross-sectional nature of the study design, causal inferences cannot be made. Future research will demonstrate whether the least frail do indeed have a lower risk of negative health outcomes. Thirdly, cut-off values were used to classify the least frail group. Although the frailty index was designed to be used as a continuous scale, different groups can, if required, be created for the sake of comparing different health states [14, 41-43]. Even though little research has been conducted with different frailty groups, the cut-off values used in this study have been shown to discriminate between different health states in the general population [14]. A fourth limitation of this study is that an *OR* could not be calculated for nine deficits due to the absence of this deficit in the least frail group. Although the complete absence of these deficits characterises the least frail group, results for these variables could not be adjusted for age, gender, level of ID and the presence of Down syndrome.

Finally, the Bonferroni correction and low number of participants in the least frail group made it hard to detect significant results. This explains our addition in Figure 3, which, in addition to the Bonferroni corrected significant *p*-values, shows *OR*s with a *p*-value < .05 and variables for which no *OR* could be calculated.

In conclusion, it has been shown that frailty is a dynamic process and that individuals can change from a frail stage to a non-frail stage and vice versa [14, 44]. However, because it is difficult to recover from frailty at a high age, it is very important to focus on prevention rather than intervention. The limited percentage of older adults with ID found in the least frail group is of concern, and emphasizes the importance to prevent and monitor early frailty in this population. In line with positive biology, our results provide health information on the least frail for the prevention of future frailty in older adults with ID.

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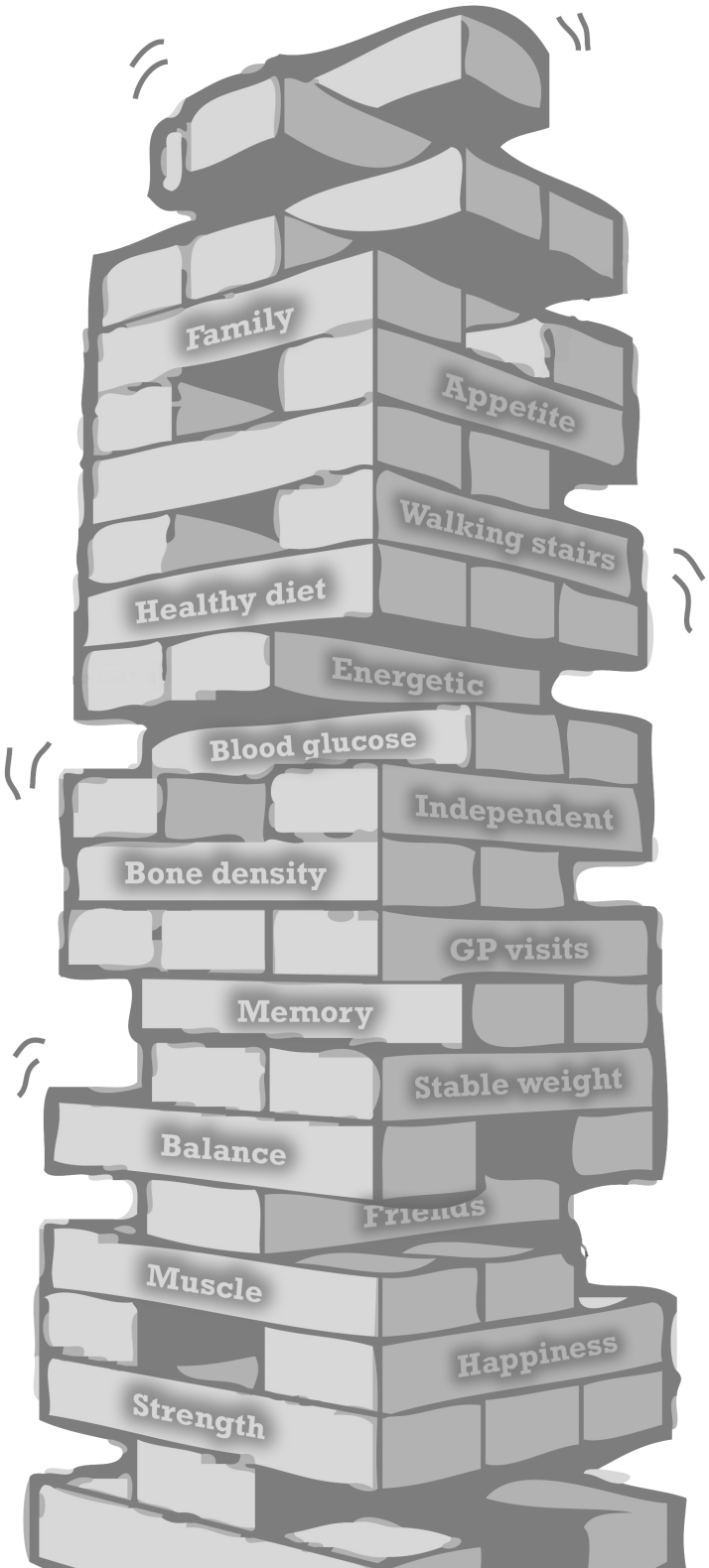
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Independent
Bone density
GP visits
Memory
Stable weight
Balance
Friends
Muscle
Happiness
Strength

Chapter 5

Biochemical measures and frailty in people with intellectual disabilities

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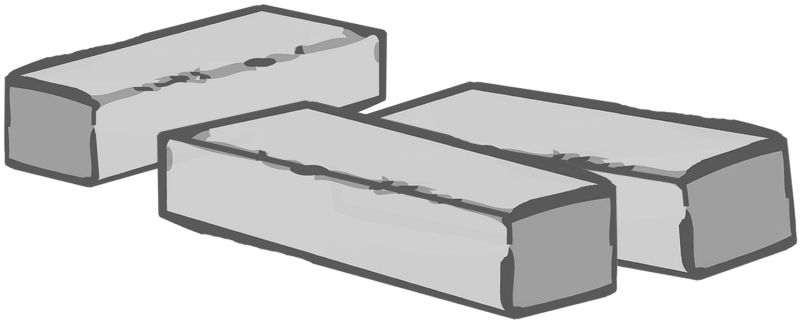
Submitted



ABSTRACT

People with intellectual disabilities (ID) are earlier frail than people in the general population. Although this may be explained by lifelong unfavorable 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, anemia, the metabolic system, micronutrients and renal functioning. Participants (n = 757) with borderline to severe ID (50+) were recruited from three Dutch ID care and support services. 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), anemia, metabolic markers (glucose, cholesterol and albumin) and renal functioning (cystatin-C and creatinine). 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 employed.

Key words: Frailty, people with intellectual disability, physiological measures, inflammation, nutritional status

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, hospitalization, institutionalization and premature death [2], can become a major problem. In people with ID, early onset and high levels of frailty were observed by us [3, 4] and others [5]. 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 [6] and incidence of frailty [7-9]. Although several biochemical measures show strong associations with frailty, there is not yet one biomarker that can adequately identify frailty [10]. 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 utilization. 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) [11].

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 unfavorable chronic conditions, environmental factors, life style and genetic factors (figure 1). Previously, Carmeli et al. found high inflammatory markers in healthy adults with unspecified ID compared to those without ID [12], 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 (inflammation, anemia, micronutrients, metabolic markers, renal functioning) in older people with ID.

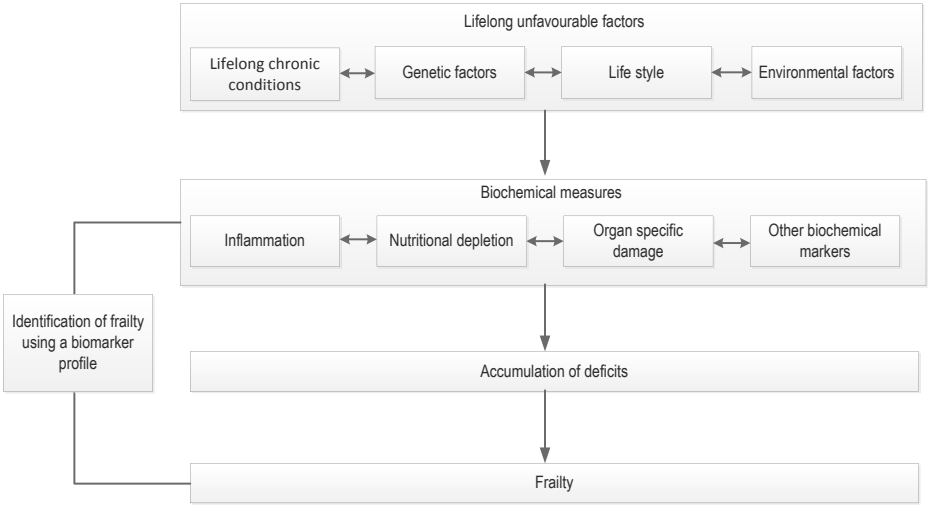


Figure 1. Schematic representation of the pathway of frailty and the role of biochemical measures.

MATERIALS AND METHODS

Subjects and study design

This study was part of the 'Healthy aging and intellectual disabilities' study (HA-ID)[13]. In this observational study, information was collected on the general health status of older people with ID using formal care in the Netherlands. Two university departments and 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. The three care organizations together provided care to 2322 clients with borderline to profound ID aged 50 years and over, who were all invited to participate. Eventually 1050 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 [13]. The Medical Ethics Committee of the Erasmus Medical Center Rotterdam (MEC-2008-234) and the ethics committees of the participating care organizations approved this study. Measurements were conducted within three main themes (1) physical activity and fitness, (2) nutrition and nutritional state, and (3) mood and anxiety. The data collection included body measurements, physical fitness tests, questionnaires, and laboratory tests in addition to file records. Data on age, gender and residential status were retrieved from the administrative systems. Residential status was categorised as centralized setting, community-based setting and living independently

or with relatives with ambulatory support. Level of ID was obtained from the scores of psychologists or test assistants, who determined level of ID from available IQ tests, Vineland scores and social emotional development. 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 hemoglobin related drugs, C10 for lipid lowering drugs, A12A for calcium supplements, and A11CC and A11CB for vitamin-D supplements.

Blood samples

Blood sample 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, hemoglobin, and all metabolic marker were analyzed 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, Swiss). IL-6 was analyzed 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#.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, an operationalization of frailty that focuses on the quantity, rather than on the nature of health problems. In other words, the more health problems an individual has, the frailer he or she is [14]. It captures physical, psychological and social health and has been shown to predict negative health outcomes in several clinical and community-dwelling populations [2, 14, 15]. Following a standardized procedure [16], we developed a frailty with data collected in the HA-ID study. The index consisted of 51 deficits that were all (1) related to health, (2) positively associated with age, (3) frequently but not too often present in the population (> 5%, < 80%), and (4) successfully in at least 70% of the participants. 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). A frailty index 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). No weighting of variables was applied, so each deficit contributed equally to the Frailty index score. Missing values

remained unscored. Information on at least 30 deficits was required before a frailty index score could be calculated. A complete list of the deficits, used measurements and cut-off values has been presented elsewhere [3]. Cholesterol, glucose (diabetes mellitus) and haemoglobin were originally included in the frailty index. Therefore, per definition these measures are somewhat correlated with the frailty index. To eliminate this correlation in the analyses, the index was recomposed without the item of interest for each biochemical measure.

Statistical analysis

First, participants for whom blood samples were available were compared with non-participants using Pearson-chi-square tests for categorical variables and *t*-tests for continuous variables. Second, regression analyses were performed with the biochemical measures as dependent variables and the frailty index as independent variable. We could not assume a linear association between all biochemical measures and frailty since for several of the markers it could be expected that either an increased or a decreased level would negatively influence the frailty status. Therefore a curve estimation procedure was used to find the best fit of the model for each biochemical measure. If required, a polynomial effect was added into the regression model. The physiological measures were incorporated into the models on a continuous scale, with an exception for IL-6, which was dichotomized at the detection limit (19.5 pg/ml). Three different linear regression models were created. The first model analyzed the unadjusted association between the biochemical measures and the frailty index (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 suppletion and the period (summer/winter) of blood collection (sun exposure), calcium was adjusted for calcium suppletion, anemia was adjusted for iron suppletion, glucose was adjusted for glucose lowering drugs, and cholesterol/HDL/triglycerides were adjusted for lipid lowering drugs. The third model incorporated all biochemical measures from the same functional category to study their association with frailty, adjusted for each other and the baseline characteristics. The following functional categories were defined: Inflammation (CRP and IL-6), anemia (hemoglobin), micronutrients (vitamin-D and calcium), metabolic markers (glucose, triglycerides, cholesterol, and albumin), and renal functioning (creatinine and cystatin-C). SPSS version 21.0 (SPSS, Inc., Chicago, IL) was used for statistical analyses. Results were considered statistically significant if the *p*-value was less than 0.05.

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

	included	excluded	all	Statistics	
				Test	*p*-value
n	757	293	1050		
Age (mean [*SD*]	61.7 (8.0)	61.6 (8.3)	61.6 (8.0)	0.43	.93
Gender (%)				0.55	.46
Male	394	145	539		
Female	363	148	511		
Level of ID (%)				4.86	.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	.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	.036
Residential Status				33.5	< .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 (% > pg/ml19.5)	622	63 (10%)			
Hemoglobin (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)			

Note, *SD* = standard deviation, ID = intellectual disability, FI = frailty index, the total number of included biochemical measurements depended on the availability and successfulness of the laboratory measurements

Table 2. The unstandardized and standardized 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 < 19.5pg/ml	594	**4.73 (1.42-8.04)**	**0.11**	**3.57 (0.76-6.39)**	**0.09**	2.50 (-0.37- 5.38)	0.06
	CRP	685	**0.14 (0.09-0.20)***	**0.20**	**0.09 (0.05-0.14)***	**0.14**	**0.08 (0.03-0.12)**	**0.11**
Anemia	Hemoglobin	691	**-5.24 (-6.31- -4.17)***	**-0.35**	**-3.66 (--4.69- -2.63)***	**-0.24**	NA	NA
Micronutrients	Vitamin-D	589	**0.04 (0.01-0.07)**	**0.11**	0.002 (-0.03-0.03)	0.01	-0.001 (-0.04-0.03)	-0.01
	Calcium	559	**-300 (-478.6- -122.1)**	**-2.94**	-132.3 (-2.84.3- -19.67)	-1.30	-137.3 (-2.89.1-14.4)	-1.35
	Calcium^2	559	**66.9 (27.0-106.7)**	**2.93**	30.85 (-3.06- 64.75)	1.35	31.15 (-2.71-65.0)	1.37
Metabolic-markers	Glucose	673	**-0.42 (-0.78- -0.06)**	**-0.09**	**-0.36 (-0.66- -0.05)**	**-0.08**	-0.21 (-0.50-0.08)	-0.04
	HDL	673	-1.20 (-3.79-1.39)	-0.04	-0.90 (-3.10-1.31)	-0.03	-0.24 (-2.78-2.32)	-0.01
	Triglycerides	673	-0.42 (-1.67-0.83)	-0.03	0.06 (-0.99-1.10)	0.00	0.52 (-0.77-1.81)	0.03
	Cholesterol	672	**-2.02 (-2.94- -1.10)***	**-0.17**	**-1.37 (-2.20- -0.53)**	**-0.11**	-0.30 (-1.25-0.66)	-0.25
	Albumin	686	**-1.21 (-1.44- -0.98)***	**-0.37**	**-0.79 (-1.01- -0.57)***	**-0.24**	**0.73 (-0.97- -0.49)***	**0.12**
Renal	Creatinine	606	**-0.37 (0.56- -0.18)***	**-0.58**	**-0.30 (0.47- -0.14)***	**-0.48**	**-0.37 (-0.52- -0.21)***	**-0.57**
functioning	Creatinine^2	606	**0.002 (0.001-0.003)***	**0.54**	**0.001 (0.001-0.002)**	**0.45**	**0.001 (0.00-0.002)**	**0.12**
	Cystatin-C	606	**12.6 (8.87-16.3)***	**0.26**	**9.53 (5.85-13.22)***	**0.20**	**17.6 (13.03-22.3)***	**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 < .005, * *p* values < .001

RESULTS

Baseline characteristics

For 757 out of 1050 of the HA-ID participants at least one biochemical measure was available. 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 excluded showed slightly lower mean frailty index scores compared to the included participants. People who lived in the community were more often excluded from the analyses.

Association between frailty and available biochemical measures

Unadjusted and adjusted for age, gender, level of ID and Down syndrome, higher frailty index scores were associated with higher levels of IL-6, CRP and cystatin-C and with lower levels of hemoglobin, cholesterol, glucose and albumin (Table 2;model 1 & 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 frailty index score; either a high or a low calcium/creatinine level was associated with higher frailty index 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 specialized support or care. Frailty was associated with inflammation (CRP and IL-6), anemia, metabolic markers (glucose, cholesterol and albumin) and renal functioning (cystatin-C).

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 [17, 18]. An association between inflammatory markers and frailty is therefore expected. For years, IL-6 has been called the cytokine for gerontologists [19], and IL-6, CRP and other inflammatory markers have frequently been associated with both aging and frailty [20-23]. In line with these results, we found that elevated levels of IL-6 and CRP were associated with higher frailty index scores.

The consequences of low levels of hemoglobin (e.g. exhaustion, fatigue, low muscle strength, cognitive decline and mortality) are frequently observed in frail individuals [24], which could explain the association we found. The scarce amount of literature on

the association between frailty and hemoglobin shows inconsistent results [25-27]. In contrast to most results observed in the general population [6, 8, 9], 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 suppletion. 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 [28]. 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 serum albumin in the general population [6, 20]. In accordance with these studies, we found that low albumin concentrations were associated with higher frailty index 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 [29]. The consequences of kidney failure could result in a higher prevalence of frailty [30]. In addition to its relation with renal functioning, cystatin-C has frequently shown to predict cardiovascular outcomes [31, 32]. Alternatively, cystatin-C may be associated with a chronic inflammatory state in frail individuals [33].

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. Aging is characterized by a low-grade chronic inflammatory status, termed 'inflammaging. Inflammaging is associated with and predictive for several chronic diseases and adverse health outcomes [34]. Although the exact etiology needs to be further investigated, we showed, in line with others, an association between inflammation and frailty. Carmeli et al. showed that overall, people with unspecified ID (n = 15), have an increased inflammatory state [12]. 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, for example TNF and oxidative stress [23, 35]. Similarly, because frailty is characterized by abnormalities across different systems, a combination of biochemical measures rather than a single biomarker is likely to be required to measure frailty [11, 23, 26, 27, 36, 37].

Our study has several limitations and results need to be interpreted with caution. 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 contrib-

uted 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 frailty index scores and were more often living in the community, leading to an overrepresentation of people living at central settings. Last, contrary to most studies, we used a frailty index 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 [38]. Even so, Hubbard et al. showed that the associations between biochemical markers and frailty are consistent across the two frailty measures [21]. In addition, the frailty index seems to be a more suitable measure for people with ID (Schoufour et al., submitted) and has shown predictive validity in this group [39-41].

In conclusion, we showed, for the first time, associations between frailty and biochemical measures in people with ID. In line with the literature, we found associations between frailty and inflammation, metabolic markers, hemoglobin 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 (combination of) biomarkers that may be used to screen for frailty in a population that has difficulties with the general frailty screening measures (e.g. self-report questionnaires or physical performance tests).

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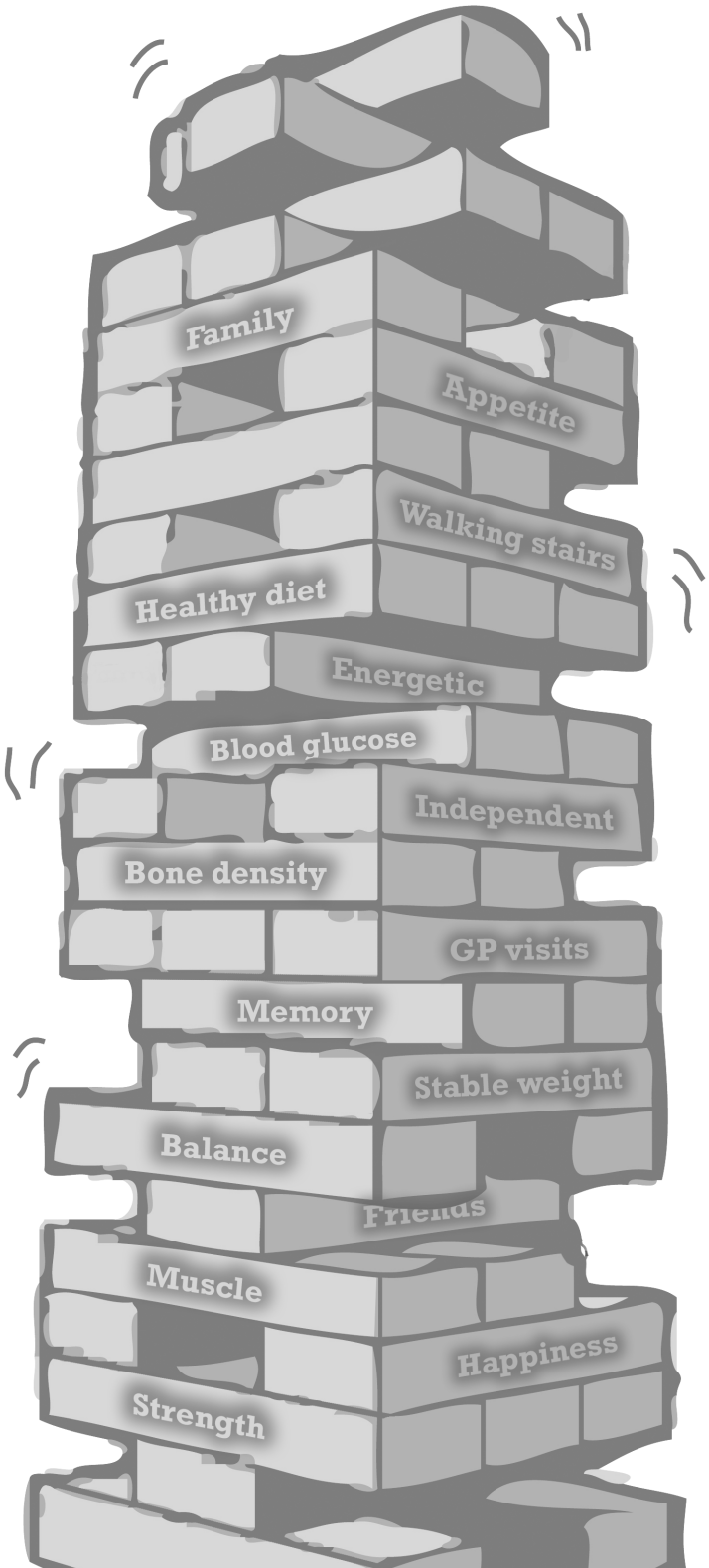
Family
Appetite
Walking stairs
Healthy diet
Energetic
Blood glucose
Independent
Bone density
GP visits
Memory
Stable weight
Balance
Friends
Muscle
Happiness
Strength

Chapter 6

Predicting disabilities in daily functioning in older people with intellectual disabilities using a frailty index

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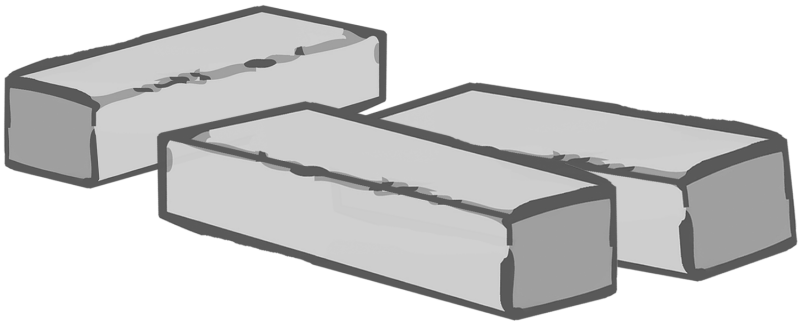

ABSTRACT

Frailty is a state of increased vulnerability to adverse health outcomes compared to others of the same age. People with intellectual disabilities (ID) are more frequently and earlier frail compared to the general population. Frailty challenges much of health care, which will likely further increase due to the aging of the population. Before effective interventions can start, more information is necessary about the consequences of frailty in this, already disabled, population. Here we report whether frailty predicts disabilities in daily functioning. Frailty was measured with a frailty index. At baseline and follow-up activities of daily living (ADL), instrumental activities of daily living (IADL) and mobility were collected by informant report. For 703 older people with ID (≥50yr) baseline and follow-up measures were known. Multivariate linear regression models were used to predict ADL, IADL and mobility at follow-up. The frailty index was significantly associated with disabilities in daily functioning independent of baseline characteristics (age, gender, level of ID, Down syndrome) and baseline ADL, IADL or mobility. The frailty index showed to be most predictive for those with relative high independence at baseline. These results stress the importance for interventions that limit the progression of frailty and, thereby, help to limit further disability.

Key words: People with ID, frailty, limitations, disability, mobility

INTRODUCTION

Frailty is a state of increased vulnerability to adverse health outcomes compared to others of the same age. The prevalence increases with age, even recognizing that older people in general are more vulnerable to adverse health outcomes as a result of decline in many physiological systems [1]. Frailty challenges much of health care, which has a single problem or single system focus [1, 2]. People with intellectual disabilities (ID) typically are at greater risk to develop frailty than others of the same age. Because they have, in addition to general aging problems, an increased risk of motor and sensory disabilities, co-morbidities, mental health problems, and syndrome specific aging problems (for example Down syndrome) [3-7]. The construct of frailty has been developed [8] and validated in relation to the risk of death in older people with ID [9]. Here we report on whether frailty also predicts for disabilities in daily functioning. This information provides insight into the consequences of frailty in this specific population, which is necessary to design effective interventions.

Which method captures frailty the best is still a matter of discussion. Several frailty instruments have emerged in recent years [10]. One broadly used method is the frailty index which is a multifactorial measure for frailty. The frailty index is based on accumulation of a broad spectrum of non-specific age-related impairments (deficits), including symptoms, signs, diseases, disabilities or laboratory measurements [11, 12]. Inasmuch as the administration of the frailty index does not necessarily involve self-report and the measure is multifactorial, which means that it is not focused on specific problems, this approach appears to offer a suitable measure for people with ID [13]. Therefore, we developed a frailty index for older (≥50 year) people with ID [8] according to a standardized procedure [14]. This frailty index showed the same characteristics (frequency distribution, correlation with age) but frailty seemed to start at a younger age compared to the general population [8, 12, 15, 16]. The frailty index showed a clear relationship with 3-year mortality. Those classified as frail were at least 8 times (95%*CI* 7.7-17.3) more likely to die compared to those classified as non-frail [9].

The relationship between the frailty index and survival underlined the problem of frailty in people with ID. It is however not yet clear whether frailty also has an impact on disability in this already disabled population. In the general population it has been shown that frail individuals have a higher risk for disabilities in activities of daily living (ADL), instrumental activities of daily living (IADL) and mobility compared to non-frail individuals [17-24]. In people with ID, activities of daily living were found, in addition to aging, to be related to cognitive functioning and mobility limitations [25-27]. As a result, people with ID often experience lifelong dependence. The relationship between

frailty and increasing dependence can therefore not be assumed to be the same as that observed in the general population. If frailty is a risk factor, frailty instruments that can identify those at risk can help selecting those who benefit from intervention programs aiming at maintaining independence and mobility. Maintaining as much independence as possible can increase the quality of life and diminish the burden for individuals, family, caregivers, and health care facilities [28, 29]. Therefore, the primary objective of this study was to analyze the association between the frailty index score and deterioration of ADL, IADL and mobility over a 3-year follow-up period in older people with ID.

METHODS

Design and participants

This study was part of the 'Healthy Ageing and Intellectual Disability' (HA-ID) study. The observational HA-ID study collected information on the general health status of older people with ID. The HA-ID study focused on (1) physical activity and fitness, (2) nutrition and nutritional state, and (3) mood and anxiety. The study was conducted in three care organizations throughout The Netherlands [30]. The Medical Ethics Committee of the Erasmus Medical Center Rotterdam (MEC- 2008-234) and the ethics committees of the participating care organizations approved this study. The three care organizations together provided care to 2322 clients with borderline to profound ID aged 50 years and over, who were all invited to participate. Those capable of understanding the available information signed the consent form themselves. Legal representatives were approached for those not able to make this decision. Written informed consent was provided for 1050 clients. They formed a nearly representative study population for the Dutch population of older adults (aged 50 and above) with ID who receive formal care, albeit with a slight underrepresentation of men ($X^2[1, N = 2322] = 0.53, p = .03$), people aged 80 and over ($X^2[8, N = 2322] = 27.41, p = .001$), and people living independently ($X^2[3, N = 2237] = 50.55, p < .001$). Three years after the baseline measurements a follow-up study evaluated health, dependence, and mobility. The follow-up study was approved by the Medical Ethics Committee of the Erasmus Medical Center Rotterdam (MEC-2011-309) and the ethics committees of the participating care organizations. All participants, or their legal representatives, who still received care from one of the care organisations were asked again to provide written informed consent for the follow-up study.

Data collection

Baseline data collection has been described in detail elsewhere [30]. The broad spectrum of data collected included physical assessments, a fitness test battery, actigraphy, pedometer measurements, mealtime observations of swallowing, nutritional question-

naires, screening questionnaires and standardized psychiatric interviews for depression and anxiety, questionnaires on life events, quality of life, IADL, ADL, mobility, dementia, social circumstances, somatic complaints, and laboratory tests. Level of ID was obtained from the scores of psychologists or test assistants. They determined the level of ID from available IQ tests, Vineland scores and social emotional development. The presence of Down syndrome was retrieved from the medical files. Baseline data were collected between February 2009 and July 2010.Three years after baseline, follow-up data were collected by informant report to limit the burden for the clients. Questionnaires on IADL, ADL, and mobility were completed by professional caregivers, as in the baseline measurement. ADL was assessed with the Barthel Index [31]. The Barthel index has been shown to be reliable and sensitive when completed by proxy [32-34]. It consisted of 10 items (feeding, bathing, grooming, dressing, bowels, bladder, toilet use, transfers [bed to chair and back], mobility on level surfaces, and mobility on stairs) with two to four answer categories. The total ADL score ranged from 0 (completely dependent) to 20 (completely independent). The Lawton scale was used to measure IADL [35]. The Lawton scale has been previously used in hospitalized older patients and is valid to be filled in by clinicians [36, 37]. The Lawton scale consisted of eight items (telephone use, groceries, food preparation, housekeeping, laundry, transportation, medication and finances) with three answer categories (not able, able with support, independent). The total score ranged from 8 (completely dependent) to 24 (completely independent).

Mobility was assessed with five questions based on the Hauser Ambulation Index and the characteristics of the Gross Motor Function Classification Scale (ability to walk: at home, work/school, less than 50 meters in a safe environment, over 50 meters in a safe environment, outside the safe environment) [38]. For each question 8 different answers were possible: 1) no help, 2) furniture or railing, 3) cane or crutch, 4) walker, 5) wheelchair, but able to move using his/her feet, 6) wheelchair, but able to move using his/her arms, 7) pushed in a wheelchair, 8) electric wheelchair, 9) bedridden. Mobility scores ranged between 0 (walking independent on all items) and 40 (bedridden). For ADL, IADL and mobility questionnaires, differences between baseline and follow-up were considered as outliers if the change exceeded 3 *SD*. Questionnaires from these participants were checked with the professional caregivers to ensure correctness. If the large difference could not be explained, the participant was excluded from the analysis.

Frailty index

A frailty index was created with 51-items from the baseline measures of the HA-ID study. Following a standard procedure, all deficits were (1) related to health, (2) positively associated with age, (3) frequently but not too often present in the population (> 5%, < 80%), and (4) measured in at least 70% of the participants. Furthermore, the items did

not correlate too strongly with each other ($r < 0.7$), and together they covered different health aspects [14]. All items were recoded to a score ranging from 0 to 1 of which 0 indicated the complete absence of a deficit and 1 the complete presence of a deficit. A frailty index score was calculated taking the proportion of deficits present, resulting in a score between 0 and 1. For each individual participant the deficits that were missing were removed from both the numerator and the denominator. For example if an individual had missing values on two items, the frailty index was calculated with a denominator of 49. A frailty index score could not be calculated for participants with less than 30 known deficits. The design of the frailty index and details on the used deficits has been described elsewhere [8]. To examine the association of frailty with daily functioning the index was rescored to exclude the mobility and disability items. Specifically, compared with the original frailty index used in this study, five ADL deficits (bladder control, dressing, walking stairs, bathing, transfer bed to chair), two IADL deficits (groceries and housekeeping) and one mobility deficit were each excluded. The intraclass correlation coefficients between the original frailty index and the frailty index without ADL, IADL or mobility items was .97, .98 and .99 respectively ($p < .001$).

Statistical analysis

For the ADL, IADL and mobility questionnaires, missing items were imputed using the mean of each respondent's answers to other ADL, IADL or mobility questions. For example, if a participant had 1 missing response on the ADL scale the missing value was substituted with the average of the remaining nine questions. No more than 30% missing values were accepted for each individual. The level of ID was classified in three categories (borderline/mild, moderate, severe/profound) and dummy variables were created to compare the ID groups with borderline/mild. Dummy variables were also created to compare the participants without Down syndrome with those with Down syndrome and those without information on Down syndrome. Characteristics of the study population were first assessed with a non-response analysis, in which those included in the follow-up study were compared to those who dropped out of the study. Pearson-chi-square tests for categorical variables and *t*-tests for continuous variables were used. Percentages of participants able to perform ADL, IADL and mobility items independently were provided for baseline and follow-up and changes over time were tested for significance with the McNemar test. Overall differences between the baseline score and follow-up score were assessed with paired-samples *t*-tests.

To analyze the univariate correlation between the frailty index score and ADL, IADL and mobility measurements the Pearson correlation coefficient was used. Multivariable linear regression with two or three steps was used to predict ADL, IADL and mobility three years after baseline. In step 1, the baseline characteristics (age, gender, level of

ID, Down syndrome) and the baseline ADL, IADL, or mobility scores were included. In step 2, the frailty index score was included (to aid interpretation, the frailty index score was multiplied by 100). It was expected that the influence of the frailty index depended on the baseline score of the ADL, IADL or mobility measurement, since those with high scores at baseline could decrease more than those with low scores at baseline and vice versa. Therefore, interactions between the frailty index score and the baseline scores of the instruments were tested and an interaction term was applied into a third step if applicable ($p < .05$). A graph was plotted to show the effect of the interaction term. This graph showed the frailty index in relation to the estimated limitations in daily functioning 3 years after baseline, standardized for a male individual with a moderate ID, aged 55 years and without Down syndrome, using the regression coefficients of step 3. For all independent variables, multicollinearity was checked with the variance inflation factor (VIF) of linear regression analysis. VIF values above 10 indicated multicollinearity, provided that variables were no interaction terms or dummy variables. A p-value < .05 was considered statistically significant.

RESULTS

Characteristics of the study population

At baseline, 989 out of 1050 (94%) respondents had completed ADL and IADL questionnaires. After 3 years of follow-up, excluding those who died ($n = 120$), moved ($n = 19$), or did not sign a consent form for follow-up measurements ($n = 148$), 737 of the questionnaires were returned. For 30 participants no questionnaires had been completed at baseline, and for four participants questionnaires were incorrectly filled out, leaving 703 participants (Figure 1). As shown in Table 1, those who dropped out were significantly older, had more often Down syndrome, were less mobile, had lower ADL scores, and had higher frailty index scores.

Differences between baseline and follow-up

Table 2 shows that, on average, almost all ADL, IADL and mobility items declined significantly over the 3 years. ADL at baseline and ADL at follow-up were highly correlated ($r = 0.82$); the mean decrease in the ADL score was 1.23 ($SD = 3.35$) ([$M_{baseline} = 14.3$, $SD_{baseline} = 5.3$, $M_{follow\text{-}up} = 13.1$, $SD_{follow\text{-}up} = 5.8$], $t(702) = 9.7$, $p < .001$). The correlation between baseline and follow-up IADL score was 0.85 with a mean decrease of 0.70 ($SD = 2.49$) points after three years ([$M_{baseline} = 12.0$, $SD_{baseline} = 4.7$, $M_{follow\text{-}up} = 11.3$, $SD_{follow\text{-}up} = 4.3$], $t(702) = 7.5$, $p < .001$). On average mobility limitations increased with 3.2 ($SD = 6.14$) points ([$M_{baseline} = 6.8$, $SD_{baseline} = 9.9$, $M_{follow\text{-}up} = 10.0$, $SD_{follow\text{-}up} = 11.4$], $t(697) = 13.6$, $p < .001$). Baseline and follow-up mobility score showed a correlation of 0.84 ($p < .001$).

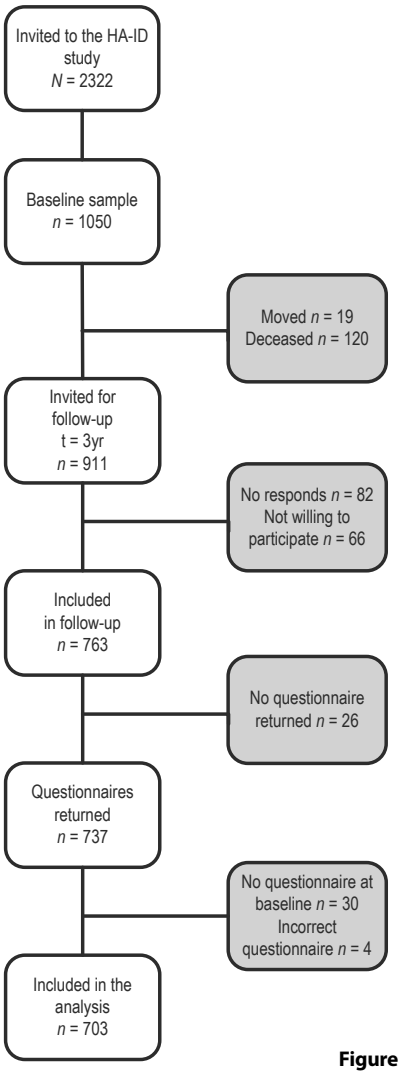

Figure 1. Flow chart of the participant inclusion throughout the study

Predicting disability with the frailty index

All VIF values, not being interaction term or dummy variables were below 10. Data for people without information on Down syndrome were not shown.

Activities of daily living

Frailty and ADL were highly correlated, with a Pearson correlation coefficient of .70 at baseline, and .68 at follow-up ($p < .001$). A linear regression model predicting ADL at follow-up, including the baseline characteristics (gender, age, Down syndrome, and level of ID) and baseline ADL, explained 72% of the variance (Table 3A). The full model

Table 1. Baseline characteristics at baseline and 3 years follow-up

Characteristics		*n* (%)			X^2	*p*-value[a]
		Baseline *n* = 1050	Follow-up			
			Included *n* = 703	Dropped out *n* = 347		
Gender	Male	539 (51%)	355 (50%)	184 (53%)	0.59	.441
	Female	511 (49%)	348 (50%)	163 (47%)		
Age (years)	50-59	493 (47%)	352 (50%)	141 (41%)	11.7	.020
	60-69	370 (35%)	239 (34%)	131 (38%)		
	70-79	162 (15%)	100 (14%)	62 (18%)		
	80+	25 (2.4%)	12 (1.7%)	13 (3.8%)		
Level of ID	Borderline	31 (3.0%)	19 (2.7%)	12 (3.5%)	8.35	.138
	Mild	223 (21%)	137 (20%)	86 (25%)		
	Moderate	506 (48%)	344 (49%)	162 (47%)		
	Severe	172 (16%)	128 (18%)	44 (13%)		
	Profound	91 (8.7%)	59 (8.4%)	32 (9.2%)		
	Unknown	27 (2.6%)	16 (2.3%)	11 (3.2%)		
Down syndrome	No Down syndrome	724 (62%)	511 (73%)	213 (61%)	4.52	.034
	Down syndrome	149 (14%)	92 (13%)	57 (16%)		
	Unknown	177 (24%)	100 (14%)	77 (22%)		

Test scores	Mean (*SD*)						*t*	*p*-value[b]
	n	Baseline	Follow-up					
			n	Included	*n*	Dropped out		
Barthel index (0-20) ↑	989	13.9 (5.77)	703	14.3 (5.29)	286	12.7 (6.66)	-4.10	< .001
Lawton IADL scale (8-24) ↑	989	11.9 (4.69)	703	12.0 (4.71)	286	11.7 (4.64)	-0.81	.420
Mobility score (0-35) ↓	989	7.80 (10.5)	703	6.82 (9.93)	286	10.2 (11.49)	4.66	< .001
Frailty index (0-1) ↓	982	0.27 (0.13)	700	0.26 (0.12)	282	0.32 (0.14)	6.46	< .001

[a] *p*-Value calculated for the difference between included and dropout participants with chi-square.
[b] *p*-Value calculated for the difference between included and dropout participants with an independent sample *t*-test.
↑↓ indicates the direction of the best score.

(step 2) explained 73% of the variance, of which 1.1% was explained by the frailty index. ADL at follow-up was independently correlated with age, Down syndrome, level of ID, ADL at baseline, and the frailty index score (Table 3A). Change in the frailty index score was important: each 0.01 increase in frailty index score predicted a 0.09 lower ADL score at follow-up, independent of the baseline ADL score and baseline characteristics. In other words, an individual with a frailty index score of 0.50 would have an ADL score at follow-up being 3.6 points lower compared to an individual with a frailty index score of 0.10. There was no additional effect of the frailty index with the addition of an interaction term (data not shown).

Table 2. Percentage of participants able to perform ADL and IADL tasks independently and the percentage of participants able to move without help, walking aid or wheelchair in different situations

Barthel Index (n = 703)	Baseline	Follow-up	X^{2a}	p-value
All	13.8	11.5	2.62	.106
1. Bowel	61.7	59.2	1.59	.208
2. Bladder	54.6	51.9	1.96	.161
3. Grooming	30.7	23.0	18.7	< .001
4. Toilet use	57.0	51.1	9.77	.002
5. Feeding	61.3	52.5	27.8	< .001
6. Transfer	78.2	70.6	22.7	< .001
7. Mobility	80.2	68.4	44.5	< .001
8. Dressing	57.3	46.5	42.0	< .001
9. Stairs	54.8	44.0	42.0	< .001
10. Bathing	36.4	29.6	17.8	< .001
Lawton IADL Scale (n = 702)	Baseline	Follow-up	X^{2a}	p-value
All	2.6	1.4	NA[b]	NA[b]
1. Telephone use	25.3	22.8	4.01	.05
2. Groceries	29.4	22.9	19.5	< .001
3. Food preparation	12.7	9.7	5.33	.02
4. Housekeeping	10.8	6.0	16.0	< .001
5. Laundry	10.8	9.1	2.52	.11
6. Transportation	12.8	10.5	4.02	.05
7. Medication	14.1	9.8	12.7	< .001
8. Finances	22.0	16.5	13.8	< .001
Mobility items (n = 698)	Baseline	Follow-up	X^{2a}	p-value
All	60.6	46.2	87.0	< .001
1. Walking in home	75.5	63.3	61.5	< .001
2. Walking at work/school	73.0	60.2	67.6	< .001
3. Walking protected area (< 50m)	70.7	58.5	67.5	< .001
4. Walking protected area (> 50m)	64.0	49.6	85.0	< .001
5. Walking unprotected area	62.4	47.4	92.1	< .001

[a] Chi-Square calculated with the McNemar test.
[b] Expected cell count less than 5, McNemar test not possible.

Instrumental activities of daily living

At baseline, 35% of the participants were unable to perform any of the IADL items (IADL score: 8). The frailty index score and IADL showed a Pearson correlation coefficient of .58 at baseline, and .56 at follow-up (p < .001). IADL at follow-up was independently correlated with age, level of ID, IADL at baseline, and the frailty index score (Table 3B). As shown in Table 3, most of the variance was explained by baseline IADL score. The interaction term between the frailty index score and baseline IADL score was significant

($\beta = 0.30$; $p < .001$; Table 3B, step 3). The frailty index score and corresponding interaction term explained 1.9% of the variance in addition to the 74% which was already explained by the baseline measurements. The slope of the regression line between the frailty index score and change in IADL differed per baseline IADL score. As shown in Figure 2, a high baseline IADL combined with a high frailty index score predicted a higher decline compared to those with low baseline IADL and high frailty index scores.

Mobility

The Pearson correlation coefficient for the frailty index score and mobility at baseline was .60 and with mobility at follow-up .60. Mobility at follow-up was significantly related to gender, age, Down syndrome, baseline mobility score and the frailty index score (Table 3C). The frailty index and the corresponding interaction term explained 1.7% of the variance in addition to the 74% already explained by the baseline measures. The significant interaction term showed that the influence of the frailty index on mobility limitations at follow-up depends on baseline mobility score. Figure 3 shows that, for those with low mobility scores (little mobility limitation) at baseline, the highest correlation between the frailty index score and deterioration in mobility was found.

DISCUSSION

We have shown that frailty is significantly associated with increasing disabilities in daily functioning in people with ID. In univariate analysis, the frailty index was highly correlated with baseline disabilities and disabilities over a 3-year follow-up period. After adjusting for gender, age, level of ID, presence of Down syndrome, and baseline disability, frailty

Table 3A. Multiple linear regression models predicting ADL at follow-up

n = 684	Step 1 $R^2 = 0.713$*				Step 2 $R^2 = 0.724$*			
	B (*SE*)	*β*	*t*	*p*-value	*B* (*SE*)	*β*	*t*	*p*-value
Gender (female)	-0.52 (0.24)	-0.04	-2.12	.034	-0.44 (0.24)	-0.04	-1.82	< .001
Age (years)	-0.10 (0.02)	-0.13	-6.11	< .001	-0.07 (0.02)	-0.10	-4.32	.069
Down syndrome	-2.10 (0.37)	-0.12	-5.65	< .001	-2.07 (0.37)	-0.12	-5.60	< .001
Level of ID								
Moderate	-1.28 (0.31)	-0.11	-4.09	< .001	-1.06 (0.31)	-0.09	-3.29	.001
Severe	-2.43 (0.39)	-0.19	-6.15	< .001	-1.99 (0.40)	-0.15	-5.02	< .001
Barthel Index Baseline	0.80 (0.03)	0.74	30.8	< .001	0.70 (0.03)	0.64	21.6	< .001
FI score (0-100)[a]	-	-	-	-	-0.09 (0.02)	-0.16	-5.27	< .001

Note. Low scores indicate low ADL capacities

* R Square change significant with a p-value < .001

[a]The frailty index was recomposed without the ADL items which are included in the original frailty index

Table 3B. Multiple linear regression models to predict IADL at follow-up

n = 683	Step 1 Adjusted R^2 = 0.738*				Step 2 Adjusted R^2 = 0.743*				Step 3 Adjusted R^2 = 0.757*			
	B (*SE*)	*β*	*t*	*p*-value	*B* (*SE*)	*β*	*t*	*p*-value	*B* (*SE*)	*β*	*t*	*p-value*
Gender (female)	0.09 (0.17)	0.01	0.55	0.55	0.21 (0.17)	0.02	1.22	.22	0.19 (0.17)	0.02	1.17	.24
Age (years)	-0.05 (0.01)	-0.08	-3.85	< .001	-0.03 (0.01)	-0.06	-2.60	.01	-0.03 (0.01)	-0.05	-2.45	.015
Down syndrome	-0.36 (0.26)	-0.03	-1.38	.17	-0.40 (0.26)	-0.03	-1.52	.13	-0.38 (0.26)	-0.03	-1.50	.133
Level of ID												
Moderate	-1.10 (0.24)	-0.13	-4.57	< .001	-1.09 (0.24)	-0.13	-4.56	< .001	-1.02 (0.23)	-0.12	-4.39	< .001
Severe	-1.39 (0.31)	-0.14	-4.48	< .001	-1.19 (0.31)	-0.12	-3.81	< .001	-1.39 (0.31)	-0.15	-4.55	< .001
IADL Baseline	0.70 (0.02)	0.77	29.8	< .001	0.66 (0.03)	0.72	25.9	< .001	0.86 (0.04)	0.95	20.9	< .001
FI score (0-100) [a]	-	-	-	-	-0.04 (0.01)	-0.10	-3.75	< .001	0.09 (0.02)	0.25	4.09	< .001
Interaction IADL-FI	-	-	-	-	-	-	-	-	-0.01 (0.002)	-0.31	-6.15	< .001

Note. Low scores indicate low IADL capacities

**R* Square change significant with a *p*-value < .001

[a] The frailty index was recomposed without the IADL items which are included in the original frailty index

Table 3C. Multiple linear regression models to predict mobility at follow-up

n = 679	Step 1 Adjusted R^2 = 0.737				Step 2 Adjusted R^2 = 0.748*				Step 3 Adjusted R^2 = 0.754*			
	B (*SE*)	*β*	*t*	*p*-value	*B* (*SE*)	*β*	*t*	*p*-value	*B* (*SE*)	*β*	*t*	*p*-value
Gender (female)	1.68 (0.46)	0.07	3.63	< .001	1.48 (0.45)	0.07	3.26	.001	1.34 (0.45)	0.06	2.99	.003
Age (years)	0.15 (0.03)	0.10	4.82	< .001	0.12 (0.03)	0.08	3.59	< .001	0.11 (0.03)	0.07	3.33	.001
Down syndrome	3.96 (0.71)	0.12	5.58	< .001	3.75 (0.70)	0.11	5.39	< .001	3.53 (0.69)	0.10	5.11	< .001
Level of ID												
Moderate	0.64 (0.59)	0.03	1.10	.27	0.01 (0.58)	0.00	0.01	.99	-0.19 (0.58)	-0.01	-0.33	.74
Severe	1.15 (0.69)	0.05	1.68	.09	-0.62 (0.75)	-0.02	-0.84	.40	-0.85 (0.74)	-0.03	-1.15	.25
Baseline mobility	0.91 (0.03)	0.80	37.1	< .001	0.82 (0.03)	0.72	28.1	< .001	1.10 (0.08)	-0.97	14.7	< .001
FI score (0-100) [a]	-	-	-	-	0.15 (0.03)	0.16	5.49	< .001	0.22 (0.03)	0.22	6.83	< .001
Interaction mob-FI	-	-	-	-	-	-	-	-	-0.008 (0.002)	-0.30	-4.04	< .001

Note. High scores indicate low mobility

**R* Square change significant with a *p*-value < .001

[a] The frailty index was recomposed without the deficit on mobility which is included in the original frailty index

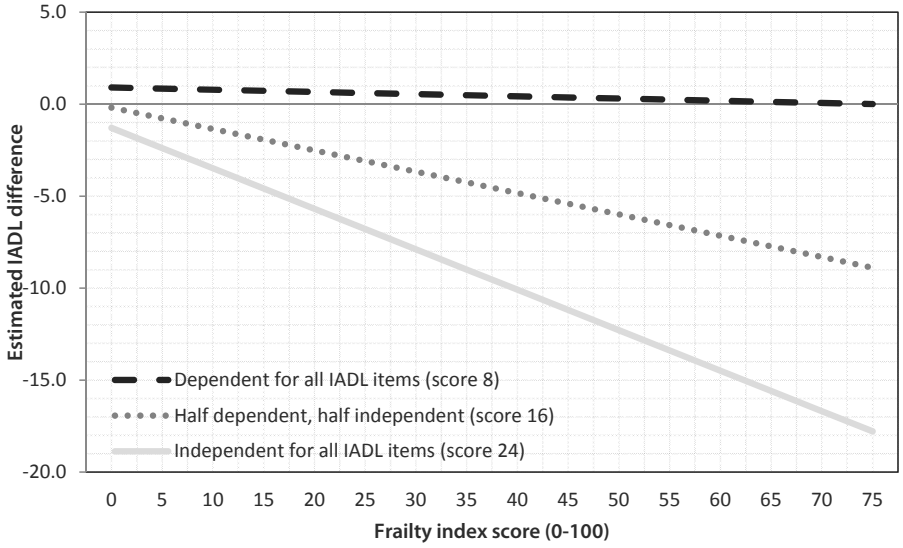

Figure 2. Correlation between the frailty index score at baseline and the estimated IADL difference 3 years after baseline. A linear regression model (including gender, age, level of ID, Down syndrome, baseline IADL, frailty index score, and interaction term for IADL and frailty index score) was used to estimate the function. Lines represent a male with moderate intellectual disability, aged 55 years, no Down syndrome and an IADL baseline score of 8 (fully dependent; striped black line), 16 (half dependent; dotted dark grey line), and 24 (fully independent; straight light grey line).

continued to be associated with disabilities in ADL, IADL and mobility three years later. In all models, frailty was better able to predict decreased health outcomes than was chronological age. Overall it was shown that within three years, the percentage of participants who were able to independently perform ADL, IADL and mobility tasks decreased.

In line with previous results, we confirm that the frailty index is a valid indicator to predict adverse health outcomes. Most studies found an association between frailty and disabilities in daily functioning, although the strength of the associations differs from study to study. This was mainly due to the variation regarding the study population, follow-up period, used instruments, study size, and confounders. Several studies have shown that physical frailty leads to ADL/IADL disability [22]. But multidimensional frailty measures are also able to identify those at risk [18, 21, 23]. Woo et al. showed that the standardized beta between the frailty index and change of ADL (Barthel index) at 3-year follow-up was -0.12 [23]. We found similar results with a somewhat higher standardized beta of -0.16. However, comparison remains difficult because the Hong Kong cohort (70 years and over), used by Woo et al., was on average older, less disabled in ADL functioning, and showed lower (i.e., better) frailty scores at baseline compared to our study population. In addition to the frailty index, the level of ID was a significant predictor for

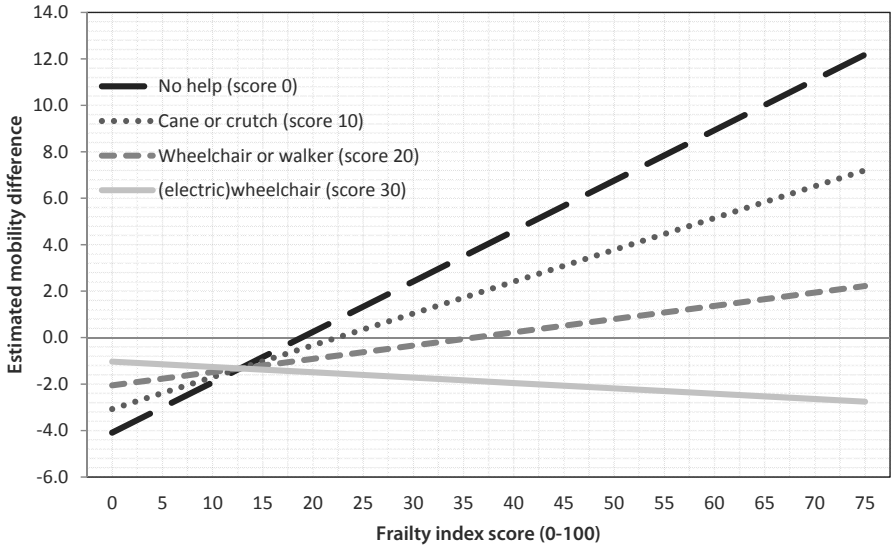

Figure 3. Correlation between the frailty index score at baseline and the estimated mobility difference 3 years after baseline (increased score predicts mobility deterioration). A linear regression model (including gender, age, level of ID, Down syndrome, baseline mobility, frailty index score, and an interaction term for mobility and the frailty index score) was used to estimate the function. Lines represent a male with moderate intellectual disability, aged 55 years, no Down syndrome and a mobility score of 0 (no limitations; black striped line), 10 (walking with a cane or crutch; dark grey round dotted line), 20 (walker or wheelchair; grey square dotted line), or 30 (wheelchair or electric wheelchair; light grey straight line).

disabilities in daily function. The association between the level of ID and disabilities in ADL and IADL was previously found in cross-sectional studies [27, 39]. Here we have shown that the level of ID is also an predictor for deterioration in ADL and IADL activities after a 3-year follow-up period. Participants with moderate or severe levels of ID were more likely to develop disabilities compared to participant with low levels of ID.

Our results show that the association between frailty and disability in IADL at follow-up depends on the baseline IADL score. More precisely, the index has the most predictive value for those who are independent at baseline, whereas in those with low baseline independence, the frailty index has little prognostic value. This was also observed for mobility. This result can be explained by the floor effects present in the used scales of the IADL and mobility questionnaires. In participants with very low baseline IADL scores, negative changes could not be observed, although they were likely to have high frailty index scores [24]. In contrast, those with better scores had more room for scores to decline, which explains the strong association between frailty and reduced IADL and mobility.

The explained variance found for the models predicting deterioration in the health outcomes was around 0.75. Most of the variance was explained by baseline functional status. Previously, it has been shown that baseline functional status is highly correlated with functional status in later life [21, 40]. The extra variance explained by the frailty index ranged between 1.1 and 1.9%, which can still be considered rather high, since little variance was left unexplained and the standardized regression coefficients showed to have a small to medium effect size. In addition, the regression coefficients showed clinically important effects. For example, according to the model, an individual with a high frailty index score (0.5) would have an ADL score at follow-up 3.6 points lower compared to an individual with a low frailty index score (0.1). This difference could mean for example that the individual is no longer able to bath independently, needs help with feeding, is no longer fully continent, and lost some mobility. Nevertheless, our data do not provide evidence that the frailty index can exclusively predict adverse health outcomes. The unexplained variance could be contributed to variables not included in the model (including protective factors) but also by noise in the data. Frailty itself is a dynamic process, and those categorized as frail could no longer be frail at follow-up or the other way around [41]. Similarly, as we had only one single follow-up assessment, we cannot be sure of the extent to which disability fluctuation might be a phenomenon in this group [42], or how trajectories of disability relate to frailty. Budget cuts, changes of a personal care giver, relocation from outpatient environment towards an intramural environment are all factors that could have caused changes in ADL, IADL, and mobility.

The strengths of our study are the prospective design, the large study population, and the completeness of the follow-up. Additionally, we chose to measure frailty with an instrument that includes multiple health aspects and is not solely focused on physical health. Although it has been shown that physical frailty indicators are important in predicting ADL disability [21, 22], multiple health domains also strongly contribute to ADL disabilities [43]. Additionally, the frailty index showed good validity across diverse clinical and community dwelling populations and is applicable to people with ID [1, 8, 44].

This study has also several limitations. First, dropout between baseline and follow-up was associated with more frailty, more ADL limitations, and more mobility limitations. Thirty-five percent of the drop-out was caused by the death of the participants. The ability of the frailty index to predict adverse health may have been underestimated because people who dropped out were more likely to have died. Second, some remarks need to be made about the questionnaires we employed in relation with the frailty index. The major advantages of using the Barthel ADL index and Lawton IADL scale are the ability to compare our results with the general population, and their known feasibility

in people with ID. Even so, the observed floor effect made negative changes in the lowest ADL, IADL and mobility categories impossible. A more sensitive instrument could have increased the predictive value of the frailty index for those who already have little independence. Also, the ADL and IADL questionnaires had been used to compose the original frailty index. Overlap between the index and the questionnaires was reduced by the development of new frailty indices excluding the ADL/IADL/mobility items. This has led to slightly modified indices. Nevertheless, Theou et al. (2012) showed that regardless of whether ADL items are included in the index, the predictive value remains, although the ADL items do contribute to the risk of developing adverse health outcomes. Additionally, we found very high correlations between the original and adjusted frailty indices and we performed all analyses also with the original frailty index and found no major differences (Appendix A). Although the VIF indicated that there was no multicollinearity, it could be that the high correlation between frailty and the disabilities in daily function caused some bias in the predictive accuracy of the frailty index.

In spite of these limitations, we demonstrated that frailty predicted declined disability and mobility in an already disabled population. The frailty index showed most predictive value for those with high baseline mobility or IADL independence. Although preferably the index would be sensitive for all subgroups within this population, those with relative high independence may benefit the most from interventions. Future research should focus on possible disability fluctuations in this group. In addition, a more sensitive ADL and IADL questionnaire can help to detect deterioration in those with very low dependence at the start of the study. Caregivers should be able to recognize frail and vulnerable people at an early stage to avoid further health decline. Interventions that limit the progression of frailty potentially also limit further disability and thereby diminish the burden for individuals and caregivers and limit health costs in this, already expensive, population.

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Appendix A.I Multiple linear regression models predicting ADL at follow-up with the original frailty index

n = 684	Step 1 $R^2 = 0.716$*				Step 2 $R^2 = 0.730$*			
	B (*SE*)	*β*	*t*	*p*-value	*B* (*SE*)	*β*	*t*	*p*-value
Gender (female)	-0.52 (0.24)	-0.04	-2.12	.034	-0.40 (0.24)	-0.03	-1.65	.099
Age (years)	-0.10 (0.02)	-0.13	-6.11	< .001	-0.07 (0.02)	-0.09	-4.02	< .001
Down syndrome	-2.10 (0.37)	-0.12	-5.65	< .001	-2.01 (0.36)	-0.12	-5.52	< .001
Level of ID								
Moderate	-1.28 (0.31)	-0.11	-4.09	< .001	-0.98 (0.31)	-0.08	-3.17	.002
Severe	-2.43 (0.39)	-0.19	-6.15	< .001	-1.92 (0.40)	-0.15	-4.87	< .001
Barthel Index Baseline	0.81 (0.03)	0.74	30.8	< .001	0.64 (0.04)	0.58	16.28	< .001
FI score (0-100)	-	-	-	-	-0.11 (0.02)	-0.22	-5.79	< .001

Note. Low scores indicate low ADL capacities
* *R* Square change significant with a *p*-value < .001

Appendix A.III Multiple linear regression models to predict mobility at follow-up with the original frailty index

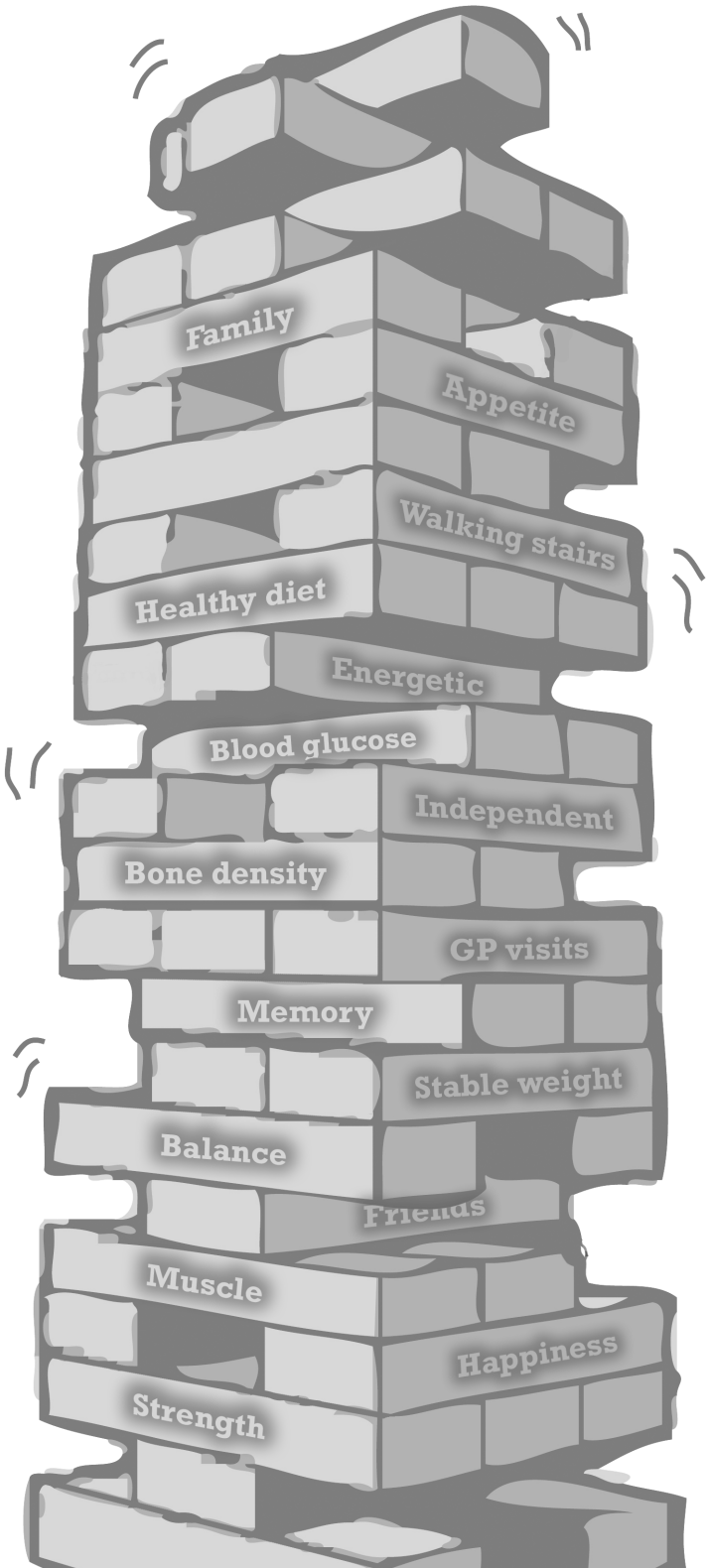
$n = 679$	Step 1 Adjusted $R^2 = 0.737$				Step 2 Adjusted $R^2 = 0.748$*				Step 3 Adjusted $R^2 = 0.754$*			
	B (*SE*)	*β*	*t*	*p*-value	*B* (*SE*)	*β*	*t*	*p*-value	*B* (*SE*)	*β*	*t*	*p*-value
Gender (female)	1.68 (0.46)	0.07	3.63	< .001	1.49 (0.45)	0.06	3.28	.001	1.34 (0.45)	0.06	2.98	.003
Age (years)	0.15 (0.03)	0.10	4.82	< .001	0.12 (0.03)	0.08	3.63	< .001	0.11 (0.03)	0.07	3.31	.001
Down syndrome	3.96 (0.71)	0.12	5.58	< .001	3.77 (0.70)	0.11	5.42	< .001	3.52 (0.69)	0.10	5.11	< .001
Level of ID												
Moderate	0.64 (0.59)	0.03	1.10	.27	0.02 (0.59)	0.00	0.03	0.98	-0.19 (0.58)	-0.01	-0.33	.74
Severe	1.15 (0.69)	0.05	1.68	.09	-0.59 (0.75)	-0.02	-0.79	0.43	-0.84 (0.74)	-0.03	-1.13	.26
Baseline mobility	0.91 (0.03)	0.80	37.1	< .001	0.81 (0.03)	0.71	26.9	< .001	1.10 (0.08)	0.97	14.62	< .001
FI score (0-100)	-	-	-	-	0.15 (0.03)	0.16	5.39	< .001	0.22 (0.03)	0.23	6.81	< .001
Interaction mob-FI	-	-	-	-	-	-	-	-	-0.01 (0.002)	-0.31	-4.17	< .001

Note. High scores indicate low mobility
*R Square change significant with a p-value < .001

Appendix A.II Multiple linear regression models to predict IADL at follow-up with the original frailty index

n = 683	Step 1 Adjusted R^2 = 0.738*				Step 2 Adjusted R^2 = 0.743*				Step 3 Adjusted R^2 = 0.756*			
	B (*SE*)	*β*	*t*	*p*-value	*B* (*SE*)	*β*	*t*	*p*-value	*B* (*SE*)	*β*	*t*	*p*-value
Gender (female)	0.09 (0.17)	0.01	0.55	.55	0.21 (0.17)	0.02	1.21	.22	0.19 (0.17)	0.02	1.12	.26
Age (years)	-0.05 (0.01)	-0.08	-3.85	< .001	-0.03 (0.01)	-0.06	-2.61	.01	-0.03 (0.01)	-0.05	-2.38	.02
Down syndrome	-0.36 (0.26)	-0.03	-1.38	.17	-0.40 (0.26)	-0.03	-1.52	.13	-0.38 (0.26)	-0.03	-1.49	.14
Level of ID												
Moderate	-1.10 (0.24)	-0.13	-4.57	< .001	-1.11 (0.24)	-0.13	-4.62	< .001	-1.07 (0.23)	-0.12	-4.58	< .001
Severe	-1.39 (0.31)	-0.14	-4.48	< .001	-1.21 (0.31)	-0.13	-3.87	< .001	-1.46 (0.31)	-0.15	-4.76	< .001
IADL Baseline	0.70 (0.02)	0.77	29.8	< .001	0.65 (0.03)	0.72	24.5	< .001	0.85 (0.04)	0.93	20.3	< .001
FI score (0-100)	-	-	-	-	-0.21 (0.01)	-0.10	-3.62	< .001	0.09 (0.02)	0.24	3.86	< .001
Interaction IADL-FI	-	-	-	-	-	-	-	-	-0.01 (0.002)	-0.29	-5.99	< .001

Note. Low scores indicate low IADL capacities
**R* Square change significant with a *p*-value < .001


Family
Appetite
Walking stairs
Healthy diet
Energetic
Blood glucose
Independent
Bone density
GP visits
Memory
Stable weight
Balance
Friends
Muscle
Happiness
Strength

Chapter 7

The use of a frailty index to predict adverse health outcomes in people with intellectual disabilities

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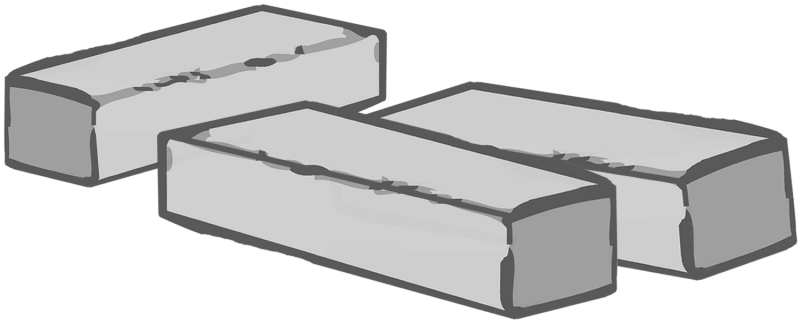

ABSTRACT

Frailty in older people can be seen as the increased likelihood of future negative health outcomes. Lifelong disabilities in people with intellectual disabilities (ID) may not only influence their frailty status but also the consequences. Here, we report the relation between frailty and adverse health outcomes in older people with ID (50 years and over). In a prospective population based study, frailty was measured at baseline with a frailty index in 982 older adults with ID (≥50yr). Information on negative health outcomes (falls, fractures, hospitalization, increased medication use, and comorbid conditions) was collected at baseline and after a three-year follow-up period. Odds ratios for negative health outcomes were estimated with the frailty index, adjusted for gender, age, level of ID, Down syndrome and baseline adverse health condition. The frailty index was related to an increased risk of higher medication use and several comorbid conditions, but not to falls, fractures and hospitalization. Frailty at baseline was related to negative health outcomes three years later in older people with ID, but to a lesser extent than found in the general population.

Key words: People with ID, frailty, adverse health outcomes, falls, comorbid conditions

INTRODUCTION

As the life span of people with intellectual disabilities (ID) increases [1, 2], age-related frailty will likely become a major problem for individuals, caregivers and health care facilities, as has been seen in the general population [3]. Nevertheless, there is no information on the causes, development and consequences of frailty in people with ID [4]. Frailty has been described as "a dynamic state affecting an individual who experiences losses in one or more domains of human functioning (physical, psychological, social), which is caused by the influence of a range of variables and which increases the risk of adverse outcomes" [5, p. 342]. Frailty can be measured with different instruments, based on different operationalizations. Previously, we measured frailty in people with ID using a frailty index [6]. A frailty index is a method that focuses on the quantity, rather than on the nature of health problems: the more problems are present in an individual, the more frail he or she is [7, 8]. It captures physical, psychological and social health and has been shown to predict negative health outcomes in several clinical and community-dwelling populations [3, 7, 9]. People with ID showed high frailty index scores compared to the general population of the same age [6, 10].

Frail individuals in the general population are more likely to fall, have fractures, get admitted to a hospital, and develop more chronic diseases including osteoarthritis, depressive symptoms, coronary heart disease, diabetes mellitus and chronic lower respiratory tract disease [11-15]. These consequences may be different for older people with ID due to their lifelong disabilities. For example, lifelong mobility limitations and low bone quality [16] may influence the relation between frailty and falls and fractures. The high levels of comorbidity [17] may lead to an increased risk of hospital admission. Contrary, the care and support provided at the care organizations may limit the necessity of hospitalization, specifically for those with severe behavioral problems or profound levels of ID. Also, gastrointestinal, neurological, sleep, and musculoskeletal problems, epilepsy, and visual and hearing impairments can be lifelong, start at a younger age, or are more prevalent compared to the general population, leading to early interventions and possibly habituation [18-22]. As a result, the relation between frailty and morbid conditions may be less strong than found in the general public. To explore how frailty is related with health problems, we used prospective data from the Healthy Aging and Intellectual Disability study (HA-ID) [23]. The main aim of our study was to analyze the ability of the frailty index to predict the occurrence of falls, fractures, hospitalization, chronic medication use, and comorbid conditions over three years.

METHODS

Study design and participants

This study was part of the 'Healthy aging and intellectual disabilities' study (HA-ID) [23]. This observational study collected information on the general health status of older people with ID using formal care in the Netherlands. All clients of the care organizations aged 50 years and over were invited to participate (N = 2322). Those capable of understanding the available information signed the consent form themselves. Legal representatives were approached for those who were not able to make this decision. Written informed consent was provided for 1050 clients, forming a nearly representative study population for the Dutch population of older adults (aged 50 and above) with ID who use formal care, albeit with a slight underrepresentation of men, people aged 80 and over, and people living independently. Baseline data collection took place between February 2009 and July 2010. The Medical Ethics Committee of the Erasmus Medical Center Rotterdam (MEC-2008-234) and the ethics committees of the participating care organizations approved this study. Details about recruitment, design, inclusion criteria, and representativeness of the HA-ID study have been published elsewhere [23]. Three years after baseline, follow-up data were collected between February 2012 and August 2013. The participants, or their legal representatives, who still received care of the care organisations were asked again to provide written informed consent for the follow-up study. The follow-up study was approved by the Medical Ethics Committee of the Erasmus Medical Center Rotterdam (MEC-2011-309) and the ethics committees of the participating care organizations.

Data collection

Details about the baseline data collection have been described elsewhere [23]. In short, baseline characteristics were retrieved from the administrative systems of the care organizations. Measurements were conducted within three main themes (1) physical activity and fitness, (2) nutrition and nutritional state, and (3) mood and anxiety. The broad spectrum of data collection included anthropometric measurements, physical fitness tests, psychiatric assessment, and laboratory tests in addition to file records (e.g. medical file). Level of ID was obtained from the records of behavioral therapists and psychologists. The presence of Down syndrome was obtained from medical files. Mobility limitations were categorized as no help, walking-aid or wheelchair use. Follow-up data were collected three years after baseline without client interference.

Falls and fractures

At baseline and follow-up, professional caregivers provided information on how often the participants fell in the past three months (not fallen, 1-2 falls, 3 -5 falls, 6-10 falls, 11

falls or more). At baseline, data on fractures having occurred over the last 5 years were requested from the physician. For the follow-up measurement, data on fractures having occurred over the last three years were requested from both the professional caregiver and the physician.

General hospital admission

Occurrences of hospitalization (no, once, twice, three times, more than three times) were collected via the personal caregiver at baseline (preceding year) and via physicians at follow-up (preceding three years). Hospitalization was defined as an admission of at least one day in a general hospital. Procedures in outpatient clinics were not taken into account. Clients with severe behavioral problems, or clients who received a high level of care from the care organization, were thought to be less likely to be admitted for a hospital stay. Therefore, an adjustment was made for participants who received intensive support or intensive support and regulation of behavior. This classification was based on long term care indications under the Dutch Act on Exceptional Medical Expenses (AWBZ)- a law that finances specialized long-term care.

Total number of used medicines

Current medication use was requested at baseline and follow-up from the physician or pharmacy. Total medication count included the total number of medicines taken at the point of measurement. Vitamins, minerals, basic skin creams (e.g Vaseline), or anti-dandruff shampoo prescribed by the physician, were not counted as medicines, with the exception of vitamin D and calcium tablets.

Comorbid conditions

Information on conditions (cardiovascular, respiratory, gastrointestinal tract, endocrine system, neurological, sleep, psychiatric, musculoskeletal, and hearing and vision), were requested from the attending physician. Additionally, the anatomical therapeutic chemical (ATC) classification system [24] was used to identify problems based on medication use, according to the organ or system they act on. Both diagnosis and ATC-code were used to classify participants as having a problem, disease or condition regarding that organ systems (Table 1). Although originally included in the ATC classification, 'antiparasitic products, insecticides and repellents' and 'antineoplatic and immunomodulating agents' were not included in the analysis because less than 1% of the participants used medication in these groups. Removing all morbidity items from the index could result in an unbalanced index. Therefore we did not test whether the frailty index was able to predict an increase in comorbidity (e.g. all comorbid conditions together).

Table 1. Classification comorbid conditions according to the anatomical therapeutic chemical classification (ATC) system and diagnosis by the physician

Anatomical main group	Diagnosis physician	First level of the ATC code
Alimentary tract and metabolism	gastroesophageal reflux disease, peptic ulcer, constipation, dysphagia, diabetes mellitus	A
Blood and blood forming organs	-	B
Cardiovascular system	heart failure, valve abnormalities, coronary heart disease, heart rate disorder, hypertension, hypercholesterolemia, intermittent claudication, stroke	C
Dermatologicals	-	D
Genitourinary system and sex hormones	-	G
Systemic hormonal preparations, excl. sex hormones and insulins	hypothyroidism, hyperthyroidism	H
Anti-infectives for systemic use	-	J
Musculoskeletal system	scoliosis, rheumatism, arthrosis, osteoporosis, spasticity	M
Nervous system	dementia, epilepsy, Parkinson's disease, sleep disorders, depression, anxiety, psychosis	N
Respiratory system	asthma, COPD, sleep apnea	R
Sensory organs	vision or hearing impairment	S

Note. The anatomical main groups are reproduced from the WHO collaborating Centre for Drugs Statistics Methodology, ATC/DDD Index 2014

The frailty index

We previously developed a frailty index using 51 deficits from the baseline measurements of the HA-ID study. Together, these deficits covered psychological, physical and cognitive health aspects. All deficits were carefully selected and fulfilled the criteria developed by Searle et al. [25]. Each deficit has to be health-related and increase with age, and the deficit should not saturate too early (no ceiling effects). All deficits were re-coded to a score between 0 (deficit absent) and 1 (deficit present). A frailty index 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). Detailed information on the selection, diagnostic methods, deficits, and used cutoff values have been reported elsewhere [6]. To examine the associations of frailty with the different adverse health outcomes, the index was rescored to exclude items that concerned that health outcome. For example, if the frailty index was correlated to falls, the fall deficit was excluded from the original index, and if the frailty index was correlated to the cardiovascular system, all deficits regarding cardiovascular conditions were excluded from the original index.

Statistical analysis

First, characteristics of the study population were assessed with a non-response analysis. Participants who provided informed consent for the follow-up study, and had medical information available at both baseline and follow-up were included in the study. Differences between participants included and excluded in the follow-up study were assessed using Pearson-chi-square tests for categorical variables and *t*-tests for continuous variables. Second, linear regression (number of medication) or logistic regression analysis (falls [one or more], fractures [one or more], hospitalization [one or more], and comorbid conditions [as defined in Table 1]) were used to analyze the association between the baseline frailty index score and negative health outcomes three years later. To aid interpretation, the frailty index score was multiplied by 100. After univariate analysis, multivariate analyses were performed, adjusting for gender (male = 0, female = 1), age (years), level of ID, and Down syndrome. Level of ID was classified in three categories (borderline/mild, moderate, severe/profound). Subsequently, dummy variables were created for level of ID and borderline/mild was used as the comparison category. Dummy variables were also created to compare the participants with Down syndrome to those without Down syndrome and those without information on Down syndrome. In order to assess the increased risk for a negative health outcome, all models were adjusted for the negative health outcome at baseline. In addition, the model to predict falls was adjusted for mobility (no help, walking-aid, wheelchair) and the epilepsy, and the model to predict hospitalization was adjusted for participants who received intensive support or intensive support and regulation of behavior. The percentage of the explained variance was represented by the Nagelkerke R^2 (logistic regression analysis) or the adjusted R^2 (linear regression analyses) statistic. A Bonferroni correction was applied to the morbid conditions (0.05/11). All statistical analyses were performed using SPSS version 21.0 (SPSS, Inc., Chicago, IL).

RESULTS

Characteristics of the study population

At baseline, 1050 participants had been included in the HA-ID study. After 3 years of follow-up, 19 moved and 120 died. The remaining 911 participants were invited for participation, of whom 763 provided informed consent. At follow-up, data from the medical records were provided for 693 participants, of which 61 did not have baseline information available, leaving 632 participants in the final analysis. Those who dropped out, more often had a borderline or mild intellectual disability, lived more often in the community, had more often been hospitalized in the preceding year, took on average more medicines, and showed on average higher frailty index scores at baseline (Table 2).

Table 2. Characteristics at baseline

Characteristics		*n* (%)				
			Follow-up			
		Baseline *n* = 1050	Included *n* = 632	Dropped out *n* = 418	X^2/t	*p*-value
Gender	Male	539 (51%)	316 (50%)	223 (53%)	1.13	.29
	Female	511 (49%)	316 (50%)	195 (47%)		
Age (years)	50-59	493 (47%)	310 (49%)	183 (44%)	4.88	.30
	60-69	370 (35%)	220 (35%)	150 (36%)		
	70-79	162 (15%)	90 (14%)	72 (17%)		
	80+	25 (2.4%)	12 (1.9%)	13 (3.1%)		
Level of ID	Borderline	31 (3.0%)	14 (2.2%)	17 (4.1%)	24.1	< .001
	Mild	223 (21%)	113 (18%)	110 (26%)		
	Moderate	506 (48%)	312 (49%)	194 (46%)		
	Severe	172 (16%)	125 (20%)	47(11%)		
	Profound	91 (8.7%)	60 (9.5%)	31 (7.4%)		
	Unknown	27 (2.6%)	8 (1.3%)	19 (4.5%)		
Down syndrome	No Down syndrome	724 (62%)	514 (81%)	210 (50%)	5.7	.02
	Down syndrome	149 (14%)	91 (14%)	58 (14%)		
	Unknown	177 (24%)	27 (4.3%)	150 (64%)		
Residential status	Central	557 (53%)	385 (61%)	172 (41%)	54.9	< .001
	Community	432 (41%)	236 (37%)	196 (47%)		
	Independent with support	43 (4.1%)	10 (1.6%)	33 (7.9%)		
	With relatives	7 (0.7%)	1 (0.2%)	6 (1.4%)		
	Unknown	11 (1.0%)	0 (0%)	11 (2.6%)		
Falls ≥1 preceding 3 months[1]		233 (24%)	137 (23%)	96 (26%)	1.15	.28
Fractures ≥1 preceding 5 years[2]		78 (8.8%)	58 (9.5%)	20 (7.4%)	1.08	.30
Hospitalization ≥1 preceding year[3]		99 (11%)	49 (9.0%)	50 (15%)	7.63	.006
Number of medicines (mean [*SD*][4]		4.1 (3.1)	3.9 (2.8)	4.5 (3.6)	3.7	.007
Frailty index (mean [*SD*][5]		0.27 (0.13)	0.26 (0.12)	0.29 (0.14)	3.5	< .001

Note. SD = Standard Deviation
[1] Falls at baseline were missing for 69 participants, 26 were included, 43 dropped out
[2] Fractures at baseline were missing for 168 participants, 22 were included,146 dropped out
[3] Hospitalization was missing for 175 participants, 88 were included, 87 dropped out
[4] Number of medicines was missing for 127, zero were included, 127 dropped out
[5] Frailty index unknown for 68 participants from the baseline participants, 22 were included, 46 dropped out

Frailty and adverse health outcomes

For 689 participants baseline and follow-up data on falls were known. Of these participants, 170 (25%) reported falls at follow-up. The frailty index at baseline was not related with falls three years later (Table 3). Those with reported falls at baseline (*OR* = 3.5, *p*

< .001), people with epilepsy (*OR* = 1.9, *p* = .013) and people without Down syndrome (*OR* = 2.1, *p* = .04) were more likely to report falls at follow-up. For 651 participants, fractures at baseline and follow-up were known. Ninety-seven (15%) participants reported to have at least one fracture during the follow-up period. The frailty index at baseline was not related with fractures during the follow-up period (Table 3). The only variables significantly associated with an increased fracture risk were being female (*OR* = 1.84, *p* = .013) and previous fractures (*OR* = 4.56, *p* < .001). For 579 participants, information on hospitalization was known at baseline and follow-up. Over three years, 114 (20%) of the participants were hospitalized at least once. Participants with a high frailty index at baseline had no statistically significant increase in their risk for hospitalization (Table 3). Higher age predicted hospitalization significantly (*OR* = 1.03, *p* = .028). At follow-up, participants took on average 1.5 (*SD* = 2.8) more medicines than at baseline. The frailty index was related with the total number of medicines three years later (*p* < .001). Also, participants with high frailty index scores tended to increase their number of medicines during the follow-up period (*B* = 0.07, *p* < .001; Table 3).

Table 3. Three-year outcomes associated with the frailty index

Outcome	*n* (events)	model	*OR/B* (95%*CI*)	*p*-value	R^2
Falls	597 (148)	Unadjusted	1.01 (0.99-1.02)	.23	0.004
		Adjusted*	1.01 (0.98-1.03)	.54	0.15[2,3,4]
Fractures	617 (97)	Unadjusted	1.00 (0.98-1.02)	.62	< 0.01
		Adjusted*	0.99 (0.97-1.02)	.32	0.09[1,3]
Hospitalization	540 (114)	Unadjusted	1.01 (0.99-1.03)	.38	< 0.01
		Adjusted*	1.01 (0.99-1.03)	.49	0.03
Medication use	601 (NA)	Unadjusted	**0.14 (0.12-0.16)**	**< .001**	**0.21**
		Adjusted*	**0.07 (0.04-0.09)**	**< .001**	**0.44[3]**

Note. The frailty index was recomposed without the outcome of interest and multiplied by 100. *OR* = Odds Ratio, *B* = Beta, events = number of events at follow-up.

*Adjusted for gender, age, level of ID, presence of Down syndrome, outcome at baseline.
Other factors significantly associated with the health outcome in the adjusted model: [1] being female, [2] absence of Down syndrome, [3] outcome at baseline, [4] the presence of epilepsy

Overall, there was an increase in comorbid conditions within the follow-up period (Figure 1). Most were related to the alimentary tract and metabolism group (baseline 73%, follow-up 79%), followed by the nervous system (baseline 63%, follow-up 72%) and the sensory organs (baseline 55%, follow-up 60%). After adjusting for the baseline characteristics and the comorbid condition at baseline, a high frailty index score was related to comorbid conditions in the alimentary tract & metabolism, dermatologicals, systemetic hormonal preparations, and nervous system, but after a Bonferroni correction only the relation with the alimentary tract & metabolism remained statically significant (Table 4).

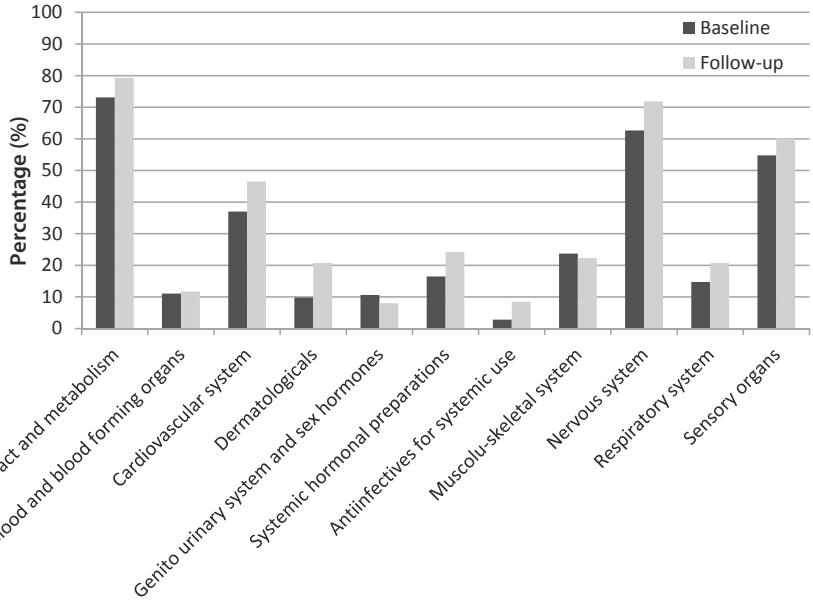

Figure 1. percentage of morbidities among participants of the HA-ID study at baseline (black bars) and after 3-year follow-up (grey bars).

DISCUSSION

We studied the relation between frailty (defined as the accumulation of deficits) and negative health outcomes in adults with ID, aged 50 years and over, during a follow-up of three years. Those with high frailty index scores at baseline, were more likely to develop new comorbid conditions and to get more medication prescriptions. The proportion of participants who reported falls, fractures or hospitalization at follow-up, was not related to the frailty index.

Falls, especially if accompanied with a fracture, can be considered negative health outcomes and are expected to be related to frailty. Nevertheless, in the general population, there is still inconsistency about the association between frailty and falls. Some study results showed a correlation [26-28], whereas others did not [29, 30]. We did not find a relation between high frailty index scores and an increased risk of falls and fractures. A possible explanation for this result is that the underlying risk factors related to falls could be different in people with ID. Failure in overall health generally starts with the highest order functions, including walking [8]. This line of thinking is supported by the finding that physical fitness is related to falls in the general population [31, 32]. Previous results from the HA-ID study showed however that physical fitness (i.e. gait

Table 4. Logistic regression models to predict comorbidity at follow-up with a frailty index

Anatomical main group *n* = 602	*n* (events)	model	*OR* (*95%CI*)	*p*-value	R^2
Alimentary tract and metabolism	602 (476)	**Unadjusted**	**1.09 (1.07-1.17)**	**< .001^**	**0.17**
		Adjusted*	**1.06 (1.03-1.09)**	**< .001^**	**0.41[7]**
Blood and blood forming organs	602 (84)	**Unadjusted**	**1.05 (1.03-1.07)**	**< .001^**	**0.07**
		Adjusted*	1.02 (0.99-1.05)	.25	0.31[5,7]
Cardiovascular system	602 (277)	Unadjusted	1.01 (0.99-1.02)	.34	0.00
		Adjusted*	1.01 (0.99-1.03)	.47	0.54[6,7]
Dermatologicals	602 (127)	**Unadjusted**	**1.02 (1.01-1.04)**	**.009**	**0.02**
		Adjusted*	**1.03 (1.01-1.05)**	**.011**	**0.08[4,7]**
Genito urinary system and sex hormones	602 (51)	Unadjusted	1.01 (0.99-1.04)	.29	0.00
		Adjusted*	1.00 (0.97-1.04)	.89	0.44[7]
Systemic hormonal preparations	602 (144)	**Unadjusted**	**1.03 (1.02-1.05)**	**< .001^**	**0.04**
		Adjusted*	**1.04 (1.01-1.07)**	**.017**	**0.68[3,7]**
Anti infectives for systemic use	602 (51)	**Unadjusted**	**1.02 (1.00-1.05)**	**.045**	**0.02**
		Adjusted*	1.02 (0.99-1.05)	.20	0.06[7]
Musculo-skeletal system	602 (135)	**Unadjusted**	**1.04 (1.02-1.06)**	**< .001^**	**0.06**
		Adjusted*	1.01 (0.99-1.04)	.33	0.44[2]
Nervous system	602 (432)	**Unadjusted**	**1.07 (1.05-1.09)**	**< .001^**	**0.13**
		Adjusted*	**1.04 (1.01-1.07)**	**.007**	**0.47[7]**
Respiratory system	602 (128)	**Unadjusted**	**1.02 (1.00-1.04)**	**.029**	**0.01**
		Adjusted*	1.02 (1.00-1.05)	.086	0.42[4,7]
Sensory organs	602 (360)	**Unadjusted**	**1.03 (1.01-1.04)**	**< .001^**	**0.03**
		Adjusted*	1.00 (0.98-1.02)	.86	0.24[1,3,5,7]

Note. The frailty index was recomposed without the mentioned diseases or conditions, which are included in the original frailty index, events = number of comorbidities at follow-up.
*Adjusted for gender, age, level of ID, Down syndrome, and baseline morbid condition.
^Significant after Bonferroni correction ($p < .05/11 = .005$)
Other factors significantly associated with the health outcome in the adjusted model: [1] increased age, [2] decreased age, [3] presence of Down syndrome, [4] absence of Down syndrome, [5] more severe level of ID, [6] less severe levels of ID, [7] baseline morbid condition.

speed, strength, balance) was not related to falls in people with ID [33]. Furthermore, frailty is generally related to an age-related decline in health. Since falls, in the general population, increase with age, this contributes to the explanation that age-related frailty is associated to increased fall risk. In this study we did not observe an increase in falls with age. Also, the explained variance of the model was low (explained variance = 13%) and mainly related to previous falls, indicating that other factors, such as epilepsy, visual deficits, behavioral problems, and polypharmacy may be more important to predict falls in people with ID [34-38]. Nevertheless, our results need to be interpreted with caution since the used measurements may have limited the accuracy of the association. We requested falls over the last three months, which is subject to problems in recall that could

have been diminished with prospective data collection (for example falls records) [39]. Also, falls were only requested at follow-up, so we do not know the complete occurrence of falls between baseline and follow-up. In addition, we were unable to classify recurrent fallers (> 1 falls) in a separate group, due to the structure of the questionnaire used in our study.

Frailty was not associated with hospital admission during the follow-up period. This result is different from several studies in the general population showing that frailty is associated with hospitalization [12, 28, 40, 41] and with a longer length of hospital stay [42]. There are several possible explanations for our results. Conditions that normally require specialist services may have been undiagnosed [43, 44]. In addition, family, personal caregivers or hospital staff may have decided that hospital treatment was not in the best interest for the client [45, 46]. Despite the attempt to adjust for this, we did not find an increased risk for hospitalizations in frail participants.

Frailty was associated with the number of used medicines and with an increased likelihood of increasing medication use, which is in line with results from the general population [47, 48]. Multiple drug use can cause severe side effects, drug-drug interactions and drug-nutrient interactions [49, 50]. The high levels of comorbidity [17, 51] and frequent prescription errors found in people with ID [52], raises concerns about the high medication consumption in frail people. Age-related physiological changes related with drug absorption, metabolism, distribution and excretion are possibly more extreme in frail individuals [53]. Potentially, this increases the risk of adverse drug reactions, and contributes to the frailty-related deterioration in health. Attempts at diminishing polypharmacy in people with ID applying systematic medication reviews is therefore recommended.

At follow-up, frailty was associated with most comorbid conditions, which has also been found in the general population [3, 14, 15, 54]. Even so, after adjusting for the condition at baseline (i.e. new comorbidities), the relation was only slight or non-significant. A longer follow-up period may be required to monitor the development of new diseases and thereby increase the power of the analysis. Because information was obtained through the medical files, undiagnosed conditions may have led to an underestimation of this association.

The comprehensive set of outcome measurements, collected via the physicians and personal caregivers, and the prospective design are the major strengths of our study. Our study has also several limitations. First, the results are influenced by specific dropout. The 418 participants who were not included in the main analysis were on average frailer,

took more medication, and had more often be hospitalized prior to the study. Almost 30% (n = 120) of the dropout was caused by the death of the participants. Previously we showed that survival was associated with higher frailty levels, more profound level of ID, higher age and the presence of Down syndrome [55]. Also, prior to death, health condition may deteriorate, leading to an underestimation of the association between frailty and health conditions. Similarly, deterioration in health could have been a reason to refuse participation in the follow-up study. Furthermore, participants living in the community, who received medical care from a general practitioner instead of a specialized ID physician, were more likely to drop out. The specific dropout limits generalization of the results to the complete older ID population. Second, frailty was only measured once. It has been shown that frailty is a dynamic process in which people can either become worse or recover from their (pre-)frail state [56, 57]. Life events [58], mood swings, and temporary illness may momentarily influence the frailty status. It is unknown how trajectories of frailty may be a phenomenon in this population and how these trajectories influence the association between frailty and negative health outcomes.

In conclusion, we demonstrated that frailty, defined as deficit accumulation, is related to negative health outcomes in people with ID, but to a lesser extent than found in the general population. The frailty index is not suitable as a tool to predict admission to general hospitals and falls in this group. The low explained variance of the models implies that specific (individual) problems may be more important risk factors than a measure of general health, such as the frailty index. The frailty index did predict an increase in medication use. This confirms that frailty is related to decreased health status. Previously, we demonstrated that frailty is common in this population, starts at a relatively young age and is related to mortality, increased care intensity, and deterioration in independence and mobility [6, 55, 59, 60]. Together, these results show that frailty has serious consequences in older people with ID, and effective interventions are required to limit this burden. In addition, future research should focus on potential for clinical application of the frailty index, i.e. on an individual level. A clinically applicable frailty index could be used to recognize frail individuals and to evaluate interventions.

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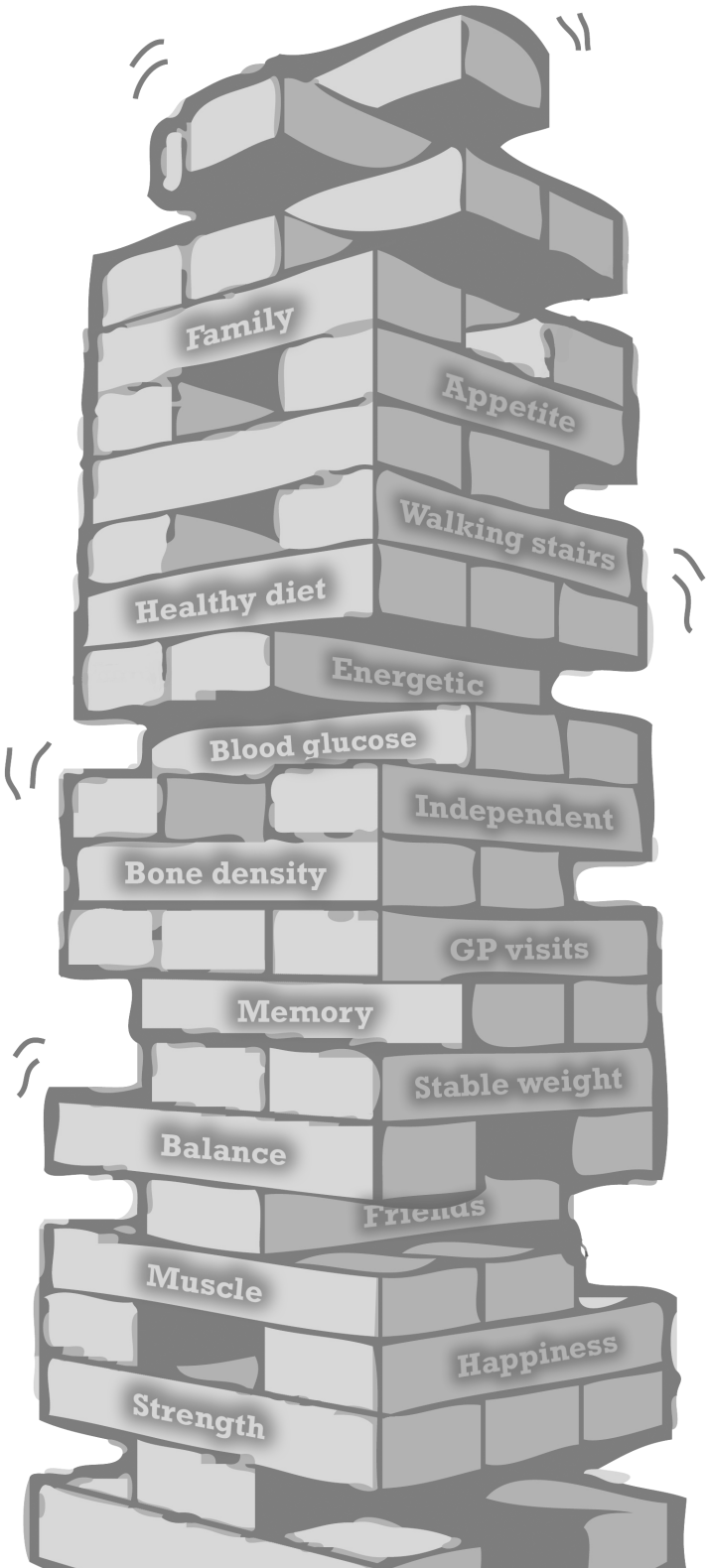
Family
Appetite
Walking stairs
Healthy diet
Energetic
Blood glucose
Independent
Bone density
GP visits
Memory
Stable weight
Balance
Friends
Muscle
Happiness
Strength

Chapter 8

The impact of frailty on care intensity in older people with intellectual disabilities

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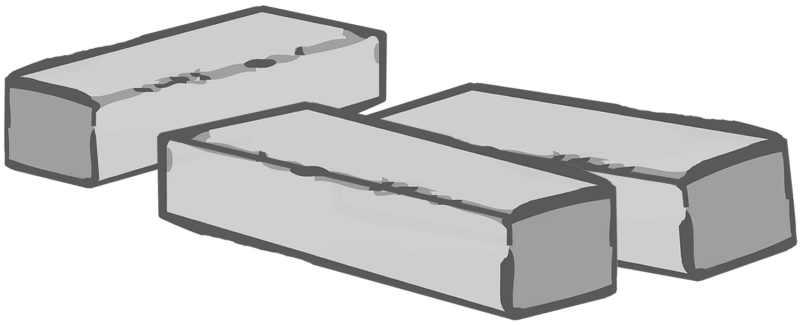
Research in Developmental Disabilities, 2014. 35(12): p. 3455-3461



ABSTRACT

Frailty appears to develop earlier and is more severe in people with intellectual disabilities compared to the general population. The high prevalence of frailty may lead to an increase in care intensity and associated health care costs. Therefore a longitudinal observational study was conducted to determine the effect of frailty on care intensity. The association between frailty and care intensity at baseline and follow-up (3 years later) was assessed. Furthermore, the ability of the frailty index to predict an increase in care intensity after three years was evaluated. This study was part of the Dutch 'Healthy ageing and intellectual disabilities' (HA-ID) study. Frailty was measured at baseline with a frailty index that included 51 health-and age-related deficits. For all participants information on care intensity in seven steps was available, based on long term care indications under the Act on Exceptional Medical Expenses (AWBZ)- a law that finances specialized long-term care. 676 participants (50 years and over) with ID were included in the final analysis. In 26% of the participants, care intensity had increased during the follow-up period. Increased care during the follow-up was related to a high frailty index score at baseline, independent of gender, age, level of ID and the presence of Down syndrome ($p = .003$). After exclusion of ADL and IADL items, the frailty index remained significantly related with increasing care intensity during follow-up ($p = .007$). Our results underline that screening instruments for early detection of frailty and effective interventions are required to limit the burden of frailty for individuals and caregivers, but also to limit health care utilization.

Key words: People with ID, frailty, frailty index, care intensity

INTRODUCTION

Improved quality of residential and healthcare has increased the life expectancy of people with intellectual disabilities (ID) [1, 2]. Much is still unknown about the effects of aging on health and health care needs in this older population. In recent years, the Healthy Ageing and Intellectual Disability (HA-ID) study provided information on a broad spectrum of health aspects and quality of life in older people with ID [3]. Among many results, it was observed that frailty develops earlier and is more severe compared to the general population [4, 5]. The high prevalence of frailty may lead to an increase in care intensity, which was evaluated in this study.

The operationalization of frailty remains controversial and various models for measuring frailty have been reported [6]. In general, researchers agree that frailty is a state in which older people are more vulnerable to negative health outcomes compared to others of the same age [7]. One frequently used operationalization is the frailty index, which is based on the non-specific accumulation of deficits [8]. Deficits can be symptoms, signs, diseases, disabilities or laboratory measurements as long as they fulfill certain criteria (e.g. health and age related) [9]. The frailty index is a robust method, showing validity across diverse clinical and community dwelling populations, and has been adapted as a useful measure to evaluate health status in older people [6, 10]. We have argued that the frailty index is a suitable measure for the ID population [5, 11] and we have confirmed its ability to predict adverse health outcome in an older ID population [12, 13].

In the general population, it has been shown that frailty predicts the transition to long-term or higher care facilities [14-16]. In people with ID, this relation has not yet been evaluated. Increase of care intensity is associated with care costs, and insight into the financial consequences of frailty can help to raise awareness towards policy makers. Our main objective was to study the predictive value of frailty for increase of intensity of care during a 3-year follow-up period. Furthermore, we provided an overview of the characteristics that are associated with intensity of care (e.g. multimorbidity, level of dependence, behavioral problems).

METHODS

Study design and participants

The HA-ID study is a longitudinal study of older adults (50 years and over) with ID [3], executed in a consortium of three large formal ID service providers in the Netherlands. These service providers offered low to high level of care and support to people with

ID. The HA-ID aimed to study the health status of people with ID within three themes: (1) physical activity and fitness, (2) nutrition and nutritional state, and (3) mood and anxiety. Baseline data collection took place between February 2009 and July 2010. Ethical clearance was provided by the Medical Ethics Committee of the Erasmus Medical Center Rotterdam (MEC 2008-234) and by the ethics committees of the participating care organizations. All clients aged 50 years and over who received care from one of the participating care organizations were invited (N = 2322) to participate. Eventually 1050 clients, or their legal representatives, provided informed consent, forming a nearly representative study population for the Dutch population of older adults (aged 50 and above) with ID who use formal care, albeit with a slight underrepresentation of men, people aged 80 and over, and people living independently. A full description of the design, recruitment, representativeness, and diagnostic methods has been published elsewhere [3]. A second wave of measurements was collected three years after baseline (between February 2012 and August 2013). The follow-up study was approved by the Medical Ethics Committee of the Erasmus Medical Center Rotterdam (MEC-2011-309) and the ethics committees of the participating care organizations. The participants, or their legal representatives, who still received care from one of the care organisations, were asked again to provide written informed consent for the follow-up study.

OUTCOME MEASURES

Client characteristics

Information on age, gender and residential status was collected through the care provider services. Residential status was categorised as centralized setting, community-based setting and living independently with ambulatory support. Level of ID was obtained from the scores of psychologists or test assistants, who determined level of ID from available IQ tests, Vineland scores and social emotional development. The presence of Down syndrome was retrieved from the medical files. Care intensity was based on a strictly standardized professional estimation of the required level of care and support and, if necessary, on behavioral problems (see section 2.2.2). Information on care and support related items were therefore also provided. Multimorbidity was defined using a list of 20 chronic conditions, assessed through physical assessment or obtained from medical files [17]. To enable comparison with other studies, multimorbidity was defined as the presence of ≥2 and ≥4 comorbid conditions. Severe behavioral problems were defined as the presence of automutilation and/or aggressive behavior (verbal or physical). To determine the levels of dependence, questionnaires on activities of daily living (ADL) and instrumental activities of daily living (IADL) were completed by professional caregivers. ADL was assessed with the Barthel Index [18]. It consisted of 10

items (feeding, bathing, grooming, dressing, bowels, bladder, toilet use, transfers [bed to chair and back], mobility on level surfaces, and mobility on stairs) with two to four answer categories. The total ADL score ranged from 0 (completely dependent) to 20 (completely independent). The Lawton scale was used to measure IADL [19]. The Lawton scale consisted of eight items (telephone use, groceries, food preparation, housekeeping, laundry, transportation, medication and finances) with three answer categories (not able, able with support, independent). The total score ranged from 8 (completely dependent) to 24 (completely independent).

Care intensity

Information on care intensity was available for all participants, based on long term care indications under the Dutch Act on Exceptional Medical Expenses (AWBZ)- a law that finances specialized long-term care. For the ID population needing chronic care or support, eight different care intensity packages (in Dutch = Zorg Zwaarte Pakket [ZZP]) exist [20]. Each package is based on how many hours of care per week are required and what kind of care and support is necessary. Package 1 offers minimal support while package 8 offers all-day support and nursing. ZZP 1-ZZP 5 and ZZP 8 are ordinally related in terms of care and financing. ZZP 6 and ZZP 7 are specific packages for subgroups needing specialized care focused on behavioral problems (Table 1). At the time the baseline measurements took place, ZZP 8 did not yet exist. A transition from ZZP 5 to ZZP 8 during the follow-up period was therefore not always related to increase of care need that period.

Table 1. ZZP classification in intellectual disability care (College voor Zorgverzekeringen, 2013; Per Saldo 2012)

ZZP	Content ZZP classification	Allocated annual budget (2013)[a]
ZZP 1 VG	Residence with minimal support	€ 30768,-
ZZP 2 VG	Residence with support	€ 36671,-
ZZP 3 VG	Residence with support and care	€ 42040,-
ZZP 4 VG	Residence with support and intensive care	€ 46286,-
ZZP 5 VG	Residence with intensive support and intensive care	€ 59415,-
ZZP 6 VG	Residence with intensive support, care and regulation of behavior	€ 55776,-
ZZP 7 VG	Residence (if necessary enclosed) with very intensive support, care and regulation of behavior	€ 74530,-
ZZP 8 VG	Residence with support and full care and nursing	€ 65509,-

Note. ZZP (in Dutch = Zorg Zwaarte Pakket) are care intensity packages
[a] Gross personal budget per person per year without transport costs

Frailty index

At baseline, frailty was measured with a frailty index, which was developed earlier and has been described in detail elsewhere [5]. In short, the frailty index consists of 51 items from the baseline measurements of the HA-ID study. A standardized procedure was followed to develop the frailty index [9]: all items were (1) related to health, (2) positively associated with age, (3) frequently but not too often present in the population (> 5%, < 80%), and (4) measured in at least 70% of the participants. Furthermore, the items did not correlate too strongly with each other ($r < 0.7$), and together the items covered a range of health problems (physical, psychological and social). All items were recoded between 1 (presence of the deficit) and 0 (absence of the deficit). A frailty index score was calculated taking the number of deficits present, divided by 51, resulting in a score between 0 and 1. In the case of missing data, the deficit was removed from both the numerator and the denominator and the frailty index was calculated with the deficits present (at least 30). ZZP classification highly depends on the level of independence. The level of independence was incorporated in the frailty index via selected questions of the ADL and IADL questionnaires. To estimate the effect of frailty without ADL and IADL items, the two ADL-and the five IADL items, originally included in the frailty index, were excluded for an additional analysis.

Statistical analysis

First, an overview of client characteristics was provided per baseline ZZP category. Descriptives were provided using means and standard deviations or percentages and were analyzed using analysis of variance or the chi-square statistic, respectively. Second, average frailty index scores were calculated per ZZP category at baseline and follow-up with corresponding 95% confidence intervals (*CI*). The Spearman's rho correlation coefficient was calculated for the ZZP categories without behavioral regulation. For the two ZZP categories with behavioral regulation an independent sample *t*-test was performed to test the differences between frailty index scores. Third, the association between frailty and increase of care intensity during the follow-up was evaluated. Increase of care was defined as a higher ZZP at follow-up than at baseline. Only participants that could receive a higher ZZP package were included in this analysis. Hereby, participants classified in ZZP 5 or ZZP 7 at baseline were excluded from this analysis, because they were the highest ZZPs in their respective categories. Logistic regression analysis was used to estimate the risk of increase care after three years. Curve estimation revealed a non-linear association between the frailty index score and increase of care. The exponential model was the best model to fit the observations. Therefore the exponent of the frailty index was used for the logistic regression analysis. In addition to the exponent of the frailty index (to aid interpretation, multiplied by 10), gender, age, Down syndrome and level of ID were incorporated into the model. The other baseline characteristics (e.g. multimorbidity) were

not incorporated because they are part of the frailty index. To illustrate the exponential effect of frailty on increased care intensity, effects of different frailty index score were calculated. The intercept and the regression coefficients from the logistic regression model were used to calculate *OR*s for different frailty index scores. Last, a second logistic regression model was created using the frailty index without ADL and IADL items. Again, the exponent of this frailty index was used, together with gender, age, Down syndrome and the level of ID. Multicollinearity limited incorporation of ADL, IADL and the original frailty index into one model. All statistical analyses were performed using SPSS statistics 20.0 for Windows (SPSS, Inc., Chicago, IL, USA). All tests were two-sided and a *p*-value of less than .05 was considered to be statistically significant.

RESULTS

Descriptive statistics

From the 1050 participants at baseline, 287 were no longer available after three years because of various reasons: participants were deceased ($n = 120$); no longer associated with the service provider ($n = 19$); or did not provide informed consent for the follow-up study ($n = 148$). Of the remaining 763 participants, another 87 were excluded because they only received day care or ambulatory support (no ZZP classification; $n = 22$) or had unknown ZZP classification at baseline or follow-up ($n = 65$). Eventually, 676 participants were included in the analysis. As shown in Table 2, gender, the presence of Down syndrome, level of ID, residential status, mobility, multimorbidity, the presence of severe behavioral problems, ADL, IADL, and the frailty index were associated with care intensity at baseline.

Frailty and care intensity

Figure 1 shows the frailty index score for each level of care with corresponding 95% CI. The packages without behavioral regulation showed a correlation with the frailty index of $r_s = .66$ ($p < .001$) at baseline and $r_s = .73$ at follow-up ($p < .001$). At baseline, no significant different frailty index score was found for ZZP 6 than for ZZP 7, $t(168) = 0.43$, $p = .67$. At follow-up, a slightly higher frailty index score was found for ZZP 7 than for ZZP 6 $t(177) = 1.99$, $p = .048$. At baseline, 366 participants received care in ZZP 1 to ZZP 4 or ZZP 6, this group was included in analyses of increase of care during follow-up. Within this group, 96 (26%) participants were indicated for a higher care package during the follow-up period, which was associated with frailty at baseline (Table 3). With each segment increase (0.1) in the frailty index, the risk for a higher care intensity at follow-up increased exponentially (*OR* = 1.09, $p = .003$; Table 3). For example, an individual with a frailty index of 0.2 had a 1.29 times higher *OR* than an individual with the same charac-

Table 2. Baseline characteristics per ZZP classification group (level of care)

n = 676	ZZP 1 VG *n* = 12	ZZP 2 VG *n* = 28	ZZP 3 VG *n* = 100	ZZP 4 VG *n* = 148	ZZP 5 VG *n* = 210	ZZP 6 VG *n* = 78	ZZP 7 VG *n* = 100	X^2/F	*p*-value
Gender								25.4	< .001
Male	7 (58%)	15 (54%)	46 (46%)	59 (40%)	105 (50%)	57 (73%)	57 (57%)		
Female	5 (42%)	13 (46%)	54 (54%)	89 (60%)	105 (50%)	21 (27%)	43 (43%)		
Age (*SD*)	61.7 (6.2)	60.7 (6.9)	61.4 (7.7)	62.0 (8.1)	61.4 (8.1)	59.5 (6.3)	59.7 (6.5)	1.73	.11
Down syndrome								22.0	< .001
Down syndrome	0 (0%)	0 (0%)	10 (10%)	19 (13%)	46 (22%)	7 (9.0%)	9 (9.0%)		
No Down syndrome	10 (83%)	25 (89%)	71 (71%)	94 (64%)	146 (70%)	62 (80%)	88 (88%)		
Unknown	2 (17%)	3 (11%)	19 (19%)	35 (24%)	18 (8.6%)	9 (12%)	3 (3%)		
Level of ID								230	< .001
Borderline	3 (25%)	1 (3.6%)	6 (6.0%)	4 (2.7%)	1 (0.5%)	0 (0%)	0 (0%)		
Mild	7 (58%)	15 (54%)	37 (37%)	26 (18%)	14 (6.7%)	14 (18%)	13 (13%)		
Moderate	2 (17%)	12 (43%)	55 (55%)	98 (66%)	82 (39%)	41 (53%)	45 (45%)		
Severe	0 (0%)	0 (0%)	2 (2.0%)	15 (10%)	71 (34%)	18 (23%)	24 (24%)		
Profound	0 (0%)	0 (0%)	0 (0%)	2 (1.4%)	41 (20%)	3 (3.8%)	15 (15%)		
Unknown	0 (%)	0 (0%)	0 (0%)	3 (2.0%)	1 (0.5%)	2 (2.6%)	3 (3.0%)		
Residential status								289	< .001
Central setting	0 (0%)	0 (0%)	19 (19%)	55 (37%)	162 (77%)	62 (80%)	98 (98%)		
Community-based	10 (83%)	27 (96%)	75 (75%)	93 (63%)	48 (23%)	16 (21%)	2 (2.0%)		
Ambulatory support	2 (17%)	1 (3.6%)	6 (6.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)		

Table 2. Baseline characteristics per ZZP classification group (level of care) (Continued)

n = 676	ZZP 1 VG *n* = 12	ZZP 2 VG *n* = 28	ZZP 3 VG *n* = 100	ZZP 4 VG *n* = 148	ZZP 5 VG *n* = 210	ZZP 6 VG *n* = 78	ZZP 7 VG *n* = 100	X^2/F	*p*-value
Mobility								112	< .001
Independent	12 (100%)	27 (96%)	88 (88%)	109 (74%)	117 (56%)	59 (76%)	90 (90%)		
Walking aid	0 (0%)	0 (0%)	9 (9.0%)	31 (21%)	38 (18%)	11 (14%)	3 (3.0%)		
Wheel chair	0 (0%)	0 (0%)	1(1.0%)	4 (2.7%)	49 (23%)	3 (3.8%)	4 (4.0%)		
Unknown	0 (0%)	1 (3.6%)	2 (2.0%)	4 (2.7%)	6 (2.9%)	5 (6.4%)	3 (3.0%)		
Multimorbidity								93.4	< .001
≥2 morbidities	4 (33%)	15 (54%)	66 (66%)	110 (74%)	192 (91%)	70 (90%)	94 (94%)		
≥4 morbidities	1 (8.3%)	3 (11%)	27 (27%)	47 (32%)	138 (66%)	64 (59%)	61 (61%)		
Number of medicines (*SD*)[a]	2.5 (2.6)	2.6 (3.0)	3.0 (2.8)	3.2 (2.7)	4.4 (2.8)	4.4 (3.1)	4.6 (2.7)	6.21	< .001
Severe behavioral problems								175	< .001
Severe behavioral problems	0 (0%)	2 (7.1%)	14 (14%)	24 (16%)	43 (21%)	40 (51%)	73 (73%)		
No severe behavioral problems	12 (100%)	24 (86%)	80 (80%)	117 (79%)	150 (71%)	34 (44%)	14 (14%)		
Unknown	0 (0%)	2 (7.1%)	6 (6%)	7 (4.7%)	17 (8.1%)	4 (5.1%)	13 (13%)		
ADL (*SD*)[b]	19.0 (1.28)	18.6 (3.84)	17.9 (2.66)	16.1 (3.38)	9.82 (5.53)	15.5 (3.94)	14.2 (4.53)	60.0	< .001
IADL (*SD*)[c]	21.1 (2.35)	18.8 (2.90)	15.8 (5.23)	12.4 (4.07)	8.92 (1.86)	10.8 (3.19)	10.0 (2.82)	86.7	< .001
Frailty index (*SD*)[d]	0.13 (0.07)	0.14 (0.06)	0.18 (0.08)	0.23 (0.09)	0.35 (0.11)	0.26 (0.09)	0.27 (0.10)	53.6	< .001
Increase of care	5 (42%)	10 (36%)	29 (29%)	34 (23%)	78 (37%)	18 (23%)	1 (1.0%)	50.6	< .001

Note. analysis of variance and the chi-square statistic were calculated without the unknown participants, ZZP (in Dutch = Zorg Zwaarte Pakket) are care intensity packages, *SD* = Standard Deviation, ADL = Activities of daily living, IADL = Instrumental activities of daily living.
[a]number of medicines were unknown for 62 participants.
[b]ADL was unknown for 21 participants.
[c]IADL was unknown for 21 participants.
[d]the frailty index was unknown for 24 participants.

teristics but a frailty index of 0.1, whereas an individual with a frailty index of 0.5 had a 2.13 times higher *OR* than an individual with a frailty index of 0.4.

The frailty index without ADL and IADL items was incorporated into a second logistic regression model (data not shown). The exponential frailty index remained a significant contributor for increased care need ($\beta = 0.09$, $SE = 0.03$, Wald = 7.38, $OR = 1.09$, $p = .007$), but the Wald statistics showed a slightly lower relation.

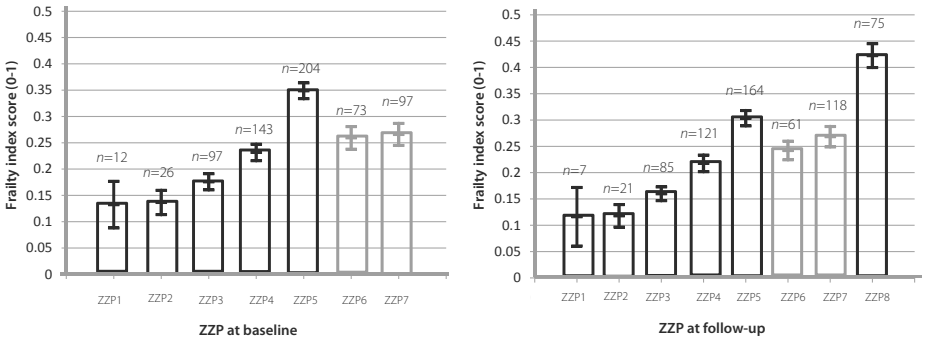


Figure 1. Average frailty index score per care intensity package (ZZP) at baseline and follow-up with corresponding 95% confidence interval. Those classified in ZZP 1-5 and ZZP 8 received increasing care and support (black bars). ZZP 6 and ZZP 7 are specific subgroups, in which support is accompanied by specialized care focused on behavioral problems (grey bars).

Table 3. Logistic regression models to predict increase of care over a 3-year follow-up period in participants classified in ZZP 1 to ZZP 4 or ZZP 6 at baseline

n = 346	Increased care *n* = 90	Stable care *n* = 256	*B* (*SE*)	Wald	*OR*	*p*-value
Frailty index	0.24 (0.10)	0.20 (0.09)	0.08 (0.03)	8.83	1.09	.003
Gender (female)	42 (47%)	131 (51%)	0.20 (0.26)	0.59	1.22	.44
Age	61 (8.4)	61 (7.1)	-0.01 (0.02)	0.21	0.99	.65
Down syndrome	14 (16%)	22 (8.6%)	0.65 (0.40)	2.62	1.92	.11
Level of ID						
Moderate	50 (56%)	150 (59%)	-0.02 (0.30)	0.00	0.98	.95
Severe	17 (19%)	21 (8.2%)	0.57 (0.44)	1.65	1.77	.20

Notes. The exponent of the frailty index was used in the logistic regression model, ZZP (in Dutch = Zorg Zwaarte Pakket) are care intensity packages, *SD* = Standard Deviation, *OR* = Odds Ratio, 20 participants were excluded because they had unknown frailty index scores (*n* = 15) or unknown level of ID (*n* = 5).

DISCUSSION

In this study we have shown that care intensity is strongly linked to health, as measured with public health measures such as multimorbidity, polypharmacy and frailty. Here, we mainly focused on frailty—defined as the accumulation of deficits. People who were frail tended to increase their care intensity three years onwards, independent of the level of ID, age, gender and Down syndrome. This chance increased exponentially with increasing frailty index scores. The frailty index remained a significant contributor for increase of care even when ADL and IADL items were excluded from the frailty index. The care intensity packages used to classify the intensity of care are directly related to health care costs (Table 1).

Studies in the general population show that frailty predicts increased health care utilization as measured by institutionalization within a 1 and 5-year follow-up period [21, 22]. The Tilburg Frailty Indicator score (consisting of physical, psychological and social domains) was, cross-sectionally, correlated with required personal care and nursing care [15]. Frailty has also been related to an increased risk of 'poor health outcome', which included either death or admission to a residential care facility or transfer to a higher level of residential care [21, 23, 24]. Furthermore, a high frailty index score predicted long-term care placement in assisted living residents [16]. In line with these studies, we showed that the frailty index was associated with care utilization and was able to predict an increase in care intensity and associated health care costs in older people with ID.

The major strengths of our study are the prospective design and the relatively large study population. Nevertheless, our results need to be interpreted with caution. First, the association between frailty and increase of care could have been influenced by selective drop-out. Earlier results from the HA-ID study showed that those who did not provide informed consent for the follow-up period, were on average frailer [13]. Over 30% (n = 120) of the dropout was caused by the death of the participants. Prior to death, health support may have increased, leading to an underestimation of the association between frailty and increased care. Similarly, deterioration in health could be a reason to refuse participation in the follow-up study. Second, we used a specific Dutch system to define intensity of care, which makes international comparisons on a level-by-level basis impossible. Nevertheless, the ZZP classification has been centrally implemented by law, is a strictly standardized and professional estimation, is used for all Dutch citizens in need of long-term care and provides a maximum rate for the care expenses. As such, ZZPs provide estimates of care costs. A major disadvantage for this study was the introduction of ZZP 8 during the follow-up period. ZZP 8 was introduced for those who required all-day care and nursing. An unknown number of participants who were in ZZP

5 at baseline, were transferred to ZZP 8 at the time of its introduction, based on their current care needs. For that reason, ZZP 5 had to be excluded from the analysis. Similarly, those classified in ZZP 7 could not receive a higher care package and were also excluded. As a result, those with the highest levels of care had to be excluded, so this analysis was not performed in a representative sample of people with ID. Also, we measured care intensity by ZZP classification only. Although the ZZP packages include a certain amount of paramedical costs, additional health care costs on for example hospitalization and outpatient hospital visits would provide a better overview of the complete effect of frailty on health care costs. Third, our results show that frailty is associated with care intensity and that it predicts increase of care. Even so, it is known that both ZZP classification and frailty are associated with activities of daily living [13, 25]. Frailty remained associated to increased care without ADL and IADL items, but this effect was less strong. Due to multicollinearity, we were unable to estimate the additional effect of frailty on top of the ADL and IADL questionnaires.

In spite of these limitations, we demonstrated that frailty is a burden for the care system. The level of ID and Down syndrome are important predictors for ZZP classification, but frailty was the only tested predictor related to increased care during the follow-up period. The exponential effect of frailty on care need implies that individuals with high frailty index scores are the most likely to increase their care needs. This exponential effect was also found for the relation between frailty and mortality in this group. It is therefore important to limit the progression of frailty in the relatively fit groups [12]. This is underlined by the result that recovering from severe frailty is hard, especially at higher age [26].

Care costs for people with ID are already high [27, 28]. Because of the increased life expectancy [1, 2], these costs will keep growing in years to come. Age-related frailty is related to a further increase of care intensity and its associated health care costs —even though this study does not provide data on direct care costs. It is therefore important that caregivers and policy makers are aware of the high prevalence and (financial) consequences of frailty in people with ID. There is an urgent need to develop, validate and implement effective interventions to limit the burden of early frailty. For example, in the general population, it has been shown that physical activity and fitness can help to delay the onset of frailty [29, 30]. The influence of such interventions on frailty should be investigated in people with ID. Previously we showed that older people with low frailty index scores were more likely to be independent in their daily activities, showed less physical disabilities, had less signs of depression and had less medical problems [31]. These characteristics may be used as starting points for the development of interventions.

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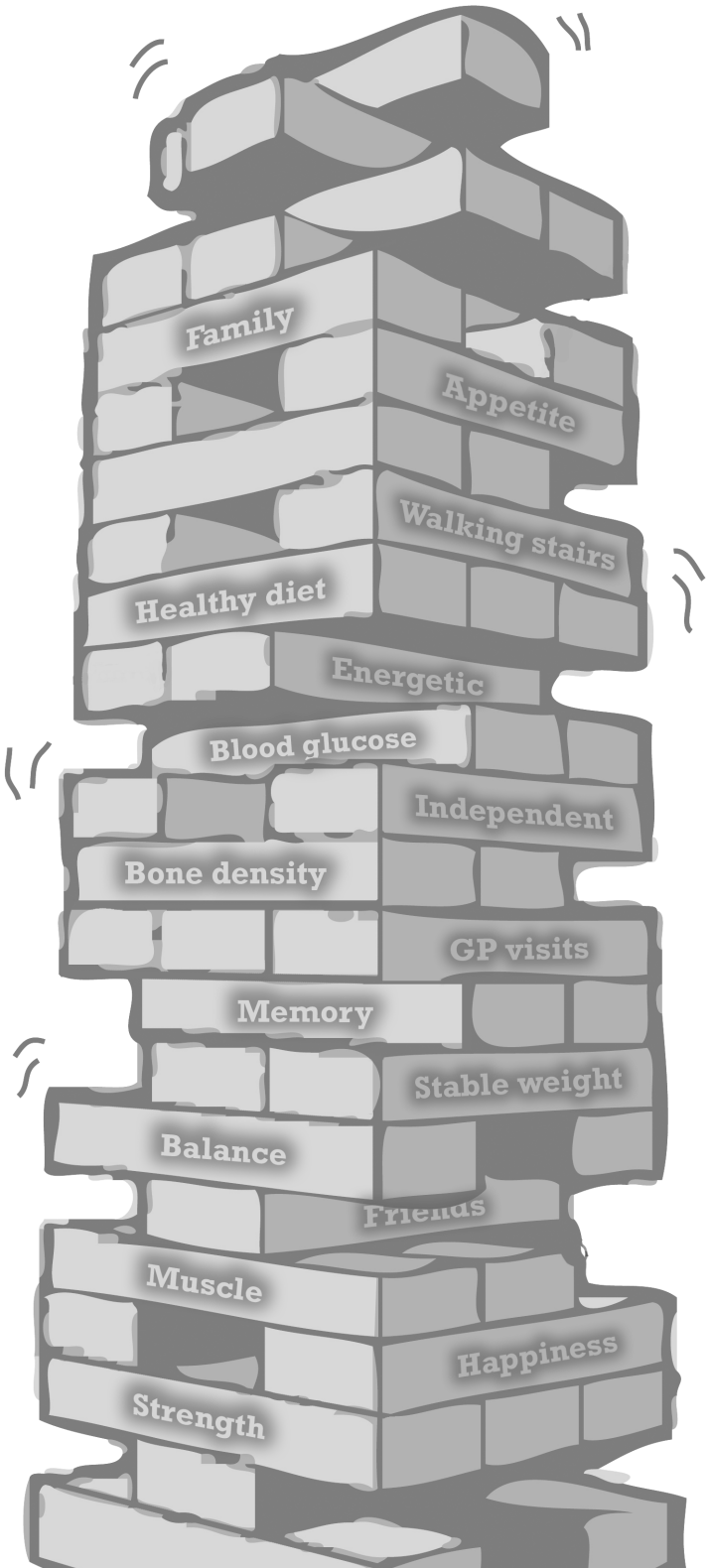
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Healthy diet
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Independent
Bone density
GP visits
Memory
Stable weight
Balance
Friends
Muscle
Happiness
Strength

Chapter 9

Predicting 3-year survival in older people with intellectual disabilities using a frailty index

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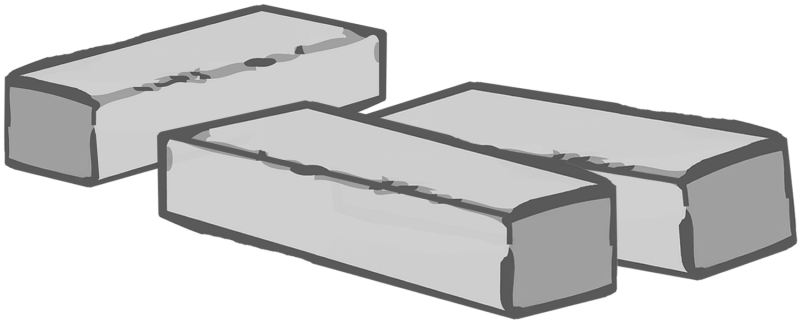

ABSTRACT

Objectives: To analyze the relationship between frailty and survival in older people with intellectual disabilities (IDs). **Design:** Population-based longitudinal observational study. **Setting:** Three Dutch care provider services. **Participant**s: Individuals with borderline to profound ID aged 50 and older (*N* = 982). **Measurements**: A frailty index including 51 health-related deficits was used to measure frailty. Mean follow-up was 3.3 years. The Cox proportional hazards model was used to evaluate the independent effect of frailty on survival. The discriminative ability of the frailty index was measured using a receiver operating characteristic (ROC) curve. **Results**: Greater frailty index values were associated with greater risk of death, independent of sex, age, level of ID, and Down syndrome. There was a nonlinear increase in risk with increasing frailty index value. For example, compared to the relatively fit (frailty index < 0.20) mortality risk for vulnerable individuals (frailty index 0.20–0.29) was 2.17 times as great (95% confidence interval [*CI*] = 0.95–4.95) and 19.5 (95% *CI* = 9.13–41.8) times for moderately frail individuals (frailty index 0.40–0.49). The area under the ROC curve for 3-year survival was 0.78. **Conclusion**: Although the predictive validity of the frailty index should be further determined, it was strongly associated with 3-year mortality. Care providers working with people with ID should be able to recognize frail clients and act in an early stage to stop or prevent further decline.

Key words: Frailty, older people with ID, survival

INTRODUCTION

Frailty, which is predictive of early mortality, dependence, and institutionalization in the general population, will become a major healthcare challenge [1]. It is not clear whether these predictions can be extrapolated to people with intellectual disabilities (ID), inasmuch as lifelong mobility and cognitive limitations could influence the consequences of frailty in this population [2]. This study focused therefore on whether frailty predicts survival in people with ID.

Neither an agreed-upon definition nor a broadly accepted measurement strategy for frailty exists [3]. Nevertheless, experts agree that frailty is a condition in which older people are more vulnerable to adverse health outcomes as a result of age-related decline in many physiological systems [1]. In people with ID, frailty has been measured using the two most commonly cited frailty instruments: the phenotypic approach and the frailty index [4-6]. Both approaches show that frailty is more common in older adults (≥ 50) with ID than in the general population [7, 8]. Even so, mobility limitations might highly influence the phenotype and therefore not be the most-suitable measure for this population [2]. In contrast, the frailty index is a multifactorial measure based on accumulation of a broad spectrum of nonspecific age-related impairments (deficits), including symptoms, signs, diseases, and disabilities [5, 9]. It has shown predictive validity in diverse clinical and community-dwelling populations [1, 10].

Although characteristics (e.g., correlation with age, maximum score, and distribution) of the frailty index for older people with ID were consistent with frailty indices in other populations, the predictive value of the frailty index for adverse health outcomes (e.g., death) in people with ID is unknown. Therefore, the aim of this study was to determine the predictive validity of the frailty index for survival in people with ID aged 50 and older for whom a frailty index was previously calculated [7]. More precisely, the objectives were to evaluate the relationship between frailty and 3-year all-cause mortality and to analyze differences in subgroups (age categories, sex, Down syndrome, level of ID), to estimate the differences in survival probability between different frailty levels, and to estimate the accuracy of the frailty index in relation to survival in older people with ID.

METHODS

Study design and participants

This is a 3-year follow-up to the Healthy Ageing and Intellectual Disability (HA-ID) Study, which aimed to establish the health status of older adults using formal care for people with ID in the Netherlands. Details about the recruitment and selection pro-

cess have been previously published [11]. Briefly, participants were recruited through three Dutch care provider services offering a broad spectrum of care, ranging from ambulatory support to residential care. One thousand fifty participants constituting a near-representative sample of people with ID using formal care in the Netherlands were included. Competent clients provided informed consent themselves, and otherwise, legal representatives were approached. The medical ethics committee of the Erasmus Medical Center Rotterdam (MEC-2008-234) and the ethics committees of the participating care organizations approved this study.

Data collection

Baseline data were collected between February 2009 and July 2010 in three main categories: physical activity and fitness, nutrition and nutritional state, and mood and anxiety. Within these categories, a broad diagnostic assessment was performed in addition to the collection of health records data. Details about the measurement have been reported elsewhere [11]. Level of ID was obtained from the records of behavioral 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 mean follow-up period was 3.3 years (range 0–4.7). All-cause mortality data (months until death) were collected through the care organizations up to July 2013. If participants no longer received care from one of the care organizations, the date and reason of relocation were requested.

Constructing the Frailty index

Based on baseline data from the HA-ID study, a 51-item frailty index was created using standardized criteria described previously [12]: the deficit is related to health, the deficit's prevalence increases with age, the deficit does not saturate too early, and all deficits together cover a broad spectrum of health. In addition, each deficit had greater than 5% prevalence and less than 30% missing values. For each individual, the deficits were scored between 0 (deficit absent) and 1 (deficit present). Deficits included activity of daily living (ADL) items, social circumstances, diseases, biomarkers, and physical measurements. Detailed information on the selection, diagnostic method, and cut-off values of the deficits has been reported elsewhere [7]. A frailty index score was calculated for each individual by dividing the total deficit score by the number of deficits measured, which resulted in a score ranging from 0 to 1. In general, a larger number of deficits measured results in a more-precise frailty index. If 30 to 40 deficits are included, it is possible to predict adverse health outcomes [10, 12], so participants with fewer than 30 known deficits were excluded. Using the terms proposed in the 7-point Clinical Frailty Scale [13], the sample was divided into five frailty groups: relatively fit (frailty index score <

0.20), vulnerable (frailty index score 0.20–0.29), mildly frail (frailty index score 0.30–0.39), moderately frail (frailty index score 0.40–0.49), severely frail (frailty index score ≥0.50).

Statistical analysis

Participants who were alive at the end of the study were compared with those lost to follow-up and those who had using chi-square (X^2) tests for categorical data and independent sample *t*-tests for continuous data. Baseline characteristics were then calculated for the different frailty groups, and the Spearman log-rank test was used to evaluate the mean differences. Next, survival analyses were performed. Data on participants who were lost to follow-up were censored for the survival analysis. The proportional hazards assumption was assessed using the scaled Schoenfeld residuals and by plotting $\beta(t)$ for the variables against time. The risk for informative censoring was evaluated by analyzing the characteristics of those lost to follow-up. Survival curves were generated using the Kaplan-Meier estimate. The log-rank test was used to evaluate differences in all-cause mortality according to baseline characteristics (age, sex, Down syndrome, level of ID, frailty groups). The Cox proportional hazards model was used to evaluate the independent effect of frailty index score on survival, adjusted for baseline characteristics. Hazard ratios (*HR*s) and corresponding confidence intervals (*CI*s) for different frailty levels were also calculated. Dummy variables were composed for Down syndrome (presence of Down syndrome or unknown status vs no Down syndrome) and level of ID (moderate, severe, profound vs borderline, mild). Then, to measure the accuracy of the frailty index in relation to all-cause mortality, a receiver operating characteristic (ROC) curve was constructed, and the area under the ROC curve (AUC) was calculated. To account for censoring, calculations were based on the nearest-neighbor estimator, which uses time-dependent sensitivity, specificity, ROC, and AUC [14]. Youden Index cutoff values that maximize the sum of sensitivity and specificity were determined for 3-year survival. Statistical analyses were performed using SPSS version 20.0 (SPSS, Inc., Chicago, IL) and R version 3.0.0 (R Core Team, Vienna, Austria). A two-sided $p < .05$ was considered statistically significant.

RESULTS

Characteristics

Mean age of the participants was 62 ± 8 (range 50–93), and 51% were male. Mean follow-up was 3.3 years (range 0–4.7 years). Of 1050 participants in the total cohort, 152 died, and 25 were relocated. Those who died tended to be older ($t = 6.7$, $p < .001$), more likely to have Down syndrome ($X^2 = 20.3$, $p < .001$), more likely to live in the central residential setting (e.g. receiving long-term 24h support; $X^2 = 23.4$, $p < .001$), and have higher frailty

index scores ($t = 14.8$, $p < .001$). Seven participants were relocated because their health was deteriorating, eleven for other reasons, and seven for unknown reasons. Those who were relocated were more likely to live in a community-based residential setting ($X^2 = 16.5$, $p = .002$) and more often had Down syndrome ($X^2 = 6.18$, $p = .01$). In 68 participants, there were too many missing data to calculate a frailty index. They did not significantly differ from the remaining participants with respect to baseline characteristics. The remaining analyses were performed on participants with known frailty index scores.

Frailty groups

Using defined cut points, at baseline, 325 (33.1%) participants were classified as relatively fit, 279 (28.4%) as vulnerable, and 315 (38.5%) as frail (frailty index score ≥0.30). Frailer people tended to be older, have greater ID, proportionately more often have Down syndrome, have more ADL and instrumental ADL (IADL) disabilities, and have more multimorbidities (Table 1).

Survival analysis

Scaled Schoenfeld residuals showed that the assumption of the proportional hazard was met. The log-rank test showed no significant differences in mortality according to sex ($X^2 = 2.54$, $p = .11$) or level of ID ($X^2 = 4.30$, $p = .12$). Participants with Down syndrome had a shorter life expectancy than those without ($X^2 = 25.9$, $p < .001$). Survival probability was lower with older age ($X^2 = 72.6$, $p < .001$; Figure 1A). Mortality was related to frailty (Figure 1B), with more than 60% of those with frailty index scores greater than 0.50 dying within the follow-up period. Overall, mortality increased nonlinearly with level of frailty (Figure 2). In a Cox model that incorporated age, sex, level of ID, Down syndrome, and frailty index score as a continuous variable (multiplied by 100 to obtain interpretable results), the *HR* for the frailty index score was 1.08 (95% *CI* = 1.07–1.10, Wald = 136, $p < .001$). In other words, independent of baseline characteristics, each point (0.01) increase on the frailty index resulted in an 8% higher *HR*. The *HR* for age was 1.05 (95% *CI* = 1.03–1.07, Wald = 20.3, $p < .001$). The regression coefficients and Wald statistics showed that the frailty index was more closely related to survival than was age. A second Cox model incorporating baseline characteristics and frailty groups (Table 2) showed that mildly frail participants were 8.0 times (95% *CI* = 3.72–17.3), moderate frail participants almost 20 times (95% *CI* = 9.13–41.8), and severely frail participants 33 times (95% *CI* = 14.8–73.9) as likely to have died as relatively fit participants. The AUC illustrated that the frailty index predicts 3-year survival with acceptable accuracy (0.78) and an optimal cutoff point of 0.3.

Table 1. Baseline Characteristics of the Healthy Ageing and Intellectual Disability (HA-ID) Study According to Frailty Status (*N* = 982)

Characteristic	Relatively Fit (FI < 0.20) *n* = 325	Vulnerable (FI = 0.20–0.29) *n* = 279	Mildly Frail (FI = 0.30–0.39) *n* = 192	Moderately Frail (FI = 0.40–0.49) *n* = 130	Severely Frail (FI≥0.50) *n* = 56	ρ	*p*-value[a]
Age, mean±*SD*	60±6.2	61±7.7	63±9.3	65±9.3	68±10.5	0.23	< .001
Sex, *n* (%)						0.05	.16
Male	176 (54.2)	151 (54.1)	83 (43.2)	65 (50)	31 (55.4)		
Female	149 (45.8)	128 (45.9)	109 (56.8)	65 (50)	25 (44.6)		
Level of ID, *n* (%)[b]						0.42	< .001
Borderline	18 (5.5)	7 (2.5)	4 (2.1)	0 (0.0)	1 (1.8)		
Mild	115 (35.4)	48 (17.2)	24 (12.5)	14 (10.8)	6 (10.7)		
Moderate	167 (51.4)	150 (53.8)	84 (43.8)	50 (38.5)	19 (33.9)		
Severe	19 (5.8)	54 (19.4)	45 (23.4)	34 (26.2)	13 (23.2)		
Profound	1 (0.3)	12 (4.3)	28 (14.6)	31 (23.8)	17 (30.4)		
Down syndrome, *n* (%)[c]						0.07	.03
Yes	32 (9.8)	46 (16.5)	30 (15.6)	20 (15.4)	14 (25.0)		
No	220 (67.7)	195 (69.9)	140 (72.9)	90 (69.2)	40 (71.4)		
Frailty index score, mean±*SD*	0.14±0.04	0.25±0.03	0.34±0.03	0.44±0.03	0.56±0.05	0.97	< .001
Deceased, *n* (%)	9 (2.8)	19 (6.8)	35 (18.2)	48 (36.9)	35 (63.5)	0.40	< .001
ADL, mean±*SD*[d]	18.4±1.9	15.5±2.9	11.6±4.3	6.68±4.7	2.84±3.47	0.80	< .001
IADL, mean±*SD*[e]	15.8±4.9	11.1±3.7	9.39±2.4	8.68±1.8	8.20±0.62	0.67	< .001
Multimorbidity, *n* (%)[f]	55 (16.9)	124 (44.4)	137 (71.3)	108 (83.1)	55 (98.2)	0.54	< .001

[a]Differences between the frailty groups assessed with the Spearman's Rho
[b]Data on level of intellectual disability (ID) were not available for 21 participants.
[c]Data on presence of Down syndrome were not available for 155 participants.
[d]Assessed using the Barthel Index; range 0 (completely dependent) to 20 (completely independent) [29]
[e]Assessed using the Lawton scale; range 8 (completely dependent) to 24 (completely independent) [29]
[f]Assessed using a list of 20 chronic conditions and defined as presence of ≥4 morbid conditions [30].
SD = standard deviation

DISCUSSION

Three-year survival is poorer with higher frailty index values, independent of sex, age, level of ID, and Down syndrome. At any time during the follow-up period, significantly more participants in the frailty groups died than those classified as relatively fit, although the *CI*s were wide and overlapped between the categories. Frailty had a stronger relationship with mortality than age did.

These results are congruent with reported relationships between frailty index score and survival in general population studies, although direct comparison with other studies is difficult because of differences in follow-up periods, cut-off values, statistical methods,

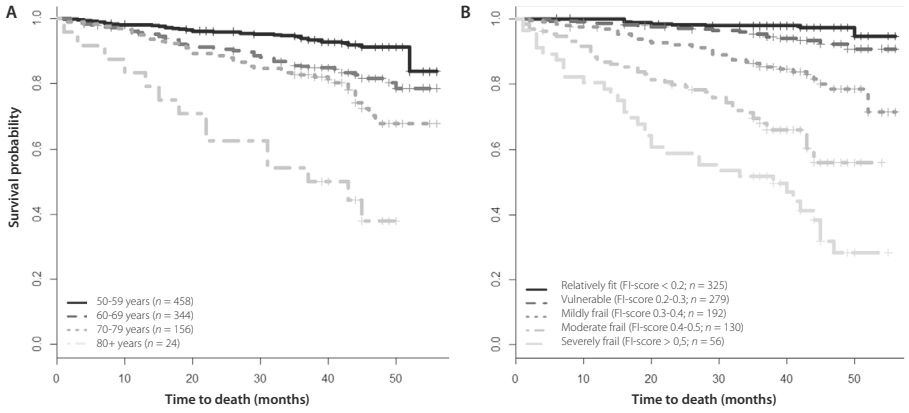

Figure 1. Kaplan-Meier survival curves stratified according to age categories (A) and frailty subgroups (B). (A) The youngest participants (upper line, solid black; 50–59) had the highest survival, the oldest participants (lowest line, long hash, light gray; ≥80) had the lowest, and the other age categories were in between. (B) Relatively fit participants (upper line, solid black; FI score < 0.20) had the highest survival, severely frail (lowest line, long dash light gray, FI score ≥0.50) had the lowest, and vulnerable (FI score 0.20–0.29), mildly frail (FI score 0.30–0.39), and moderately frail (FI score 0.40–0.49) were in between.

selection of frailty index items, and populations. If frailty is analyzed on a continuous scale, studies in the general older population show that, with each deficit increase, the risk of death rises by 1% to 8% [15]. The current study found an 8% greater risk of death with each 0.01-point increase in frailty index score, although there was a nonlinear relationship between the *HR* for mortality and frailty index score. In other words, if the frailty index score was high, additional deficits strongly decreased the chances of survival, whereas additional deficits had less effect in participants with low frailty index scores. The slope between survival time and survival probability was consistently steeper for participants with high frailty index scores than for those with low frailty index scores, which has also been observed in the general population [16,17]. The nonlinear relationship between frailty and mortality made the frailty subgroup analysis more applicable to the current study's dataset than analyzing continuous frailty index score, although the frailty index was designed to be used on a continuous scale, and validated cut-off points to classify frail and nonfrail individuals do not exist. Nevertheless, different groups can be created to compare different health states, as has been done before [17-20], although these values remain arbitrary.

A difference between the current study results and previously reported studies is that the current study found greater risk of mortality for those classified as at least mildly frail (frailty index score ≥0.30), whereas in the general population, the frailty index already discriminates mortality risk in frailty subgroups with scores below 0.30 [15,

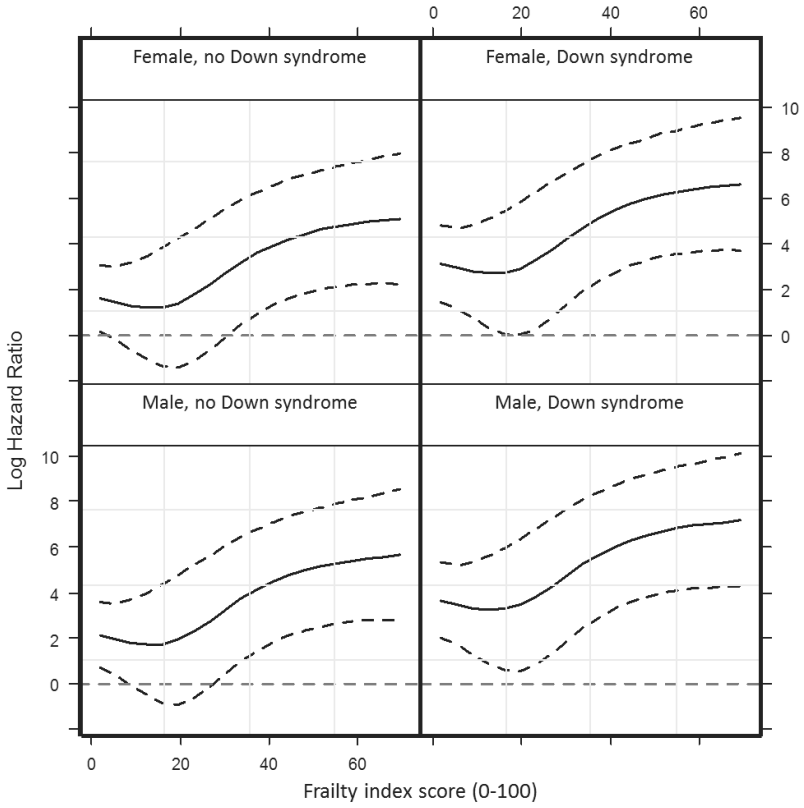

Figure 2. Frailty index score in relation with the log hazard ratio stratified for gender and the presence of Down syndrome using centered age and mild level of ID. Dashed lines represent the 95% confidence intervals.

21-23]. Similarly, mortality does not seem to increase before the frailty index score is 0.20 or greater. There seems to be a threshold that limits the frailty index to predict mortality at low scores, suggesting that older people with ID can manage a number of deficits before their mortality risk increases. It could be that lifelong disability has lower prognostic significance than disabilities acquired in later life. Even so, more than twice as many participants in the vulnerable (frailty index score ≥ 0.20–0.29) group died as in the relatively fit (frailty index score < 0.20) group.

These results need to be interpreted with caution. First, although frailty was measured in 982 participants, which is the largest frailty study in people with ID, this is fewer than in many other studies. Nevertheless, construct validity and characteristics of the frailty index were found to be similar to the general public (e.g., maximum frailty index score, frequency distribution, relationship with age independent of the items used to construct

Table 2. Multivariate Survival Analyses of Frailty in Relationship to Survival: Cox Regression Analyses for Time Until Death ($N = 961$)

Covariate	*B* (Standard Error)	Wald Statistic	*p*-value	Hazard Ratio (95% Confidence Interval)
Age	0.05 (0.01)	18.5	< .001	1.05 (1.03–1.07)
Female	–0.54 (0.18)	9.25	.002	0.59 (0.41–0.83)
Down syndrome		45.0	< .001	
Present	1.53 (0.23)	44.8	< .001	4.61 (2.95–7.22)
Unknown	0.56 (0.26)	4.57	.03	1.75 (1.05–2.92)
Level of ID		13.0	.02	
Moderate	–0.53 (0.23)	5.32	.021	0.59 (0.37–0.92)
Severe	–0.96 (0.27)	12.9	< .001	0.38 (0.23–0.65)
Frailty Index		119.8	< .001	
Vulnerable	0.77 (0.42)	3.38	.07	2.17 (0.95–4.95)
Mildly frail	2.08 (0.39)	28.3	< .001	8.02 (3.72–17.3)
Moderate frail	2.97 (0.39)	58.7	< .001	19.5 (9.13–41.8)
Severely frail	3.50 (0.41)	72.5	< .001	33.0 (14.8–73.9)

Of the 982 with known frailty index scores, 21 were excluded from the analyses because their level of intellectual disability (ID) was unknown.

the frailty index) [7]. Second, it was not possible to study the trajectories of frailty because it was measured only at baseline, so it remains unknown whether people recover or become frailer over time. Third, at least seven participants were lost to follow-up because of poor health. It is therefore likely that these participants were lost to follow-up for reasons related to time of death, so censoring might have been informative. This could have led to an underestimation of the predictive value of the frailty index. Even so, because major differences were not found between participants who were lost to follow-up and the remaining participants, and only a small number of participants were involved, it is likely that the influence was limited. Fourth, a very high *HR* was found for the moderately and severely frail compared with the relatively fit. These numbers may have been inflated because of the small number of cases in the relatively fit group. Last, more-severe intellectual disability was related to lower mortality risk. A possible explanation could be that there is a survival effect in the population, that only relatively fit people with severe ID reach the age of 50. In addition, those with more-severe ID may live in a more-protective environment, with ample care and support.

Trials and longitudinal observational studies have shown that frailty is a dynamic process and might be reversible [1, 20, 24-26]. These studies emphasize the importance of instruments that can adequately identity frail individuals. The frailty index, as used in the current study, might not be applicable in clinical practice because of the extensive

and complex data collection required. Nevertheless, as part of routinely collected data, the frailty index, or a modified version, may be clinically applicable, as has been shown in the general population [27,28]. Even so, this option needs to be further explored, and the validity, reliability, and sensitivity of the adapted version need to be tested. Furthermore, it is necessary to study which modifiable factors contribute to frailty or can protect people against becoming frail. Some important characteristics (e.g., no mobility limitations) of the least-frail older people with ID have previously been shown [18]. Eventually, knowledge of these factors and a valid screening instrument can help to monitor and prevent or delay frailty in this population.

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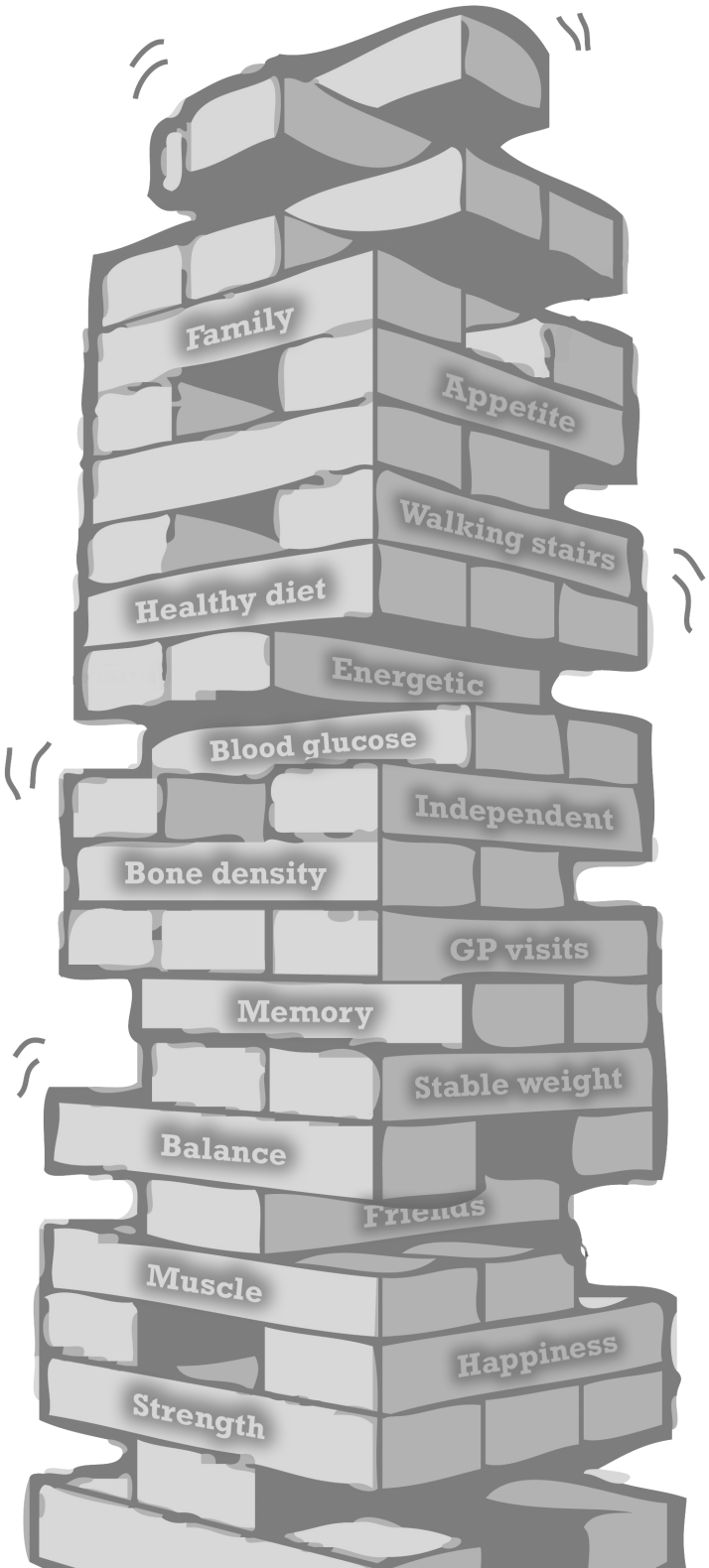
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Walking stairs
Healthy diet
Energetic
Blood glucose
Independent
Bone density
GP visits
Memory
Stable weight
Balance
Friends
Muscle
Happiness
Strength

Chapter 10

Comparing two frailty measures in their ability to predict mortality among older people with intellectual disabilities

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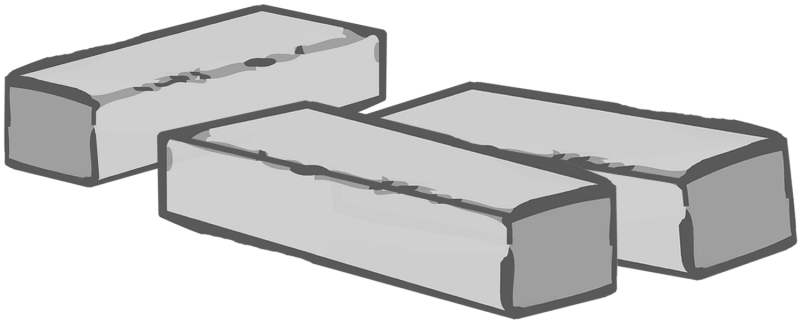
Submitted



ABSTRACT

Objectives: To compare the ability of two frequently used frailty approaches, the frailty index and the frailty phenotype, to accurately predict 3-year all-cause mortality in people with intellectual disabilities (ID). Furthermore, the influence of motor disabilities on the predictive ability of the two instruments was established. **Design**: Three-year prospective study. **Setting:** Dutch care provider services offering care and support to people with ID. **Participants:** 1050 elderly people aged 50 years or over with an intellectual disability. **Measurements:** The frailty phenotype and the frailty index were used to assess frailty at baseline. The feasibility and mutual agreement (kappa statistics) of the approaches were calculated. Furthermore, adjusted risks of three-year all-cause mortality were estimated (Cox proportional hazard model). **Results:** The frailty index could be applied to a larger part of the dataset (94%) than the frailty phenotype (81%). There was a slight agreement between the approaches (kappa = 0.3). However defined, frailty was related with mortality in people with ID. Nevertheless, the frailty index showed a higher discriminative ability and a stronger relation with mortality than the frailty phenotype, especially when adjusted for motor disabilities. **Conclusion**: The wide range of factors included in the frailty index seems to be more important to predict negative health outcomes than physical parameters alone (frailty phenotype).

Key words: Frailty, people with ID, Frailty index, Frailty phenotype, Predictive accuracy, Agreement

INTRODUCTION

Frailty is a complex cascade that involves several age-related physiological alterations, eventually leading to loss of function and failure to response to a stressor event [1]. Longitudinal observational studies and trials have shown that frailty is a dynamic process and might be reversible by interventions [1-4]. These results emphasize the importance of early identification of frail individuals. Several frailty measures emerged in recent years. Which one can best be used for people with early disabilities, such as people with intellectual disabilities (ID) is however unknown. This paper aims to shed light on this void of knowledge.

The frailty 'phenotype' by Fried and colleagues [5], and the frailty index developed by Rockwood and Mitnitski [6, 7] are the most evaluated and most frequently used frailty instruments [8]. The first is based on five core clinical features that together form the frailty phenotype [5]. The second approach is based on a-specific accumulation of health problems (deficits). Where the frailty phenotype is based on pre-defined physical variables, the frailty index focuses on the total number of deficits in an individual and pays less attention to the exact nature of the problems. Both measures have been applied in several populations and have shown predictive validity in terms of survival and health indices [8-10]. A number of studies showed that the frailty index has a somewhat stronger relation with negative health outcomes than the phenotype approach [11-15].

These results can however not directly be applied to people with ID, because their lifelong disabilities (e.g. motor and sensory disabilities, comorbidities, cognitive limitations) can influence both the development and the consequences of frailty [16]. Previously, the frailty phenotype and the frailty index approach were applied to a population of older people with ID in the Healthy Ageing and Intellectual Disabilities (HA-ID) study. Both instruments showed a higher prevalence of frailty in people with ID compared to the general population of the same age [17, 18]. The frailty index was able to predict mortality, and increased of disabilities over a three-year follow-up period [19-21]. It was observed that, according to the frailty phenotype, those with mobility limitations were 10 times more likely to be frail than those without mobility limitations. Therefore, as hypothesized previously, it could be that lifelong motor disabilities in this population limit the predictive validity of this approach [16]. However, the predictive validity of the frailty phenotype was not previously evaluated in people with ID.

Information on which method can best be applied in the ID population, can help to select individuals at risk for negative health outcomes. The purpose of the present study was therefore to assess the feasibility of the frailty phenotype and the frailty index and

to calculate their agreement. Furthermore, the ability of the frailty phenotype and the frailty index to predict 3-year all-cause mortality was evaluated. In addition, we assessed the influence of motor disability on the predictive ability of the two instruments.

MATERIALS AND METHODS

Study design and participants

This study was part of the HA-ID study. This study addressed the health of 1050 older people with ID in the Netherlands. Details about the recruitment and selection process have been described elsewhere [22]. Briefly, the study population consisted of clients, 50 years and over, from three Dutch care provider services offering a broad spectrum of care and support to people with ID. All clients aged 50 years and over ($N = 2322$) were invited to participate. Eventually 1050 clients, or their legal representatives, provided informed consent, forming a nearly representative study population for the Dutch population of older adults (aged 50 and above) with ID who use formal care, albeit with a slight underrepresentation of men, people aged 80 and over, and people living independently. Ethical clearance was provided by the Medical Ethics Committee of the Erasmus Medical Center Rotterdam (MEC 2008-234) and by the ethics committees of the participating care organizations.

Data collection

Baseline data were collected between February 2009 and July 2010 within three main themes: (1) physical activity and fitness, (2) nutrition and nutritional state, and (3) mood and anxiety. Within these themes the participants underwent an extensive diagnostic assessment including a physical assessment, a fitness test battery, several questionnaires (regarding e.g. nutrition, depression, disabilities), and laboratory tests in the addition to the collection of health records data. Data on age, gender and residential status were collected through the care provider services. Level of ID was obtained from the scores of psychologists or test assistants. The diagnosis of Down syndrome was retrieved from medical files. Up to July 2013, all-cause mortality data (time of death) were collected through the care organizations.

Frailty phenotype

Previously, frailty phenotype was applied using the criteria of the Cardiovascular Health Study [5, 17]. According to these criteria an individual should be classified as frail if at least three of the following five are present: weight loss, weakness, slowness, low physical activity, and poor endurance or exhaustion. Briefly, weight loss was defined as losing more than 3 kg within 3 months. Weakness was assessed using a handgrip

dynamometer (Jamar Hand Dynamometer [#5030J1, Sammons Preston Rolyan, Dolgeville, NY]). Slowness was assessed using comfortable walking speed, measured as the average of three recordings of the time to complete a distance of 5 meter. Participants in a wheelchair and participants unable to perform the walking test due to physical limitations were also classified as having a slow walking speed. Low physical activity was defined as walking fewer than 5000 steps/day measured with pedometers (NL-1000; New Lifestyles, Lees Summit, MO). Participants in a wheelchair and participants unable to perform the test due to physical limitations were also classified as having low physical activity. Exhaustion was defined as answering 'moderate problem' or 'severe problem' to the 'lacks energy' item from the Anxiety, Depression and Mood Scale [23]. Individuals with one or two criteria present were classified as pre-frail. Individuals with no criteria present were classified as non-frail or 'robust'. At least three out of five criteria needed to be known before the frailty phenotype could be applied.

Frailty index

A frailty index was previously created with 51 baseline items from the HA-ID study [18]. A standardized procedure was followed to develop the frailty index [24]: all items were (1) related to health, (2) positively associated with age, (3) frequently but not too often present in the population (> 5%, < 80%), and (4) measured in at least 70% of the participants. Furthermore, the items did not correlate too strongly with each other ($r <$ 0.7), and together the items covered a range of health problems (physical, psychological and social). All items were recoded between 1 (presence of the deficit) and 0 (absence of the deficit). Individual deficits and their cut off values are available elsewhere [18]. The frailty index score was calculated as the total number of deficits present as a proportion of those counted (e.g. 12 deficits in a 51-item frailty index results in a frailty index score of 12/51 = 0.24). In the case of missing data, the deficit was removed from both the numerator and the denominator, but at least 30 deficits were required per individual. The frailty index is a continuous measure allowing to stratify people by their risk of adverse outcomes in as many groups as the data permits [25]. However for the sake of direct comparisons with Fried phenotype, we used previously identified cut points: a frailty index of less than 0.2 was considered as non-frail or 'robust', a score between 0.2-0.35 as 'pre-frail', and a score above 0.35 as 'frail' [11, 12].

Statistical analysis

First, baseline characteristics (gender, age, level of ID, presence of Down syndrome), the mean frailty index score and the percentage of non-frail, pre-frail and phenotypic frail participants were provided as the percentage for categorical variables and the mean (with *SD*) for continuous variables. Second, the feasibility of the instruments was analyzed by calculating the percentage of participants able to complete the frailty assessments.

A non-response analysis was performed to compare the participants with and without completed data for frailty, using a Pearson Chi-square for categorical data and ANOVA for continuous data. Third, the Cohen's Kappa statistic was used to estimate agreement between the instruments. For this analysis the categorized frailty index was compared with the frailty phenotype (e.g. non-frail, pre-frail, frail). Agreement was considered as poor for Kappa values lower than 0.21, slight for 0.21-0.40, moderate for 0.41-0.60, good for 0.61-0.80, and excellent for values 0.81-1 [26]. Fourth, the ability to predict 3-year all-cause mortality was calculated for both instruments and compared to each other in two different ways. In the first analyses, the hazard ratio's (*HR*) for mortality were calculated for the frailty phenotype and for the categorized frailty index in separate Cox regression models. Dummy variables were composed for the pre-frail and frail groups to compare their mortality risk with the non-frail group. A comparative analyses was performed by including both frailty instruments in the same Cox regression model. This analysis was repeated with a frailty index that excluded the criteria that were also used for the frailty phenotype. In other words, the deficits walking speed, grip strength, fatigue and weight loss were excluded from the frailty index. All models were adjusted for age (years), level of ID (with dummy variables for moderate and severe/profound), gender and the presence of Down syndrome. A receiver operating characteristics (ROC) curve was constructed and the area under the ROC curve (AUC) was calculated to measure the discriminative ability of the instruments in relation to survival. These calculations were based on the Nearest Neighbor Estimator, which uses time-dependent ROC and AUC, to account for censoring. Because the frailty index is not meant to be categorized, and forced boundaries may reduce its precision, we performed a second analysis. The relation between the continuous frailty index and mortality within each strata of the frailty phenotype was assessed. Again, these models were adjusted for age, level of ID, gender and the presence of Down syndrome. Within each stratus the AUC was calculated. Fifth, the influence of motor disability was assessed by including motor disability in a Cox regression model. For all survival analyses the data on participants who were lost to follow-up were censored and the proportional Hazards assumption was tested with the scaled Schoenfeld residuals. Statistical analyses were performed using SPSS version 20.0 and R version 3.0.0. A two-sided p-value of $< .05$ was considered significant.

RESULTS

Sample characteristics

The mean age of the study population (n = 1050) was 61.6 (SD = 8.0). Nearly half of them were female (n = 511, 49%), nearly half of them had a moderate level of ID n = 506 (48%), and 14% (n = 149) was diagnosed with Down syndrome. According to the frailty

phenotype, 230 (27%) were classified as non-frail, 508 (60%) as pre-frail, and 110 (13%) as frail. The mean frailty index score was 0.27 (*SD* = 0.13).

Feasibility

Less than a third of the participants (*n* = 307, 29%) could complete the full frailty phenotype assessment as intended. By including all participants with at least three known frailty phenotype criteria, the frailty phenotype could be applied to 848 (81%) participants. The 202 excluded participants were on average more intellectually disabled (X^2 = 32.8, $p < .001$), and had on average a higher frailty index score (*M* = 0.31, *SD* = 0.12) than those included ([*M* = 0.27, *SD* = 0.13], $t(982) = 3.28$, $p = .001$). For other baseline characteristics no significant differences between the included and excluded participants were found. In 68 participants, there was too much missing data to calculate a frailty index. There were no significant differences between the participants with a known frailty index score (*n* = 982, 94%) and those without, with respect to gender, age, level of ID and Down syndrome.

Agreement

For 838 participants the frailty phenotype and the frailty index were known. The Cohen's Kappa agreement between the categorized frailty index and the frailty phenotype was 0.30, corresponding with slight agreement. Four hundred sixty four out of 838 (55%) of the participants were identically categorized by both methods (Table 1).

Table 1. Agreement among the frailty index and the frailty phenotype based on three frailty categories.

n = 838		Frailty phenotype			
		Non-frail	Pre-frail	Frail	Total
Frailty index	Non-frail < 0.2	151	146	2	299
	Pre-frail 0.2-0.35	68	232	27	327
	Frail > 0.35	5	126	81	212
	Total	224	504	110	838

Survival

First, survival analyses were performed for the three frailty states (non-frail, pre-frail, frail). Table 2 shows the HR's for pre-frail and frail individuals, using the non-frail state as a reference group. However defined, frailty was significantly related to mortality. Those classified as pre-frail or frail using the frailty phenotype were, respectively, 2.40 and 5.16 times more likely to die during the follow-up period than those classified as non-frail. Those classified as pre-frail or frail with the frailty index, were respectively 3.26 and 16.0 times more likely to die than the non-frail group. If both instruments were included in one Cox regression model, the frailty phenotype did no longer predict

Table 2. Hazard ratio's for 3-year all-cause mortality according to the three level frailty index and frailty phenotype.

Frailty measure		Single frailty instrument			Both frailty instruments			Motor disability		
	Status	*HR* (95%*CI*)	Wald	*p*	*HR* (95%*CI*)	Wald	*p*	*HR* (95%*CI*)	Wald	*p*
Frailty phenotype	Pre-frail	2.40 (1.26-4.61)	6.99	.008	1.24 (0.60-2.56)	0.33	.56	1.97 (1.01-3.82)	3.97	.046
	Frail	5.16 (2.54-10.5)	20.6	< .001	1.26 (0.56-2.83)	0.32	.57	2.73 (1.26-5.92)	6.44	.011
Frailty index	Pre-frail	3.26 (1.54-6.88)	9.56	.002	2.79 (1.26-6.20)	6.35	.012	3.15 (1.49-6.68)	8.98	.003
	Frail	16.0 (7.69-33.2)	55.1	< .001	14.1 (6.18-32.3)	39.5	< .001	13.1 (6.09-28.2)	43.3	< .001

Note. HR = hazard ratio, *CI* = confidence interval, the non-frail state was used a reference category for each frailty instrument. All models were adjusted for age, gender, level of *ID*, and Down syndrome. The model *motor disability* was adjusted for the level of motor impairment, 'no walking impairment' was used as a reference category.

mortality, whereas the frailty index did. If all frailty phenotype items were excluded from the frailty index, virtually the same results were obtained. Although the *HR* for the frailty phenotype groups slightly increased, they remained not significant (data not shown). The ROC curve showed that the categorized frailty index had a higher discriminative ability in relation to all-cause mortality (AUC = 0.78) than the frailty phenotype (AUC = 0.64). The advantage of the frailty index is that it is an interval measure, not a point-measure. Therefore we also looked at the original, continuous scaling, within the strata of the three levels of the frailty phenotype. Within these strata, participants with high frailty index score had worse survival than those with low frailty index scores (Table 3). In addition, the AUC within the strata showed that the frailty index has was still an accurate measure to predict mortality.

Motor disability and frailty

Information on mobility was known for 989 participants. At baseline, 731 (74%) participants walked independently, 151 (15%) walked with support and 107 (11%) were wheelchair dependent. Those who walked with support were 2.31 (95%*CI* = 1.96-3.18, *Wald* = 14.3) times, and those who were wheelchair dependent 4.32 (95%*CI* = 2.81-6.66, *Wald* = 44.2) times, more likely to have deceased during the follow-up compared to those who walked independently. The last column in Table 2 shows the relation of the two frailty approaches with survival, independent of motor disability at baseline. Although both approaches remain significantly related with mortality, the frailty phenotype loses much of its predictive value.

Table 3. Characteristics of the frailty index within each phenotypic stratum

	Non-frail *n* = 224	Pre-frail *n* = 504	Frail *n* = 110
Mean FI-score (*SD*)	0.17 (0.08)	0.28 (0.11)	0.43 (0.11)
FI-score Range	0.04-0.53	0.06-0.61	0.18-0.69
Deceased *n* (%)	10 (4.3%)	72 (14%)	37 (34%)
HR (95%*CI*)	1.14 (1.06-1.23)	1.11 (1.08-1.13)	1.06 (1.02-1.10)
AUC	0.67	0.77	0.72

Note. FI = frailty index, *SD* = standard deviation, *HR* = Hazard ratio, AUC = Area under the curve, *CI* = Confidence interval

DISCUSSION

We compared two approaches to frailty, the phenotype of frailty and the frailty index, in people with ID. However defined, frailty was related with mortality in people with ID. Nevertheless overall, the frailty index was more often applicable and showed a stronger relation with mortality than the frailty phenotype, specifically after adjustment for motor disability. Previously, we suggested that the frailty index might be a more suitable approach for this population because of lifelong disabilities [17]. The current results confirm this suggestion.

The frailty index could be calculated for 94% of the participants, whereas the frailty phenotype was applicable to 81%. For less than a third of the participants, all frailty phenotype criteria could be measured. This is in agreement with results from studies among assisted-living participants, where nearly 40% could not complete the assessment [13, 27]. Dropout for the frailty index appeared to be random, whereas for the frailty phenotype, selective dropout was observed: those who dropped out were on average more intellectually disabled and had higher frailty index scores. These results are in line with results observed in the general population: persons in whom the phenotype cannot completely be measured are more likely to die, significantly more disabled, have more chronic diseases and have a higher frailty index score [28, 29]. In accordance with findings in the general population, we found that the predictive value of the frailty index is stronger than that of the frailty phenotype [11-15]. There are several explanations for these results.

First, the frailty index has a much broader approach than the frailty phenotype. It may include all factors that are considered important for frailty (e.g. nutritional status, physical activity, energy, cognition) [9, 30]. Contrary, the frailty phenotype focuses on physical frailty only. It appears that, among the highly heterogeneous ID population, physical parameters do only explain part of the variance. In other words, the risk for a

negative health outcome is better predicted by including a broad spectrum of health aspects. Second, and in line with the first suggestion, the frailty phenotype seems to be too determined by mobility limitations. Indeed, the frailty phenotype had only limited additional predictive value to motor disabilities alone. This limits the predictive value of the frailty phenotype, because motor disabilities appear to be less strong predictors for mortality than observed in the general population [31, 32]. Lifelong or early motor impairment, which is common in this population, is likely to be less predictive than motor impairment acquired in later life. Third, the phenotype approach has the advantage that it focuses on five core clinical features, that are, in theory, easy to measure. Nevertheless, these pre-defined elements are not measurable in all individuals with an ID. This appears less of a problem with the frailty index approach, which does not require the use of a pre-defined set of variables, or even the same number of variables [33]. We were therefore able design a frailty index for the ID population, whereas the elements of the frailty phenotype are designed for the general population. Fourth, we were unable to apply the exact parameters as those proposed in the Cardiovascular Health Study to measure the frailty phenotype. This could have led to an unknown shift in its predictive validity. In addition, the analysis was applied to participants with at least three elements of the frailty phenotype measured. It is likely that this caused an underestimation of the true frailty prevalence. Measurements that are more feasible for the ID population could have increased the predictive validity of the frailty phenotype. For example, it is known that physical activity is hard to measure with pedometers in people with ID [34]. Using an instrument such as the StepWatch or GPS could have led to more valid results for the element 'physical activity' (Schijndel-Speet et al., unpublished results).

Nevertheless, overall the frailty phenotype showed a strong relation with mortality, indicating that physical fitness and mobility are important to lengthen lifespan. It has shown in the HA-ID study that elements from the frailty phenotype (e.g. grip strength, walking speed) predict disability in mobility and activities of daily living [35]. In the general population, physical activity and fitness can reduce or prevent frailty [36, 37]. Whether increased physical fitness and activity will also reduce or delay frailty in people with ID needs to be investigated.

The main strength of our study is its large scale and prospective population-based design, whereas we used standardized and internationally accepted methods to measure frailty. Nevertheless, several limitations need to be taken into account. First, our results may not apply to all people with ID. Our study did not include older people with ID who do not receive formal care or support. Furthermore, there was a slight underrepresentation of people with severe or profound ID, people above the age of 80 and males [22].

In conclusion, these results imply that the frailty index is a better approach to measure frailty than the frailty phenotype in the population of older people with ID. The wide range of frailty factors included in the frailty index are more predictive than physical parameters alone. Future research needs to focus on the clinical applicability of the frailty index. Particularly, it should be studied whether routinely collected data can be used to construct a frailty index for people with ID.

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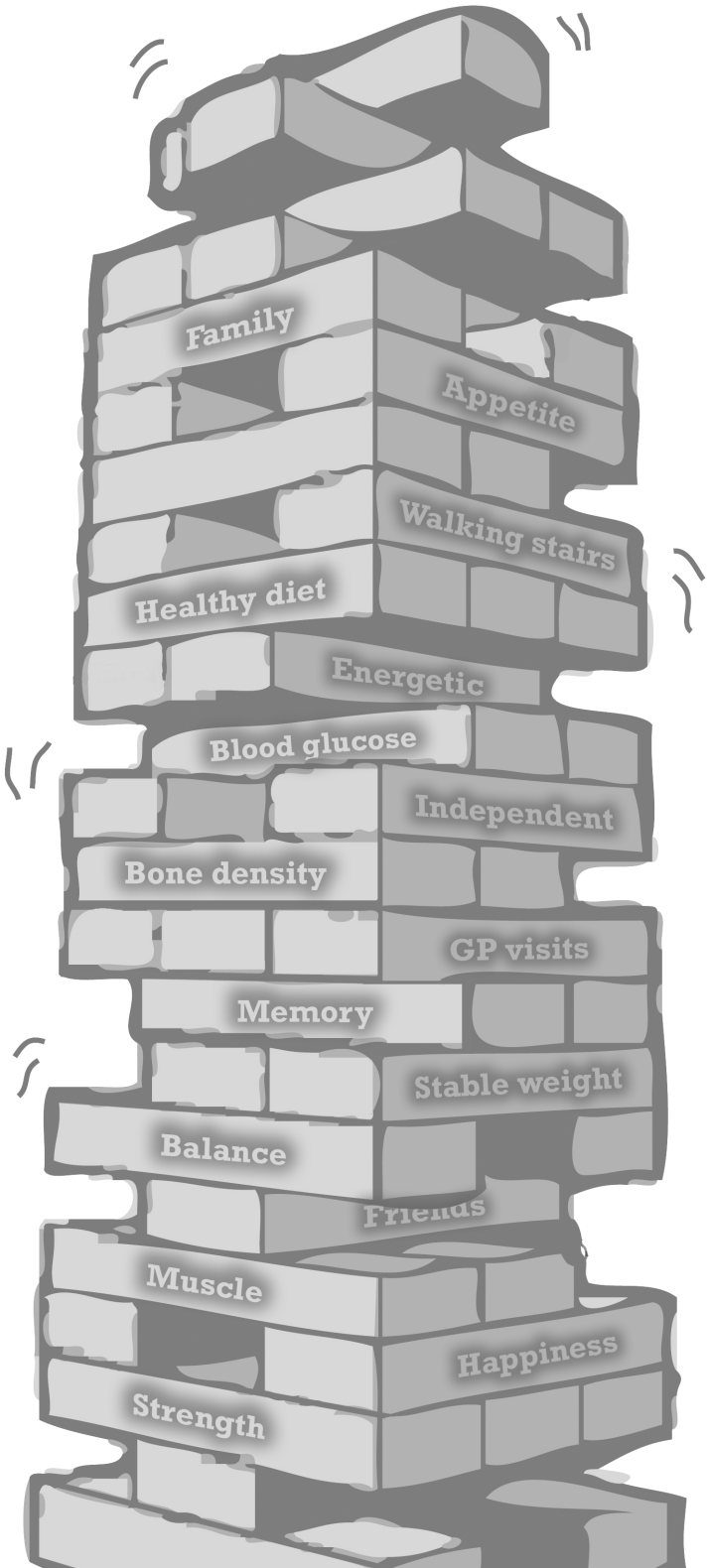
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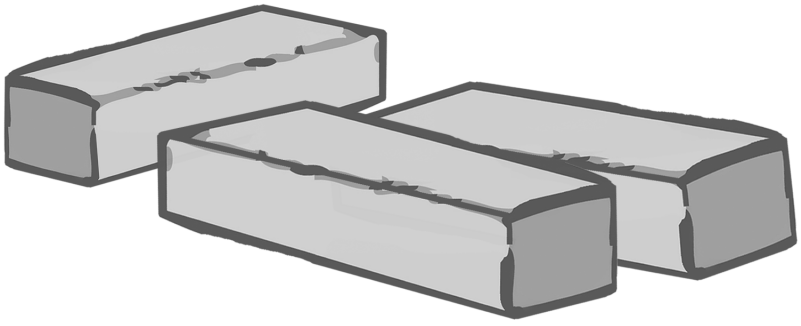
Appetite
Walking stairs
Healthy diet
Energetic
Blood glucose
Independent
Bone density
GP visits
Memory
Stable weight
Balance
Friends
Muscle
Happiness
Strength

Chapter 11

General discussion: towards untangling the ageing riddle in people with intellectual disabilities: an overview of research on frailty and its consequences

To be submitted to Research in Developmental Disabilities



INTRODUCTION

During the past two years, we have reported about our subsequent steps in the development of a frailty measurement for people with intellectual disabilities (ID), its predictive validity for adverse health outcomes, and the distribution of frailty in this population with lifelong disabilities. We performed this work because of the lack of comprehensive insight into the effect of ageing on health aspects in this group. Although premature ageing and its genetic basis have been established in people with Down syndrome, there was no evidence indicating a more rapid aging process in those with other causes of ID. The aging process in people with ID was never described in terms of known aging mechanisms.

One method to study aging is trough frailty, a state of increased likelihood of adverse health outcomes [1]. We were not certain that the concept of frailty would apply to people with early disabilities in the same way as to the general population. Indeed, given the characteristics of the population, it could be that once we would have an applicable diagnostic measure, a majority would be found frail. In that case, frailty would not appear a distinctive concept in this population. The relationship between frailty and disability, intensively discussed for the general older population [2, 3], seemed to us even more complicated for a population with early disabilities. Because, in that case, disabilities can be life-long and are more likely to result in frailty than be a result of frailty, as seen in the general population [2-4].

The Healthy Ageing and Intellectual Disability study (HA-ID) among older participants with ID, producing a wealth of data on a broad range of health aspects, offered an opportunity to start and investigate the concept of frailty in this group, addressing the following comprehensive questions: 1. Is it feasible to measure frailty in people with ID?, 2. How frail are people with ID compared to people from the general population?, 3. Does frailty predict deterioration of health and (relative) independence in the same way as it does in the general population?, and 4. Which characteristics are associated with frailty? In this review, we will critically consider all outcomes of this study and their implications for clinical practice and for future research.

HEALTHY AGEING AND INTELLECTUAL DISABILITY STUDY

The frailty study was embedded in the HA-ID study, a population-based study on the health of 1050 people with ID, aged 50 years and over. All clients receiving care or support from three care organizations were invited to participate. The participation rate was

45% (1050/2332). Assessments included physical examinations, mealtime observations of swallowing, nutritional questionnaires, screening questionnaires and standardized psychiatric interviews for depression and anxiety, questionnaires on life events, quality of life, IADL, ADL, mobility, dementia, social circumstances, and laboratory tests as well as the collection of data from the medical and location files. Further information about the HA-ID study is available elsewhere [5]. Three years after the baseline measurements, all participants were invited for a follow-up study. To limit the burden of participants, information was gathered from files or by proxy questionnaires, without client interference. From the 1050 participants, 19 moved and 120 were deceased. From the 911 that were invited, 84% (n = 763) provided informed consent for participation.

Frailty was measured with the two internationally most frequently used approaches [6]: the frailty 'phenotype' developed by Fried and colleagues [7], and the frailty index developed by Rockwood and Mitnitski [8]. The frailty phenotype is based on five clinical core features (unintended weight loss, weakness, slowness, low physical activity, and poor endurance or exhaustion). Participants with at least three of these features are defined as frail, participants with one or two are considered pre-frail and participants with none are called robust. In contrast, the frailty index is a quantitative measure of frailty, based on non-specific accumulation of impairments (deficits). These deficits can be symptoms, signs, diseases, disabilities or laboratory measurements [8, 9]. Although the content of a frailty index is flexible, deficits need to adhere to several rules. A deficit can only be included if (1) the deficit can be considered an aspect of health, (2) the deficit is associated with age, (3) the deficit does not saturate too early or be very rare, (4) together, the deficits must cover different health aspects, and (5) at least 20-30 deficits are considered [8, 10]. The HA-ID dataset provides over 400 possible deficits, of which 51 fulfilled all inclusion criteria and together formed our frailty index [11]. The deficits included a broad spectrum of objective measurements (e.g. grip strength, walking speed, serum glucose), informer reports (e.g. fatigue, depression symptoms, dressing) and medical information (e.g. medication use, general hospital admission, asthma).

RECAPITULATION OF THE RESULTS

Is it feasible to measure frailty in people with ID and how frail are people with ID compared to people from the general population?

Both applied frailty approaches were able to identify different levels of frailty: we did not find a ceiling effect of frailty in the population people with ID. The characteristics of the frailty index for people with ID were comparable to those obtained in the general population: positively skewed distribution, correlation with age and an observed

maximum score around 0.7 [8, 9, 12]. Furthermore, the index's correlation with age was not influenced by the choice of the deficits, which shows structural validity. There is no strict, validated cut off value to determine the prevalence of frailty, but the score is used on a continuous scale. Our results showed that the average frailty index score for people with ID was 0.27, equivalent to the prevalence of 14 out of 51 deficits. Results from general elderly populations usually show a mean score between 0.08 and 0.17 [8, 9, 13, 14]. We compared our results directly to a general European population (50+) and observed that people with ID accumulate more deficits and that this accumulation starts at much younger age [14]. Although the frailty index was clearly able to show differences in frailty levels, we did not detect any person that had no deficits at all, in other words belonged to the so-called zero-state [15]. Additionally, only few (6.6%) could be classified as 'least frail' (frailty index score ≤ 0.10), whereas in the general population this percentage ranges between the 43 and 76% [14-16]. According to the frailty phenotype, 11% of those aged 50-64 years, and 18% of those aged 65 years and over were frail [17]. Compared to the general population (7-9% of those aged 65 years and over were found to be frail), these percentages are rather high, especially for those aged 50-64 years [7, 18, 19]. We conclude that frailty can be measured in people with ID, using existing instruments. The distribution of frailty of the 50+ ID population is comparable with the 70+ general population. Compared to the general 50+ population frailty seems to start earlier and with higher average frailty index scores. There is an increased health risk from a young age onwards compared to the general population. The question remained whether frailty would show the same predictive value as observed in the general population, because lifelong impairments could have led to early rehabilitations or habituation.

Does frailty predict deterioration of health and independence?

The most frequently used adverse outcome measure to validate frailty instruments is mortality. We found that, however defined, frailty predicts mortality in people with ID during 3 years, but the frailty index showed a stronger relation with mortality, especially after adjustment for motor disability (Schoufour et al., accepted; Schoufour et al., submitted). People classified as pre-frail or frail according to the frailty phenotype, were respectively 2.4 (*CI* = 1.26-4.6) and 5.2 (*CI* = 2.5-10.5) times more likely to die within three years. People classified as vulnerable (frailty index score 0.2-0.3), mildly (frailty index score 0.3-0.4), moderately (frailty index score 0.4-0.5) or severely frail (frailty index score > 0.5) by the frailty index had respectively 2.2 (*CI* = 0.9-5.0), 8.0 (*CI* = 3.7-17.3), 20 (*CI* = 9.1-41.2) or 33 (*CI* = 14.8-73.9) times higher likelihood to die than to those classified as relatively fit (frailty index score < 0.2). In the introduction, we mentioned that frailty could be influenced by lifelong disabilities, such as motor disabilities. Indeed, we found that, if adjusted for motor disability, the frailty phenotype lost much of its predicted value, whereas the frailty index remained strongly related with mortality (Schoufour et

al., submitted). As hypothesized previously, frailty, defined by the physical orientated frailty phenotype, seems to be too determined by motor disabilities in this population [20]. This limits its predictive ability, because motor disabilities by themselves predict mortality less strong than seen in the general population [21, 22]. Life long, or early developed motor disabilities are less predictive than motor disabilities acquired in later life. Above mentioned results imply that the frailty index, because of its broad range of deficits, is more applicable to the ID population than other known frailty measures, as we have argued in detail elsewhere [20, 23]. An additional advantage of the frailty index is the relative free choice of deficits, which enabled us to adapt the content to the ID population. Therefore, analysis of the predictive validity for outcomes other than mortality were only performed using the frailty index. We found that people with a higher frailty index scores were more likely to deteriorate in their activities of daily function (ADL), instrumental activities of daily function (IADL), and mobility [24] than people with low frailty index scores. For example, an individual with a rather high frailty index score (frailty index score = 0.5) was estimated to loose 3.6 ADL-points during three years, meaning that for example, the person was no longer able to use the toilet independently, needed increased help with dressing, and could no longer walk the stairs. Furthermore, high frailty index scores were related to an increased number of chronic morbidities and medication prescriptions (Schoufour et al., accepted), in line with results from the general population [25, 26]. Also, we found that the risk of increased care need was exponentially associated with frailty index scores [27]. These results are comparable to results found in the general population [28, 29]. Contrary to results from the general population, we did not find a relation between high frailty index scores and hospitalization [30-33] (Schoufour et al., accepted). The latter could be explained by undiagnosed conditions that normally require hospitalization, or that family/caregivers decide that hospitalization is not in the best interest for the client. Neither did we found a relation between falls, fractures and frailty.

In conclusion, both the frailty phenotype and the frailty index were able to predict early mortality. The frailty index was able to predict deterioration of health and independence in the same way as found in the general population, with exception of hospitalization. It can therefore be concluded that the frailty index is a valid measure for frailty in this early handicapped population.

Which characteristics are associated with frailty?

As to be expected, we found that high frailty index scores were associated with higher age, more severe ID, and Down syndrome. After adjustment for the level of ID, women had higher frailty index scores than men, but seem to cope with these deficits better, shown by a higher survival probability. These results are in line with results from the

general population [34, 35] and underline that women have, somehow, a higher capability, or more physiological reserves, to cope with a higher deficit load [36]. Cross-sectional results showed that frailty in people with ID is associated with increased inflammation markers (CRP and IL-6), anemia, metabolic markers (glucose, cholesterol and albumin) and decreased renal functioning (Schoufour et al., submitted). Furthermore we found that the least frail participants (frailty index score ≤ 0.10) were characterized by better mobility and physical fitness, relative independence, less signs of depression/dementia and less chronic diseases [15]. These results provide the first understanding to why people with ID are at a relatively young age relatively frail compared to the general population. But what exactly is the impact of cognitive limitation, genetic disorders, and lifelong disabilities on frailty? Or, is the early onset of frailty simply explained by chronic co-morbidities, especially in people with Down syndrome and severe ID? Extensive future research is required before definite answers can be provided. Nevertheless in the next paragraph we try to draft the differences between our population and the general population that could help to understand the early onset of frailty.

REFLECTION: UNDERSTANDING THE MECHANISMS OF FRAILTY IN PEOPLE WITH ID

In a recent review by Clegg et al., frailty is said to be the result from lifelong accumulation of molecular and cellular damage, influenced by genetic and environmental factors. Up to a certain point, the human body can resist and repair this damage, but eventually physiological reserves are depleted and a person becomes frail [1]. Frail individuals have little reserves, so that even a minor stressor (e.g. a urinary tract infection) can have serious consequences (figure 1). We have found that, in people with ID, frailty is more prevalent and starts at a younger age. The question is why, and how can this be prevented? We point out several important aspects that could intervene with the early onset of frailty.

As proposed by Clegg et al., genetic factors, environmental factors and the interaction between the two are the origin of frailty. Starting with the former, healthy aging and life expectancy are partially explained by genetic predisposition. It has been estimated that genetic factors explain around one third of the variation in life expectancy in the general population [37-39]. In the ID population, genes could have a much more pronounced effect on healthy aging and frailty than observed in the general population. The intellectual disability often has a genetic origin [40]. Early developed or congenital disorders, originated from either genetic/chromosomal abnormalities or pre-natal errors could, in addition to their effect on childhood cognitive impairment, highly determine the frailty status in late adulthood. First of all, the problems themselves add to frailty, trough

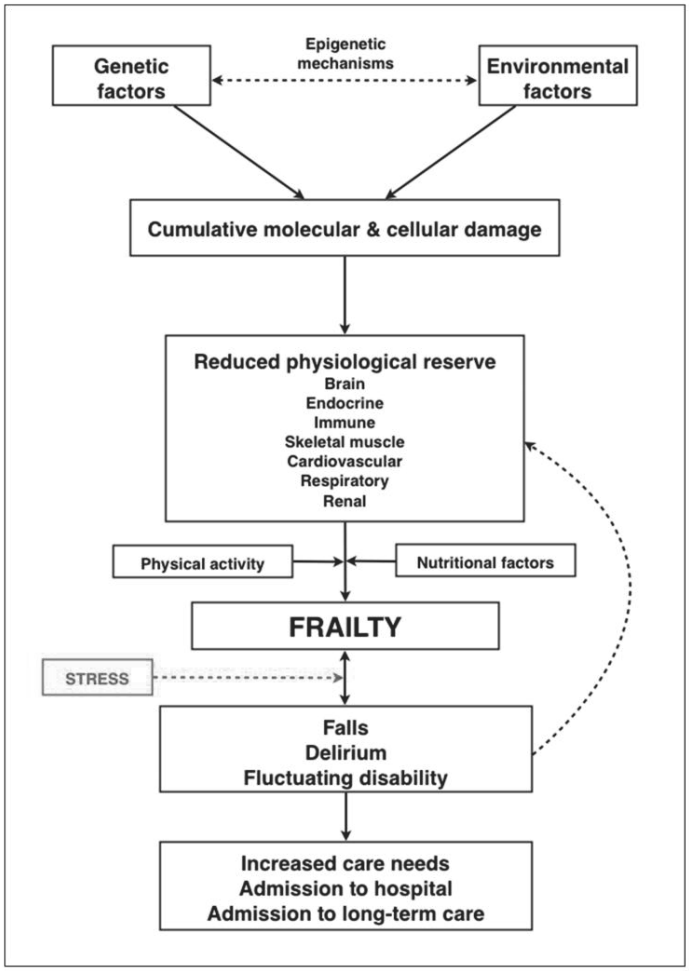


Figure 1. Schematic representation of the pathophysiology of frailty in the general population (adapted from *frailty in elderly people*, Clegg et al., Lancet 2013 [1])

comorbidity, for example mobility limitations, visual impairments, ADHD, and autism. Second, these problems are not isolated, but could lead to a whole cascade of other problems, such as fatigue, pain, reduced fitness, decreased health literacy, inadequate health behavior, and social isolation. Third, genetic predisposition could lead to a decreased defense mechanism or reduced physiological reserves. As a result of childhood cognitive impairment, environmental factors are different than in the general population. Depending on the level of ID and living circumstances, environmental factors could either protect them from becoming frail, or result in a further predisposition to develop frailty. It could be that people living within an institution, receiving professional care and support, be less exposed to certain stressor events, such as financial problems, or to be neglected. On the other hand, it has been shown that, starting at young age, physi-

cal activity and nutritional quality can be substantially improved in the ID population [41-46]. Additionally, life events (e.g. movement, loss of a loved one), social isolation, medication (e.g. antipsychotics), disturbed sleep rhythm, and undiagnosed conditions, could further add to the high frailty status. An additional remark needs to be made for people with borderline or mild levels of ID, who are often living independently, with only little support. Their frailty levels were on average less high than people with severe ID, because they have less comorbidities and better cognitive functioning. Still, their frailty levels are rather high compared to the general population. It is very likely that lifestyle more importantly contributes to frailty than genetic predisposition in this subpopulation. Indeed, results from the HA-ID study show that people with borderline and mild ID have worse nutritional habits and higher risk for cardiovascular risk factors than people with more severe ID. Results from the general population already showed that the social-economic status is important for healthy aging [47-51].

Summarized, early or congenital disabilities, genetic predisposition, unfavorable environmental factors, and their mutual interaction and possible synergetic effect, could lead to an early depletion of physiological reserves resulting in the early onset of frailty. An important finding to support this hypothesis is the increased inflammatory status in people with ID compared to age-matched controls [52] and the association between frailty and inflammation (Schoufour, submitted). Although this field seems promising, much of research is required before causal relations between above mentioned factors and frailty can be shown.

RECOMMENDATIONS FOR FUTURE RESEARCH

Fundamental research

The above-mentioned hypothetic pathway of the development of early frailty calls for fundamental research. First, the current knowledge in genome sequencing is a promising field to better understand the genetic vulnerability for the development frailty. In addition, as suggested in the previous paragraph, the influence of chronic inflammation and reduced physiological reserves needs to be further investigated.

Epidemiologic research

We found that frailty is already frequently seen in people aged 50 years and over, and has significant consequences for the health status. If the almost linear line between age and the frailty index is extrapolated to younger age categories, frailty could, on average, already start around the age of 30. It is therefore important to examine the existence of frailty at younger age. People with severe health conditions, or those severely frail at

young age, are likely to have died before the age of 50. It is unknown if frailty is a useful concept for the younger, severely disabled ID population. In addition, it would be interesting to know how the frailty status of people with ID develops over time. Is it possible to determine risk groups that deteriorate rather quickly? Or to identify people that stay away from frailty during the aging process? This group could add very important knowledge about 'protective' variables. Last, up to now we could only study cross-sectional associations between possible determinants of frailty. It would be interesting to study determinants (specifically modifiable risk factors) that lead to the incidence of frailty.

Above mentioned questions can be answered in a large cohort, with extensive and multiple measurements over time. Amore applicable and easier way to address these questions is using routinely collected data. For example, if for each participant a minimum amount of variables is collected each year, these data can be used to construct a frailty index. Previously it has been demonstrated that a frailty index can, validly, be based on a standard comprehensive geriatric assessment [28, 53]. Data that are routinely collected within the care organisations could be used to measure frailty, follow people over time and identify important determinants. We therefore suggest, that health institutions collaborate to use the same, validated, instruments to measure health variables. This would not only help to further study frailty, but will provide an enormous dataset that can be used to answer various other research questions.

The HA-ID study included participants who received specialized care from care organizations. Therefore, people with borderline or mild ID that live independently were not included in this study. It would be interesting to study frailty in this population and to identify associated risk factors that can be used for preventative approaches.

Screening instrument

To identify frail people there is a need to develop predictive screening instruments that are applicable in clinical practice. Our frailty index can be used as a basis for such a screening instrument. Nevertheless, several steps are necessary before clinical applicability is justified. First, the used items in our frailty index were selected from validated questionnaires, but the validity of these items within the different context of the frailty index is unknown. Second, some items might be relevant for frailty but are difficult to be clinically implemented, such as the fitness battery and expensive biochemical markers. It should be studied whether the frailty index remains valid after the removal of clinically less suitable measures. Third, to evaluate the stability of the frailty index, the test-retest reliability should be determined. Fourth, the ability of the frailty index to measure change in someone frailty status should be evaluated in order to monitor the frailty status closely. Last, the sensitivity and specificity of the screening instrument need to be evaluated, providing validity on an individual level. Another way to examine frailty

would be via biochemical markers. This would be of special interest for people with communication difficulties. We showed that several biochemical markers are associated with frailty. It should be further studies whether a combination of biochemical measures could form a frailty index, as has been recently done for the general population [54].

IMPLICATIONS AND RECOMMENDATIONS FOR CLINICAL PRACTICE

Frailty can be a slowly progressing state that involves the accumulation of all possible health problems, of which many by themselves are no reasons for major concern. One simple intervention that prevents or even reverses frailty for a whole population is therefore unlikely to exist. Furthermore, congenital disabilities and comorbidities, related to the ID, influence frailty but are complicated, if not impossible, to prevent. Hence, it is of paramount importance to closely monitor individuals at risk and develop an individual health care plan that takes into account all health aspects (social, physical and physiological) and that aims at the highest quality of life. We recommend that more knowledge about frailty is provided to care givers, including physicians and daily care givers. One should be aware of the slowly progressing decline in health that could eventually lead to the clinical manifestation of frailty.

Screening and monitoring of frailty should be broadly implemented. Recovering from a very frail state is complicated, especially at high age [55]. It is therefore important to be able to recognize people at risk to develop frailty. In the long run, it would be very beneficial if, using routinely collected data, a frailty index is automatically calculated yearly for each individual. This would enable care givers to notice small changes in health status, and intervene at an early stage. Furthermore, frailty indices (either composed from routinely collected data or clinical instruments) are advised to be used in the evaluation of health interventions.

Furthermore, there are several recommendations for clinical practice that could positively influence the overall frailty status in the ID population. In recent years, results from the HA-ID study and others, showed ample opportunities to improve the care for people with ID. Some examples: 1. levels of physical fitness and physical activity are extremely low [46, 56], and dietary habits are poor [42], both offer much room for improvement, 2. Depression and anxiety symptoms are often present but inadequately recognized [57, 58]. Early detection, the limitation of life events, sufficient social support and proper treatment are therefore important, 3. To limit the severe side-effects of antipsychotics, discontinuation should be considered [59-61] and regularly medication reviews are advised to limit the number of prescription errors [62], 4. Cardiovascular risk factors

(e.g. high serum triglyceride, elevated blood pressure) are frequently present but often undiagnosed [63-65]. Pro-active screening and treatment is therefore recommended.

These recommendations show the complexity of frailty, but also show many opportunities to improve the ID care. Nevertheless, in large and complex organizations such as those taking care of people with ID, the implementation of lifestyle interventions is complex and several aspects need to be taken into account. First of all, as mentioned before, it is of paramount importance to create awareness of the frailty problem and possible solutions throughout the care organization. Without understanding, care givers will not be motivated to implement interventions, or adapt their everyday care. Second, screening for the areas that ask for improvement (e.g. nutrition, physical activity, depression), obtained by scientific research need to be implemented. Third, effective interventions, with corresponding protocols need to be readily accessible. Fourth, time and money need to be made available to actually offer the required care. It is therefore required that clearance is provided about who is responsible for what in the ID sector.

These points are already complicated within specialized ID organizations, but may be even more complicated outside the organizations. People with borderline or mild ID who do not use any form of formal care will not benefit from interventions offered by the care organization. This group will further increase in years to come because of a recent change in health care legislation that assigns the care for this group to general practitioners, geriatricians and informal caregivers in municipalities. In addition, a large degree of self-management among this group of older people with ID is now expected. Education about frail older people with ID and related problems for physicians and other formal and informal caregivers is essential to raise awareness for frailty. Furthermore, it is important that physicians can discuss their cases with specialized ID physicians. In the Netherlands, this has been taken care of in terms of specialized ID outpatient clinics. But this option needs to be further implemented, apparent from the indication of general practitioners that they lack knowledge about this specific group [66]. Additionally, people with ID that do not use any form of formal care or support, need to be educated themselves about a healthy lifestyle. This will ask for specific and carefully designed programs, because it is known that people from lower social classes are difficult to reach with interventions.

CONCLUSION

In line with others, we predict that frailty is, and will increasingly become a major health care concern, that not only threatens the quality of life of older people with ID but

also leads to increased health care costs. People with ID are already the most expensive diagnostic group in the Netherlands [67] and these costs have been growing in recent years (2007-2012) [68]. Results from the HA-ID study show that frailty is a useful method to measure overall health, also in people with life-long physical and cognitive disabilities. The accumulation of molecular and cellular damage may have a higher frequency in people with ID, leading to an earlier depletion of physiological reserves. Additionally, people with ID may have less redundancy or repair mechanisms to limit the accumulation of damage. Early developed or congenital disorders, originated from either genetic/chromosomal abnormalities or pre-natal errors contribute, via cognitive limitation and comorbidities, strongly to frailty in people with ID. Nevertheless, there are ample opportunities to improve the environmental factors. In addition, we suggest that awareness is created about the accumulation of health problems that lead to frailty. Future research should be performed to develop a valid screening instrument, study trajectories of frailty and evaluate the suggested mechanisms of frailty in people with ID.

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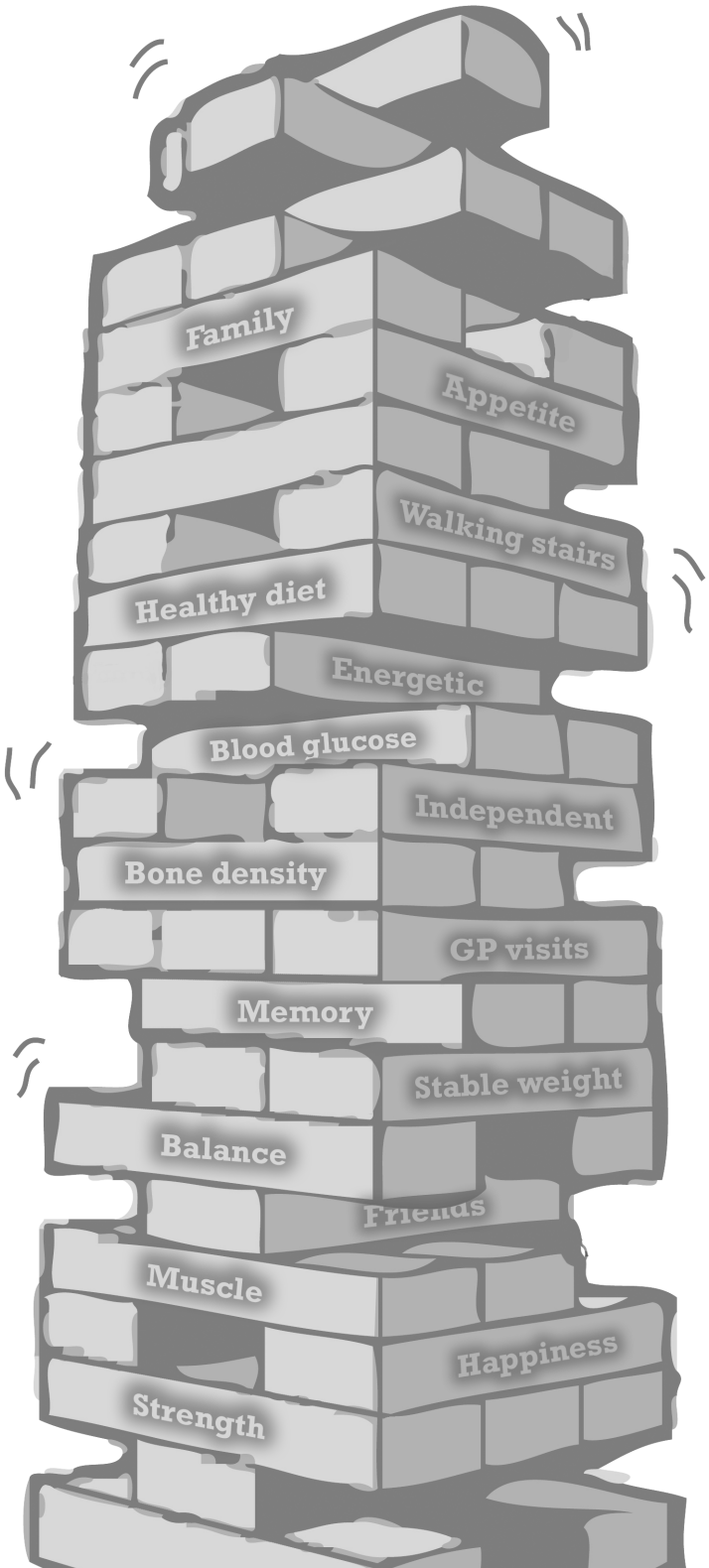
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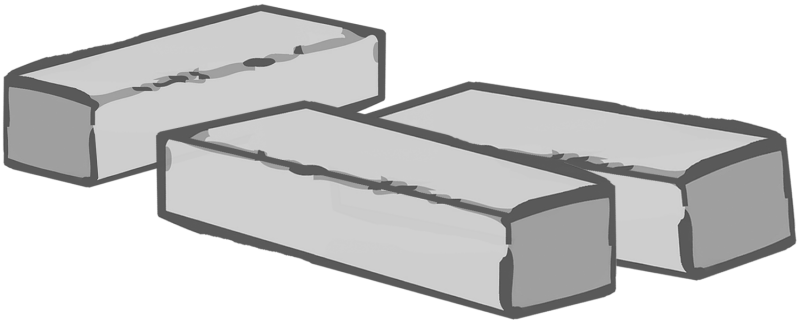
Happiness
Strength

English summary



CHAPTER 1: INTRODUCTION

As the number of older persons is increasing, healthy aging becomes a major challenge for individuals, care givers and health care policy makers. To maintain a high quality of life for elderly people and to limit the burden on the health care system, knowledge on healthy aging and its trajectories is essential.

Improved health care, knowledge, advocacy and services have also increased the life expectancy of people with intellectual disabilities (ID). People with ID are characterized by limitations in both intellectual functioning and adaptive behavior that start before the age of 18 (diagnostic criteria DSM, 2000). The prevalence of people with ID has been estimated to be 1.5 to 2% in the Western countries. Although people with ID reach a higher age, it has long been a common understanding that people with ID are already showing clear signs of old age at the age of 50, because there seems to be an early onset of functional decline. A better understanding in this observed so-called 'early aging' would provide targets for preventive medicine and could identify specific risk groups.

A useful method for studying the ageing process and the transition from health to disease is frailty. Frail individuals are more likely to deteriorate in their daily functioning, develop mobility limitations, are more often hospitalized, develop more often chronic diseases and have shorter survival probabilities. To a large extent, frailty is preventable and reversible. This thesis focuses on the measurement, frequency, determinants, and consequences of frailty in older people with ID. This thesis is part of the large Healthy Ageing and Intellectual Disability' (HA-ID) study that has been performed among 1050 people with ID, aged 50 years and over, who received formal care from an ID specialized care organization. Participants were followed for a period of three years.

CHAPTER 2: FRAILTY AND INTELLECTUAL DISABILITY: A DIFFERENT OPERATIONALIZATION?

Frailty has been broadly recognized as a state of increased vulnerability for adverse health outcomes.

Nevertheless, there is yet not one generally accepted definition or measurement strategy. In this chapter we describe the most commonly used instruments and their possible applicability for the ID population. One frequently applied, physically oriented operationalization, developed by Fried et al, is the frailty phenotype that defines frailty as the presence of three out of five clinical symptoms (unintentional weight loss, weakness, slow walking speed, self-reported exhaustion, and low physical activity). We hypothesized that this frailty definition would be too much influenced by motor disability and, because of the frequently prevalent chronic comorbidities, social isolation,

medication use, life events and disabilities, a broader definition of frailty would be better suited. The Tilburg Frailty Indicator by Gobbens et al., is a valid measure for frailty in the general population that includes a social, physical and psychical domain. Nevertheless, we concluded that most items of this questionnaire are complicated to be filled in by, or for, people with moderate to severe ID and items will not sufficiently discriminate (e.g. education level). We argued that, possibly, the frailty index, developed by Rockwood and Mitnitski, would be a suitable measure for frailty in people with ID. The frailty index is based on a-specific accumulation of health problems, called deficits. It does not focus on a specific set of variables and can therefore be adapted to the ID population.

CHAPTER 3: DEVELOPMENT OF A FRAILTY INDEX

Based on data from the Healthy Aging and Intellectual Disability study, we developed a frailty index with 51 health related deficits. The 51 deficits include a broad spectrum of objective measurements (e.g. grip strength, walking speed, serum glucose), informer reports (e.g. fatigue, depression symptoms, dressing) and medical information (e.g. medication use, general hospital admission, asthma). A frailty index score was calculated taking the number of deficits present, divided by 51, resulting in a score between 0 (no deficits present) and 1 (all deficits present). The characteristics of our frailty index were comparable to frailty indices designed for the general population: skewed distribution, correlation with age and an observed maximum frailty index score of around 0.7. Further robustness was demonstrated by correlating 50 frailty indices based on random selections of 75% of the deficits, with age, showing that the index's correlation with age was not influenced by the choice of deficits, which shows structural validity.

Results with the frailty index showed that the mean frailty index score for people with ID was 0.27, equivalent to the prevalence of 14 out of 51 deficits. The frailty index score was positively correlated with age and the presence of Down syndrome. More severe ID was associated with higher frailty index scores. Results from the general elderly population show usually a mean score between 0.08 and 0.17. Compared to a general European population (50+), people with ID accumulate more deficits and this accumulation starts at much younger age.

CHAPTER 4: CHARACTERISTICS OF THE LEAST FRAIL

Most ageing research focus on the question "what causes pathology?" This so-called 'negative biology' perspective has led to advances in the understanding, and treatment, of the age-related diseases. Nevertheless, understanding why some people age without

diseases and in good health, (or 'positive biology') could yield important insights into successful ageing and maintenance of health in older age. In line with the positive biology perspective, we studied the characteristics of the least frail (frailty index score ≤ 0.10) participants. Our first conclusion was that there were very few participants with such low frailty index scores: 6.6%, whereas in the general population this percentage is estimated to be at least 43%. Second, we concluded that the health of the least frail participants was better in several health domains: they were characterized by better mobility and physical fitness, relative independence, less signs of depression/dementia and less chronic diseases.

CHAPTER 5: BIOCHEMICAL MEASURES AND FRAILTY

We examined several biological measures that could help to identify pathophysiological pathways involved in the observed early onset of frailty in people with ID. We found that frailty was associated with inflammation (CRP and IL-6), anemia, metabolic markers (glucose, cholesterol and albumin) and renal functioning (cystatin-C). These results imply that mainly inflammation and nutritional state are important contributors of frailty. Furthermore they provide an important basis for future research into both the understanding of frailty in people with ID and the possibility to identify frailty using biochemical measures. We only measured a selective set of biochemical measures, but many more are known to be associated with frailty (e.g. oxidative stress and TNF), and need to be studied in people with ID as well. Furthermore, the possibility to measure frailty using a set of biochemical measures should be studied. This could be of special interested for those with communication difficulties.

CHAPTER 6: PREDICTING DISABILITIES IN DAILY FUNCTIONING

In the general population it has been shown that frailty leads to disabilities in daily functioning such as activities of daily living (ADL), instrumental activities of daily living (IADL) and mobility. On the contrary, in people with ID, disabilities in daily function can be life-long and are more likely to result in frailty than the other way around. Even so, frailty could lead to a further decrease in dependency. Therefore we evaluated the relation between the frailty index and deterioration of ADL, IADL and mobility over a three year follow-up period. As suspected, the frailty index was not related with decreased daily functioning in people with no or limited independence at baseline. For people who could further decrease their dependence we found a strong relation between the frailty index score and deterioration of ADL, IADL and mobility.

CHAPTER 7: PREDICTING ADVERSE HEALTH OUTCOMES

Longstanding disabilities in people with ID may not only effect their frailty status, but also its consequences. In addition to the effect of frailty on disability (chapter 6), we were interested in its relation with falls, fractures, chronic comorbid conditions, medication use and hospitalization. We did not find a relation between frailty and falls, fractures and hospitalization three years onwards. In the general population, the former two show inconsistent results. However, in the general population, frailty is frequently related to hospitalization and increased hospital stay. Our results could be explained by the fact that, conditions that normally require specialist services remain sometimes undiagnosed, or that family, personal caregivers or hospital staff may have decided that hospital treatment was not in the best interest of the client. We did find a relation between frailty and an increased number of prescribed medication and comorbid conditions. This implies that frailty is related to an increased risk for negative health outcomes, also in a population with lifelong disabilities.

CHAPTER 8: THE IMPACT OF FRAILTY ON CARE INTENSITY

We argued that, because frailty in people with ID is related to adverse health outcomes, it will also be related to increased health care costs. To study this, we evaluated the relation between frailty and an increase in care intensity three years later. Care intensity was estimated using Care Intensity Packages (in Dutch = Zorg Zwaarte Pakket [ZZP]). In total there are 8 ZZP packages, ranging from minimal support (ZZP1) to intensive all-day care and support (ZZP8). For each individual classified in a ZZP category an allocated annual budget is available for care and support. For 26% of the participants, care intensity had increased during a follow-up of three years. Increased care was related with high frailty index scores, independent of the level of ID, age, gender and Down syndrome. These results show that frailty does not only effect individual health, but also increases the burden on the health care system.

CHAPTER 9: PREDICTING 3-YEAR SURVIVAL

In this study we focused on whether the frailty index predicts survival in people with ID. We divided the sample in five frailty groups: relatively fit (frailty index score < 0.20), vulnerable (frailty index score 0.20-0.29), mildly frail (frailty index score 0.30-0.39), moderately frail (frailty index score 0.40-0.49) and severely frail (frailty index score ≥ 0.5). Significantly more participants in the frailty groups died than those who were classified

as relatively fit. These results are congruent with other studies that also show strong relations between the frailty index score and survival. A difference was that, in the general population, individuals with a score around 0.2 already have a higher mortality risk than people with a score around 0.10. We did not find significant differences in mortality risk between the relatively fit and the vulnerable group. These results suggest that older people with ID can manage more deficits than the general population before their mortality risk increase. It could be that lifelong disabilities are less predictable for mortality than disabilities acquired in later life.

CHAPTER 10: COMPARING TWO FRAILTY MEASURES

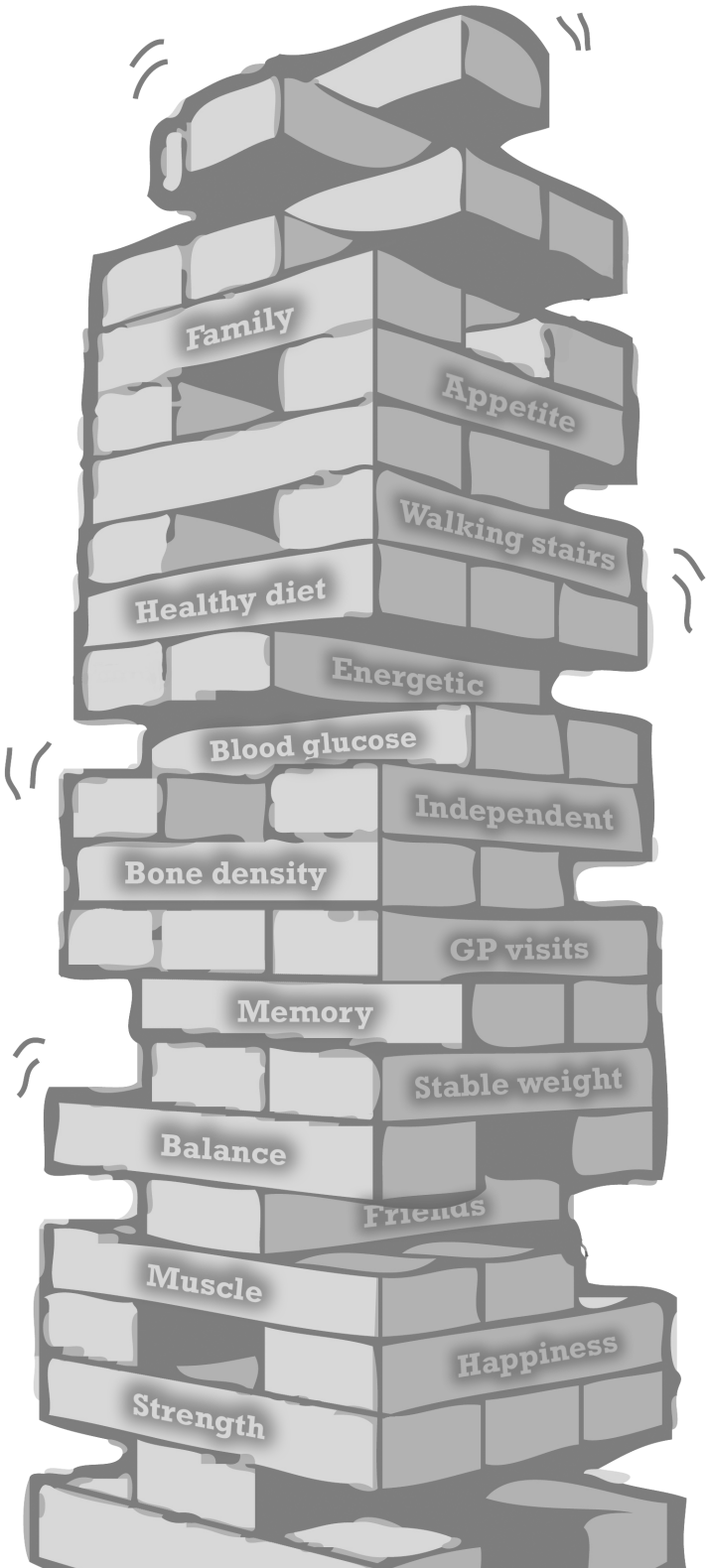
To evaluate which frailty method was most applicable and most valid to the ID population, we directly compared two frequently used frailty instruments: the frailty index and the frailty phenotype. Additionally, we were interested whether motor disability influenced the relation between frailty and mortality. Because it could be expected that frailty is influenced by lifelong motor disabilities.

We found that the frailty index was more often applicable (94%) than the frailty phenotype (81%). Both frailty measures were related to mortality three years later, although the frailty index showed a stronger relation than the phenotype. If adjusted for motor disability, the frailty phenotype lost much of its predicted value, whereas the frailty index remained strongly related with mortality. It seems that the frailty phenotype is too much determined by motor disabilities in this population and is therefore less predictive of mortality. Furthermore, we were able to adapt the frailty index to the ID population, which could have increased its validity.

CHAPTER 11: GENERAL DISCUSSION

In this final chapter, the most important results are summarized, the implications for clinical practice and future research are discussed. Frailty seems to start earlier and is more severe in people with ID than observed in people in the general population, but consequences on health outcomes and care are similar. The observed early frailty in people with ID could be explained by both genetic and environmental factors, their interaction, and possible synergetic effect. The high frequency and serious consequences of frailty ask for immediate action for people living within the care organization, but also for those living independently. Congenital problems and comorbidities are complicated and are likely to influence frailty without many opportunities for prevention. Nevertheless, improvement of lifestyle and sleep quality, the early recognition of treatable

conditions, and the prevention of life events (e.g. trauma's) could prevent or delay frailty to some extent. Future longitudinal research should address the causality between risks (e.g. chronic inflammation, low physical activity) and the onset of frailty. Furthermore, there is a need to develop a predictive screening instrument for clinical practice.


Family
Appetite
Walking stairs
Healthy diet
Energetic
Blood glucose
Independent
Bone density
GP visits
Memory
Stable weight
Balance
Friends
Muscle
Happiness
Strength

Nederlandse samenvatting

Kwetsbaarheid bij ouderen met een verstandelijke beperking: operationalisering, risico en opsporing

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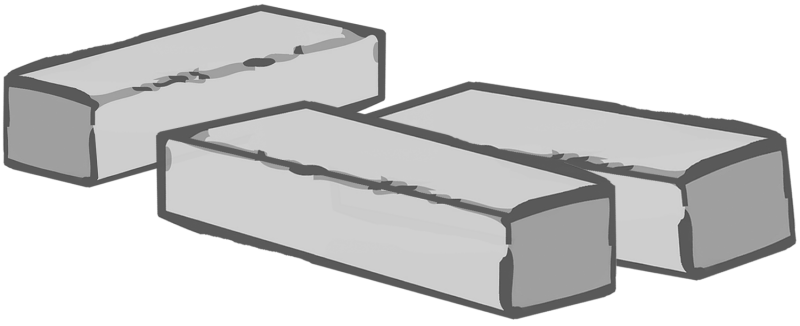


INTRODUCTIE

De levensverwachting van mensen met een verstandelijke beperking neemt steeds verder toe en hierdoor stijgt ook het totaal aantal ouderen met een verstandelijke beperking [3]. Ondanks de toename in de levensverwachting lijkt er sprake te zijn van een vroegtijdige functionele achteruitgang. Ouderen met een verstandelijke beperking hebben aanzienlijk meer gezondheidsproblemen dan andere ouderen, wat mogelijk consequenties heeft voor hoge zorgconsumptie en kosten. Tot in het eerste decennium van deze eeuw was de wetenschappelijk onderbouwde kennis over de gezondheid van deze groeiende groep ouderen beperkt. In 2008 is daarom gestart met het `Gezond Ouder met een verstandelijke beperking (GOUD)'-onderzoek, een grootschalig onderzoek naar de gezondheid van cliënten van 50 jaar en ouder, van gespecialiseerde zorgaanbieders in Nederland. Resultaten uit dit GOUD-onderzoek bevestigen de vroegtijdige ongezondheid. Zo blijkt de gemiddelde fitheid van 50ers vergelijkbaar met die van 70-80 jarigen in algemene populaties [6]. Ook werd gevonden dat veel cliënten een verstoord slaap-waak ritme hebben [7, 8], evenals al hoge preventies van sarcopenie, diabetes en obesitas [9-11].

Deze resultaten tonen de hoge urgentie van detectie van specifieke bedreigingen van de gezondheid en van passende zorg gericht op preventie. Zowel vanuit de wetenschap als de verstandelijk gehandicaptenzorg rees daarom de vraag of het mogelijk was gezondheid te meten met een overkoepelende publieke gezondheidsmaat. Voorbeelden van veelvuldig toegepaste gezondheidsmaten zijn multimorbiditeit, polyfarmacie en kwetsbaarheid. Uit het GOUD-onderzoek bleek dat multimorbiditeit, gedefinieerd als twee of meer chronische aandoeningen die een negatieve invloed hebben op het functioneren van het dagelijks leven, voorkomt bij 80% van de deelnemers [13]. Deze prevalentie is vergelijkbaar met die van de Nederlandse verpleeghuispopulatie. Polyfarmacie, in het GOUD-onderzoek gedefinieerd als het chronisch gebruik van 5 of meer middelen, kwam bij 40% van de studiepopulatie voor. Slechts 11% gebruikte helemaal geen medicijnen, en 6% gebruikte 10 of meer medicijnen. Voordat er uitspraken gedaan konden worden over de derde overkoepelende gezondheidsmaat, kwetsbaarheid, moest eerst worden onderzocht welke operationalisering toepasbaar was en of kwetsbaarheid op dezelfde wijze als in de algemene bevolking een achteruitgang in gezondheid en zelfstandigheid voorspelt [14]. Hier vatten wij de belangrijkste resultaten samen. Verder, beschrijven we via welke route wij tot een keuze zijn gekomen van een geschikt kwetsbaarheidsinstrument, wat de resultaten waren van cross-sectionele metingen binnen de GOUD-populatie, en hoe voorspellend deze methode was voor gezondheid en zelfstandigheid in een follow-up van drie jaar. Op basis hiervan gaan wij kort in op de toekomstige stappen die genomen kunnen worden om kwetsbaarheid en de gevolgen te verminderen.

HET GOUD-ONDERZOEK

Het GOUD-onderzoek is een grootschalig epidemiologisch onderzoek naar de gezondheidstoestand van 1050 mensen met een verstandelijke beperking (50 jaar en ouder) [15]. Deelnemers werden verworven bij drie Nederlandse zorgaanbieders (Ipse de Bruggen, Abrona & Amarant), die gespecialiseerd zijn in ondersteuning voor mensen met een verstandelijke beperking, variërend van ambulante ondersteuning of dagbesteding tot woonbegeleiding met intensieve zorg en begeleiding. Alle cliënten van 50 jaar of ouder werden uitgenodigd (*N* = 3222), waarvan 1050 toestemming gaven voor deelname. De deelnemers vormden een vrijwel representatieve populatie voor de gehele Nederlandse populatie mensen met een verstandelijke beperking die zorg ontvangen van een gespecialiseerde zorginstelling. Het onderzoek werd opgezet vanuit het perspectief van preventie. Binnen drie thema's (Lichamelijke activiteit en Fitheid, Voeding en Voedingstoestand, Depressie en Angst) werd een breed scala aan gegevens verzameld. Binnen deze thema's werden de deelnemers uitvoerig onderzocht met onder andere een fitheidstestbatterij, slaap-waakonderzoek (actiwatch), stappentellers, voedingsdagboeken, lichamelijk onderzoek, bloedonderzoek en een breed scala aan vragenlijsten, onder andere over voedingstoestand, zelfstandigheid, angst en depressie. Tevens werden er gegevens verzameld uit het (medisch) dossier.

Drie jaar na de baseline metingen zijn er vervolgmetingen verricht. Tijdens dit vervolgonderzoek werden er door woonbegeleiders vragenlijsten ingevuld over de huidige zelfstandigheid en mobiliteit van de cliënten. Zelfstandigheid werd uitgedrukt in activiteiten van het dagelijks leven (ADL; b.v. naar het toilet gaan, eten) en de instrumentele activiteiten van het dagelijkse leven (IADL; b.v. huishoudelijke klussen, telefoneren). Bij de arts werden ziekenhuisopnamen over de afgelopen 3 jaar en het huidige medicatie gebruik opgevraagd. Tot slot werd nagezocht welke cliënten overleden waren.

OPERATIONALISERING VAN KWETSBAARHEID

Onderzoekers zijn het er over eens dat een kwetsbaar individu een grotere kans heeft op achteruitgang van de gezondheid vergeleken met een niet kwetsbaar individu van dezelfde leeftijd [16]. Er zijn de afgelopen decennia verschillende conceptuele en operationele definities van kwetsbaarheid in gebruik geraakt [17]. Elk van deze definities heeft zijn voor- en nadelen. Wij zochten de operationalisering die toepasbaar was voor mensen met een verstandelijke beperking. Brehmer en Weber in Wenen waren de eersten die kwetsbaarheid in kaart brachten bij mensen met een verstandelijke beperking. Hiervoor maakten ze gebruik van een zelf ontworpen vragenlijst, de Vienna Frailty Questionnaire

for people with ID, die bestaat uit vier domeinen (sociaal, cognitief, fysiek en psychisch) [18]. Zij vonden dat ruim een kwart van de 50+ deelnemers kwetsbaar was. Echter, de studiepopulatie was zeer klein en de uniekheid van de vragenlijst maakt vergelijking met de algemene populatie niet mogelijk. Voor de algemene Nederlandse populatie wordt de Tilburg Frailty Indicator (TFI) veelvuldig gebruikt, waarbij kwetsbaarheid omschreven wordt als "het resultaat van tekorten in diverse domeinen van lichamelijk, cognitief, sensorisch en psychosociaal functioneren" [19]. De vereiste zelfrapportage maakt echter dat dit instrument voor mensen met een matige of ernstige verstandelijke beperking of communicatieproblemen niet toepasbaar is. De twee operationaliseringen die internationaal het meest worden gebruikt zijn het kwetsbaarheidsfenotype van Fried et al. en de kwetsbaarheidsindex van Rockwood en Mitnitski. Beide zijn toegepast tijdens het GOUD-onderzoek. Bij de eerste wordt kwetsbaarheid gedefinieerd als de aanwezigheid van tenminste drie van de volgende vijf criteria: onbedoeld gewichtsverlies, lage spierkracht, langzame wandelsnelheid, lage lichamelijke activiteit en slecht uithoudingsvermogen [20]. In de algemene populatie blijkt dat ouderen die kwetsbaar zijn volgens het fenotype een hogere kans hebben om te overlijden [21]. Het kwetsbaarheidsfenotype bleek toepasbaar bij 81% van de GOUD-populatie. Van de totaal geïncludeerde populatie bleek 13% kwetsbaar te zijn, een gemiddelde dat hoger is dan dat gevonden bij de algemene populatie. Van de mensen met een lichte verstandelijke beperking was 6% kwetsbaar. Zoals verwacht hing de gevonden kwetsbaarheid sterk samen met mobiliteit [22].

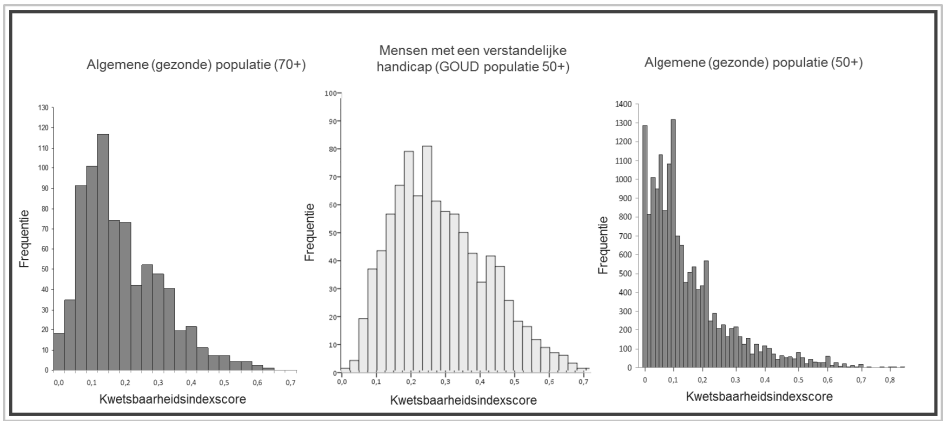
De tweede operationalisering, de kwetsbaarheidsindex is gebaseerd op de aspecifieke opeenstapeling van gezondheidsproblemen [1, 23]. De keuze van items en het exacte aantal items is vrij mits er minstens 30 items worden gekozen, de items gerelateerd zijn aan leeftijd, er voldoende variatie is (geen plafond-of bodemeffect) en alle gezondheidsdomeinen (lichamelijk, functioneel, sociaal en psychologisch) zijn vertegenwoordigd. De kwetsbaarheidsindex is valide gebleken, in de zin van voorspellend voor achteruitgang van gezondheid, in verschillende populaties, inclusief zeer oude en functioneel beperkte groepen [17, 23]. Wij vermoedden dat de kwetsbaarheidsindex, bij mensen met een verstandelijke beperking, beter toepasbaar en sterker voorspellend zou zijn dan het kwetsbaarheidsfenotype. De belangrijkste reden hiervoor was dat het kwetsbaarheidsfenotype puur gericht is op fysieke gezondheid, terwijl de heterogene problematiek die wordt gezien bij mensen met een verstandelijke beperking leek te vragen om een multifactoriële operationalisering van kwetsbaarheid. Ten tweede, daar waar het kwetsbaarheidsfenotype gebruik maakt van een vaste set van variabelen kan de kwetsbaarheidsindex flexibel worden ingevuld en daarmee worden aangepast aan een specifieke populatie. Tijdens het GOUD-onderzoek is onderzocht of de kwetsbaarheidsindex daadwerkelijk toepasbaar was bij mensen met een verstandelijke beperking.

Van de ruim 400 mogelijke items, alle verzameld tijdens het GOUD-onderzoek, bleken er 51 te voldoen aan alle eisen die aan een kwetsbaarheidsindex gesteld worden: correlatie met leeftijd, geen bodem of plafondeffect, voldoende vaak gemeten (> 30%), gezondheidsaspect [1, 5]. Deze items kwamen veelal overeen met items die in kwetsbaarheidsindexen voor de algemene populatie zitten, maar een aantal was specifiek voor deze populatie, zoals slikstoornissen en scoliose. Alle 51 items werden gecodeerd naar een score tussen de 0 (deelnemer heeft dit probleem niet) en 1 (deelnemer heeft dit probleem). Alle item-scores werden bij elkaar opgeteld en gedeeld door het totale aantal items. Zo werd voor elke deelnemer een kwetsbaarheidsscore berekend die liep van 0 (totaal niet kwetsbaar) tot 1 (extreem kwetsbaar). Er kon een kwetsbaarheidsindex berekend worden voor 97% ($n = 982$) van de deelnemers. Voor 68 deelnemers hadden we te weinig gegevens om een kwetsbaarheidsindex score te berekenen. De gemiddelde score was 0.27 [5]. Uitgaande van de vele problemen bij mensen met een verstandelijke beperking, verwachtten wij een hoger gemiddelde te vinden dan dat in de algemene populatie. Dit bleek te kloppen: de gemiddelde kwetsbaarheidsscore van 50-plussers met een verstandelijke beperking kwam overeen met die van de algemene 70-plus populatie (figuur 1). We vonden dat kwetsbaarheid vaker voorkwam bij mensen met een ernstige mate van verstandelijke beperking en bij mensen met het Down syndroom en toenam met de leeftijd (tabel 1). Dit was te verwachten, omdat ernstige verstandelijke beperking gepaard gaat met een hoge comorbiditeit, terwijl, zoals bekend is, mensen met het Down syndroom een verhoogd risico hebben op vroeg optredende zintuiglijke stoornissen, hypothyreoïdie en Alzheimer dementie.

Het feit dat reeds vanaf 50 jaar regelmatig sprake is van kwetsbaarheid, maakt aannemelijk dat problemen zich al voor het 50ste levensjaar opstapelen. Dit is begrijpelijk, gezien de in de inleiding genoemde vroege beperkingen en multimorbiditeit. Omdat niet eerder kwetsbaarheid is onderzocht in een vroeg-gehandicapte populatie, vroegen wij ons af of de kwetsbaarheidsindex op dezelfde wijze als in de algemene populatie voorspellend zou zijn voor een (verdere) achteruitgang in gezondheid.

DE RISICO'S VOOR KWETSBARE OUDEREN

Figuur 2 laat de Kaplan Meier survival curves zien voor verschillende maten van kwetsbaarheid. Het risico op overlijden stijgt significant bij een kwetsbaarheidsscore van 0.3 en neemt daarna exponentieel toe [4]. In de algemene populatie ligt dit punt rond de 0.2 [2]. Desalniettemin was de sterfte onder mensen met een kwetsbaarheidsindex tussen de 0.2-0.3 twee keer zo hoog als onder mensen met een score onder de 0.2.

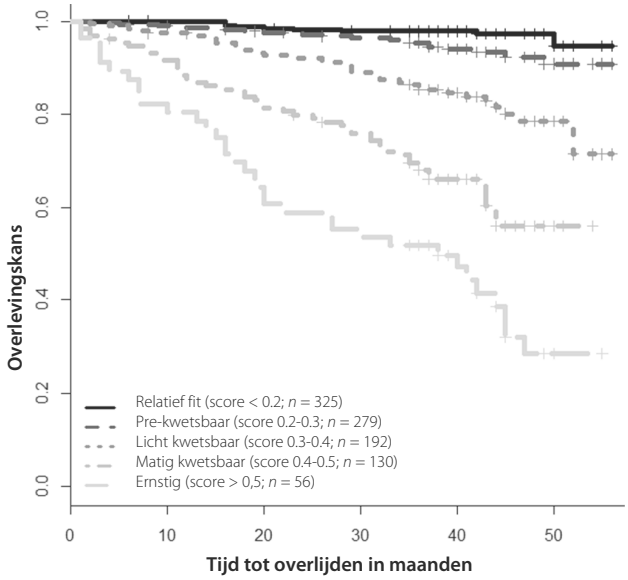


Figuur 1. Verdeling van de kwetsbaarheidsindexscore voor drie verschillende populaties (links 754 deelnemers uit de algemene (gezonde) populatie (70+) [1], in het midden de GOUD-populatie bestaande uit 982 ouderen (50+) met een verstandelijke beperking [5] en rechts een Europese (n = 29905) 50+ populatie [12].

Tabel 1. Kenmerken van de deelnemers van het GOUD-onderzoek en bijbehorende kwetsbaarheidsindexscore op baseline

Kenmerken	*n*	Gemiddelde KI-score	*SD*	*p*-waarde
Totale populatie	982	0.27	0.13	-
Geslacht				.159[a]
Mannen	507	0.27	0.13	
Vrouwen	475	0.28	0.13	
Ernst verstandelijke beperking				< .001[b]
Zwakbegaafd	29	0.19	0.11	
Licht	191	0.21	0.12	
Matig	432	0.26	0.12	
Ernstig	147	0.33	0.12	
zeer ernstig	82	0.41	0.10	
Leeftijdscategorie				< .001[b]
50-59 jaar	458	0.25	0.12	
60-69 jaar	344	0.28	0.12	
70-79 jaar	156	0.34	0.12	
80-89 jaar	21	0.41	0.14	
90 jaar en ouder	3	0.42	0.03	
Oorzaak verstandelijke beperking				.007[a]
Andere oorzaken	732	0.27	0.13	
Down syndroom	142	0.31	0.13	

KI = Kwetsbaarheidsindex, *SD* = standard deviatie
[a]Verschil tussen de categorieën getest op significatie met een t-toets voor onafhankelijke steekproeven
[b]Verschil tussen de categorieën getest op significatie met een univariaat regressie model

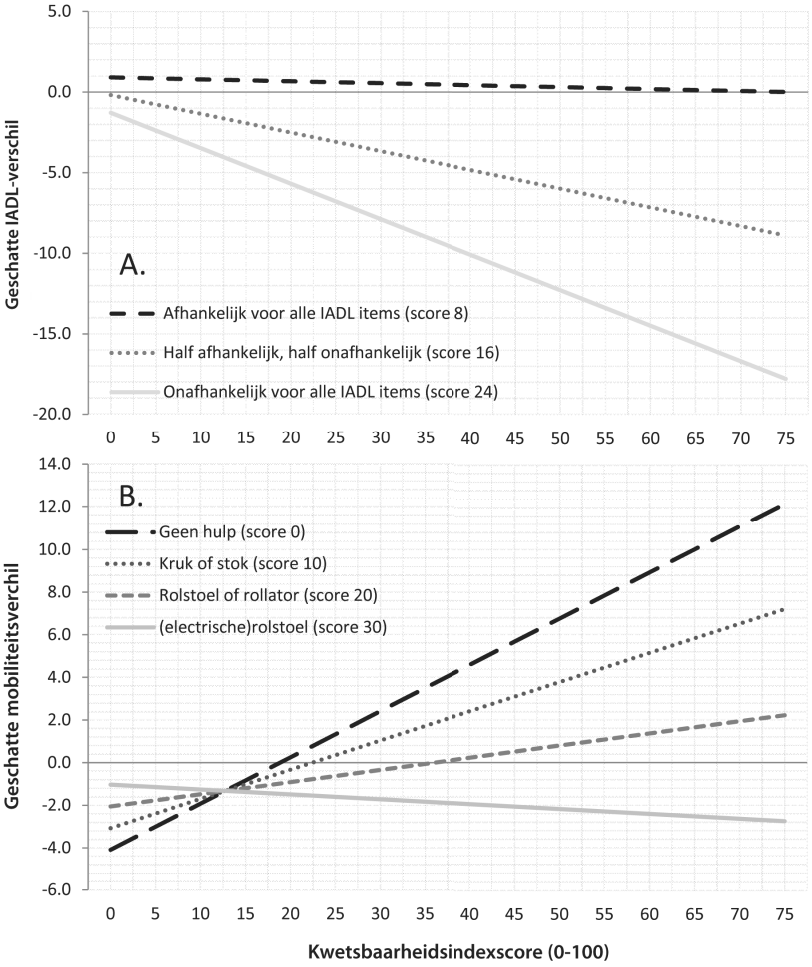


Figuur 2. Kaplan-Meier curve gestratificeerd voor verschillende kwetsbaarheidsindexscores op baseline. De relatief fitte groep (bovenste, zwarte lijn; score < 0.2) heeft de hoogste overlevingskans, de ernstig kwetsbare groep (score > 0.5) heeft de laagste overlevingskans, de licht, matig, en ernstig kwetsbare groepen zitten daar tussenin. De pre-kwetsbare groep heeft geen significant hogere kans op overlijden. De licht, matig en ernstig kwetsbare groepen hebben alleemaal een significant hogere kans te overlijden vergeleken met de relatief fitte groep ($p < .001$). Figuur gebaseerd op een eerdere publicatie in *the Journal of the American Geriatrics Society* [4].

Naast een verhoogd risico op overlijden vonden we dat deelnemers met een hogere kwetsbaarheidsindex meer achteruitgingen in hun zelfstandigheid [2], overeenkomstig de bevindingen in de algemene ouderen populatie [24-26]. Voor mensen die op baseline al de minimale score voor zelfstandigheid hadden op de gebruikte ADL, IADL en mobiliteit vragenlijsten, kon geen verdere achteruitgang gemeten worden. Anderzijds, mensen die een maximaal hoge score hadden konden relatief verder achteruitgaan gedurende de follow-up periode. Om hiervoor te corrigeren, werd een interactieterm tussen de kwetsbaarheidsscore en de baseline IADL of mobiliteitsscore toegevoegd aan een lineair regressiemodel (voor ADL bleek dit niet nodig). Figuur 3 geeft de geschatte relatie tussen de kwetsbaarheidsindex en achteruitgang in IADL en mobiliteit weer, gestratificeerd voor verschillende baseline IADL en mobiliteitsscores. De kwetsbaarheidsindex kon geen achteruitgang voorspellen bij deelnemers die op baseline al volledig afhankelijk waren of gebruik maakte van een rolstoel. De sterkste voorspellende waarde had de kwetsbaarheidsindex voor mensen die relatief onafhankelijk waren en zonder hulpmiddelen konden lopen. Het ontbreken van een relatie tussen kwetsbaarheid en

achteruitgang bij de functioneel slechtste groep wil niet zeggen dat deze er niet is. Maar de gebruikte IADL en mobiliteit vragenlijsten maakten het meten daarvan niet mogelijk.

In tegenstelling tot wat vermeld wordt in literatuur over de algemene populatie vonden we geen relatie tussen kwetsbaarheid en aantal ziekenhuisopnamen [24, 27-29]. Dit zou verschillende oorzaken kunnen hebben. Enerzijds is het mogelijk dat aandoeningen die normaliter behandeling in het ziekenhuis vereisen, minder snel gediagnostiseerd worden in deze populatie. Anderzijds kunnen familie, persoonlijk begeleiders of zieken-



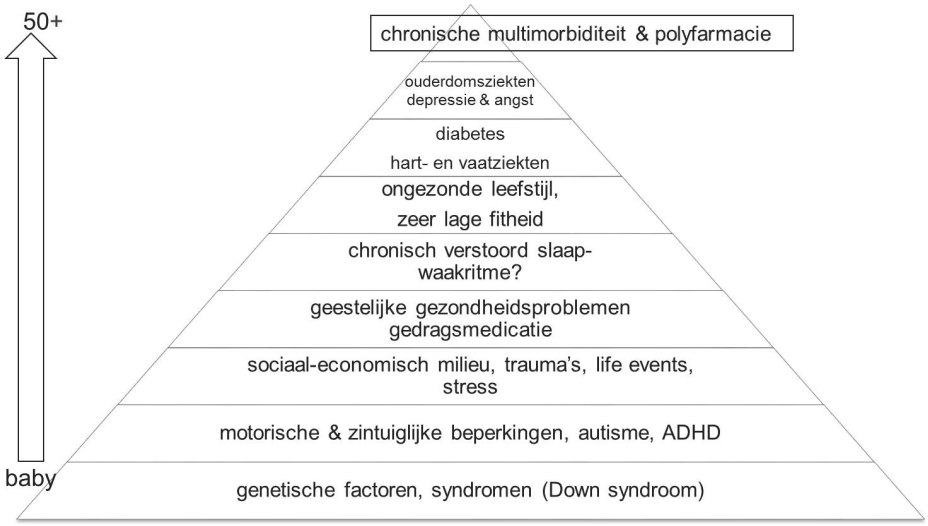
Figuur 3. Relatie tussen de kwetsbaarheidsindex op baseline en de geschatte IADL (A) en mobiliteit (B) achteruitgang drie jaar later. De lijnen vertegenwoordigen verschillende baseline IADL/mobiliteit scores voor een man van 55 jaar met een matige verstandelijke handicap en geen Down syndroom. Figuur gebaseerd op een eerdere publicatie in *Research in Developmental Disabilties* [2].

huispersoneel besluiten dat ziekenhuisopname te belastend is voor de cliënt, of dat de verzorging bij voorkeur plaats vindt in de zorginstelling in plaats van het ziekenhuis. We vonden tevens dat de hoogte van de kwetsbaarheidsindex gerelateerd was aan een toename van het aantal medicamenten [27]. Dit resultaat werd eerder gevonden in de algemene ouderen populatie [30, 31]. Tot slot vonden we dat mensen met een hoge kwetsbaarheidsindex een grotere kans hadden meer zorg te gaan gebruiken binnen drie jaar [32]. Samenvattend kunnen we zeggen dat in deze vroeg gehandicapten populatie de kwetsbaarheidsindex een sterke voorspeller is voor overlijden en achteruitgang van zelfstandigheid mobiliteit en gezondheid.

OPSPORING EN BEHANDELING VAN KWETSBARE OUDEREN

De kwetsbaarheidsindex is een geschikt instrument gebleken om epidemiologisch, populatiegericht onderzoek te doen. De klinische toepasbaarheid van het instrument in de verstandelijk gehandicapten populatie is nog onbekend. Echter, de sterke relatie tussen kwetsbaarheid en achteruitgang van zelfstandigheid, mobiliteit, toename van medicatiegebruik en overlijden, maakt individuele opsporing essentieel. Temeer omdat uit de algemene populatie bekend is dat kwetsbaarheid een dynamisch proces is, dat geremd kan worden of zelfs reversibel is door effectieve interventies [17, 33-35]. Er zou dus een instrument moeten komen dat, vroegtijdig, mensen identificeert die een grote kans hebben kwetsbaar te worden of te zijn. De gebruikte kwetsbaarheidsindex in het GOUD-onderzoek was gebaseerd op vele informatiebronnen waaronder breed lichamelijk, psychisch en laboratorium onderzoek, dit kan te belastend en duur zijn voor routinematig klinisch gebruik. Bovendien is de index alleen nog gevalideerd op populatieniveau, op basis van gemiddelde scores. Voor klinisch individueel gebruik is besliskundige analyse noodzakelijk (sensitiviteit en specificiteit). Door te analyseren welk van de 51 items zowel klinisch gemakkelijk toepasbaar zijn als sterk samenhangen met de volledige kwetsbaarheidsindex, wordt er op dit moment door ons onderzocht of een kortere versie van het instrument mogelijk en valide is. Bepaald moet worden of de korte versie net zo voorspellend is voor een achteruitgang in gezondheid en zelfstandigheid als de volledige kwetsbaarheidsindex.

Intussen kan beleidsmatig al gestart worden met de preventie van vroege kwetsbaarheid. Resultaten uit het GOUD-onderzoek laten zien dat de minst kwetsbare groep vaak relatief mobiel en actief is, minder vaak ziektes heeft en minder medicatie gebruikt [36]. In figuur 4 is een door ons opgesteld hypothetisch model weergegeven over de opeenstapeling van ongunstige factoren die kunnen bijdragen tot het vroegtijdig ontstaan van kwetsbaarheid bij mensen met een verstandelijke beperking. Een aantal van de



Figuur 4. Een hypothetisch model over de opeenstapeling van ongunstige factoren die kunnen leiden tot het vroegtijdig ontstaan van kwetsbaarheid bij mensen met een verstandelijke beperking. Figuur eerder gepubliceerd in het *Nederlands Tijdschrift voor Geneeskunde* [40].

genoemde ongunstige factoren zou kunnen dienen als leidraad voor interventies. Zo zou een breed geïmplementeerd beweegprogramma, gericht op behoud van mobiliteit en verbeteren van fitheid, zoals gezien in de algemene populatie, kwetsbaarheid kunnen remmen. De toepasbaarheid en effectiviteit van een beweegprogramma, specifiek ontworpen voor ouderen met een verstandelijke beperking, werd eerder al aangetoond [37]. Daarnaast zullen ook andere componenten van gezondheid aandacht moeten krijgen. Uit het GOUD-onderzoek blijkt bijvoorbeeld dat mensen met een verstandelijke beperking veel life events (bijvoorbeeld een verhuizing, overlijden van een dierbare, verandering van persoonlijk begeleider) ondervinden, wat samenhangt met depressie- en angstsymptomen [38]. Life events zullen beter gemonitord moeten worden, en natuurlijk zoveel mogelijk moeten worden voorkómen. Het systematisch invoeren van medicatiereviews en een proactieve aanpak van specifieke clusters van comorbiditeit [13] zouden ook kunnen bijdragen aan de preventie van kwetsbaarheid. Daarnaast zou er meer aandacht moeten komen voor gezonde voeding.

In aanvulling op het beleid van zorginstellingen zou ook de gemeente een belangrijke rol kunnen spelen. Binnenkort gaan lichtere vormen van zorg en ondersteuning uit de Algemene Wet Bijzondere Ziektekosten (AWBZ) over naar de Wet maatschappelijke ondersteuning (Wmo). Dit betekent dat gemeenten voor een groot deel verantwoordelijk worden voor de zorg voor mensen met een lichte of matige vorm van verstandelijke beperking. Door aanvullingen op het beroepsonderwijs voor verzorgenden en verplegenden kan

meer kennis en bewustwording worden gecreëerd bij beroepsbeoefenaren die nu of binnenkort met deze doelgroep te maken krijgen. Daarnaast is het zaak dat de huisarts of geriater met vragen terecht kan bij een arts voor verstandelijk gehandicapten (AVG). De circa 80 AVG-poliklinieken kunnen hierbij een belangrijke rol spelen (www.nvavg.nl).

DRUKKE TIJDEN VOOR ONDERZOEKERS

Het voorkómen en bestrijden van gezondheidsproblemen van ouderen met een verstandelijke beperking zou hoog op de prioriteitenlijst moeten staan, zoals blijkt uit het GOUD-onderzoek. Echter, veel kennis ontbreekt nog. Allereerst, zoals eerder vermeld, is er een klinisch toepasbaar instrument met een goede sensitiviteit en specificiteit nodig om kwetsbare ouderen te selecteren. Daarnaast moet er worden onderzocht welke interventies effectief zijn in deze populatie.

Ook kunnen andere relevante gezondheidsuitkomsten zoals specialistische consulten en kosten onderzocht worden om inzicht te krijgen in de financiële gevolgen van kwetsbaarheid. Omdat het voorkómen van kwetsbaarheid dienend is voor een goede oude dag, moet ook gekeken worden naar welbevinden en kwaliteit van het levenseinde.

Belangrijk is ook te onderzoeken waar het vroegtijdig ontstaan van kwetsbaarheid precies vandaan komt. Onderzoek dat zich richt op het ontstaan van kwetsbaarheid bij jongvolwassenen en de ontwikkeling van kwetsbaarheid gedurende het leven kan veel informatie verschaffen over de oorzaken van het vroege ontstaan. Ook liggen er fundamentele vraagstukken met betrekking tot het vroegtijdig ontstaan van kwetsbaarheid. Zo is het bijvoorbeeld bekend dat mensen met een verstandelijke beperking een hogere ontstekingsstatus hebben dan de algemene populatie [39]. In het GOUD-onderzoek werd gevonden dat een verhoogd inflammatoire niveau (IL-6 en CRP) vaker voorkomt bij mensen met een hoge kwetsbaarheidsindex. Onderzoek naar de causale relatie tussen inflammatie en het ontstaan van kwetsbaarheid is van belang.

CONCLUSIE EN AANBEVELINGEN

Uit de resultaten van het GOUD-onderzoek blijkt dat een groot aantal mensen met een verstandelijke beperking al op relatief jonge leeftijd kwetsbaar is. Kwetsbaarheid, gemeten met een kwetsbaarheidsindex, leidt ook in deze vroeg-gehandicapte populatie tot een sterke achteruitgang in zelfredzaamheid en mobiliteit, tot een toename van ziektes en medicijngebruik en tot eerder overlijden.

De ontwikkeling van kwetsbaarheid kan een langdurig proces zijn, waarbij verschillende problemen zich opstapelen. Los vormen deze problemen niet altijd een reden voor ongerustheid, waardoor kwetsbaarheid pas in een laat stadium wordt geobserveerd. Kwetsbaarheid is een dynamisch proces. Echter, hoe hoger de mate van kwetsbaarheid is, des te lastiger is het te keren [35]. Het is daarom essentieel dat kwetsbare ouderen vroegtijdig worden geïdentificeerd en effectieve interventies worden gestart om te komen tot meer gezonde, zelfstandige en kwalitatief bevredigende levensjaren voor deze groep.

Toekomstig onderzoek zal zich moeten richten op een valide screeningsinstrument en het ontwerpen van effectieve interventies. Daarnaast zou aanvullend epidemiologisch onderzoek gedaan kunnen worden naar de oorzaken van kwetsbaarheid bij mensen met een verstandelijke beperking. Tot slot is het van belang dat mensen die werken in de zorg (zorgverleners en beleidsmedewerkers) zich bewust zijn van de jonge leeftijd waarop mensen met een verstandelijke beperking kwetsbaar worden, de frequentie van het probleem en de ernstige gevolgen, zodat er eerder gestart wordt met maatregelen. Preventief beleid en toekomstig onderzoek zullen moeten bijdragen aan het terug dringen van de effecten van kwetsbaarheid op zowel het individu als de zorg.

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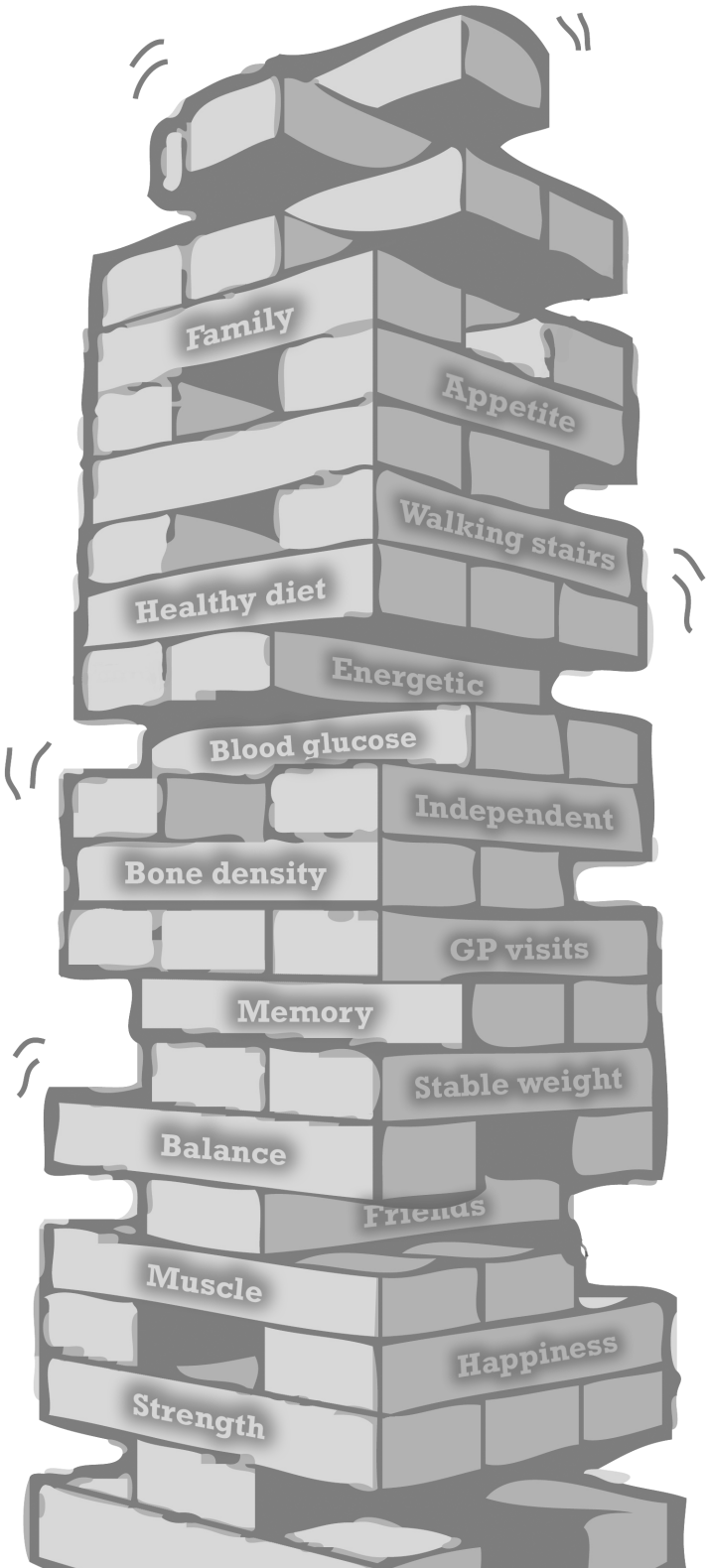
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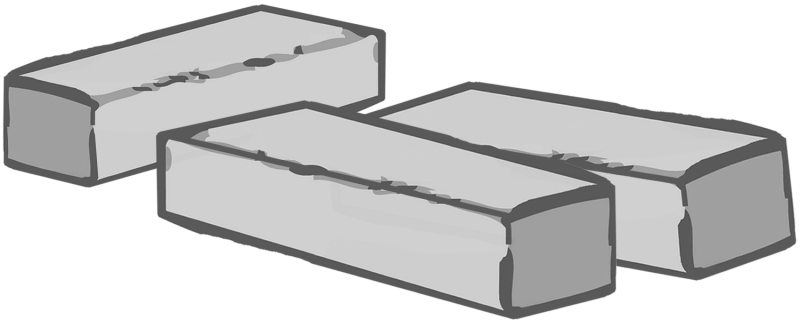
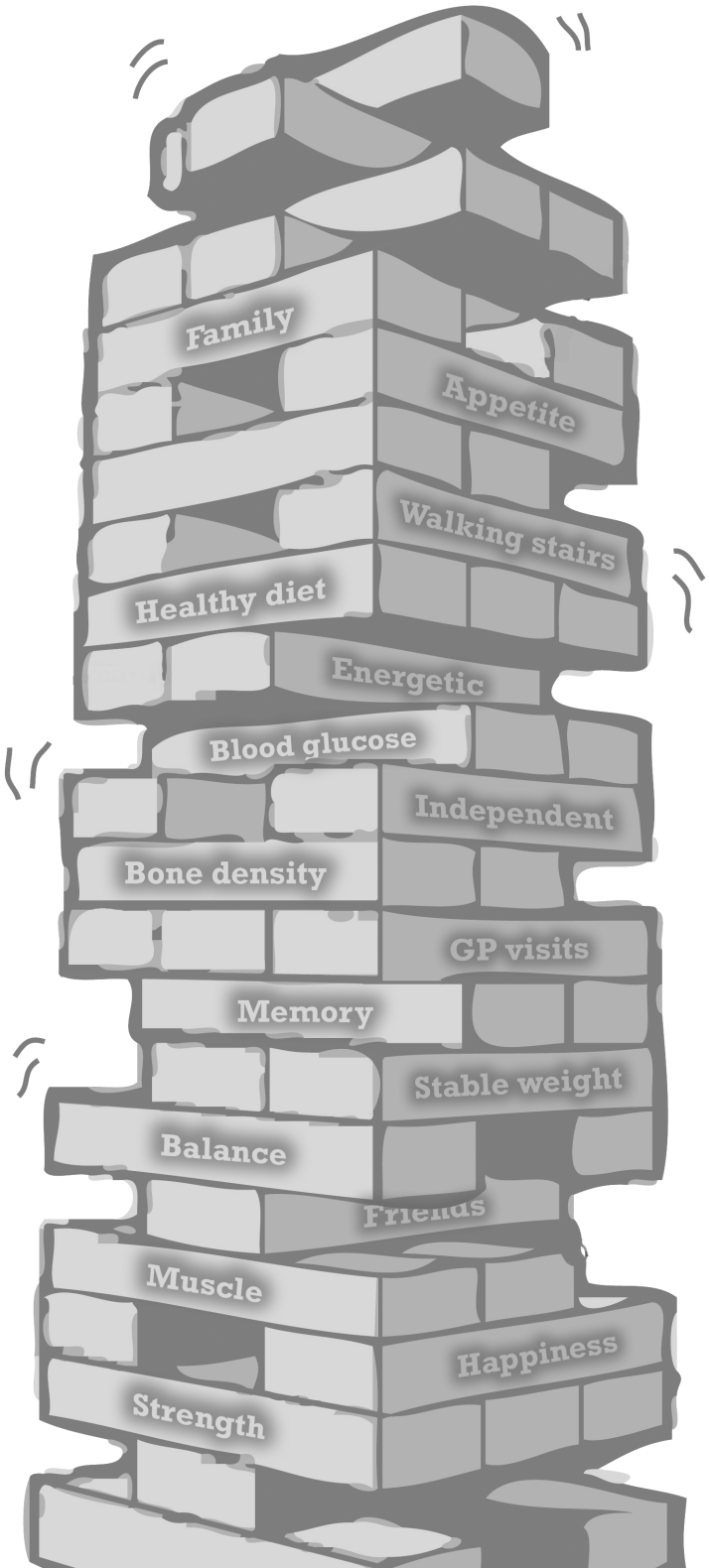
Curriculum Vitae



Josje Dorothea Schoufour werd op 10 oktober 1985 geboren te Amsterdam. Het VWO diploma behaalde zij aan het Montessori Lyceum Amsterdam. Na een half jaar werken en een half jaar reizen door Kenya en Amerika, begon zij in 2005 aan de Bachelor Voeding & Gezondheid aan de Wageningen Universiteit. De Master voedingsfysiologie werd eveneens behaald aan de Wageningen Universiteit, met als afstudeeronderwerp het effect van medicatie op de micronutriëntenstatus van ouderen.

Na omzwervingen door Azië en midden Amerika vestigde zij zich in 2011 in Den Haag om vandaar uit te beginnen aan haar promotie aan het Erasmus MC bij de leerstoelgroep Geneeskunde voor Verstandelijk Gehandicapten. Dit promotieonderzoek maakte deel uit van het 'Gezond ouder met een verstandelijke beperking' (GOUD) onderzoek, met als overkoepelend doel de gezondheid van mensen met een verstandelijke beperking in kaart te brengen. Als promovenda was zij verantwoordelijk voor de follow-up meting van het GOUD onderzoek, waarbij gegevens over zelfredzaamheid, ziekte, mobiliteit en sterfte werden verzameld. Josje richtte zich specifiek op het meten van kwetsbaarheid bij mensen met een verstandelijke beperking en de negatieve gevolgen van kwetsbaarheid op de gezondheid, waarvan de resultaten zijn beschreven in dit proefschrift.

Op dit moment woont Josje samen met Thomas in Amsterdam en werkt ze als Postdoc op de afdeling epidemiologie van het Erasmus MC, waar zij onderzoek doet naar de effecten van voeding op gezonde en ongezonde veroudering.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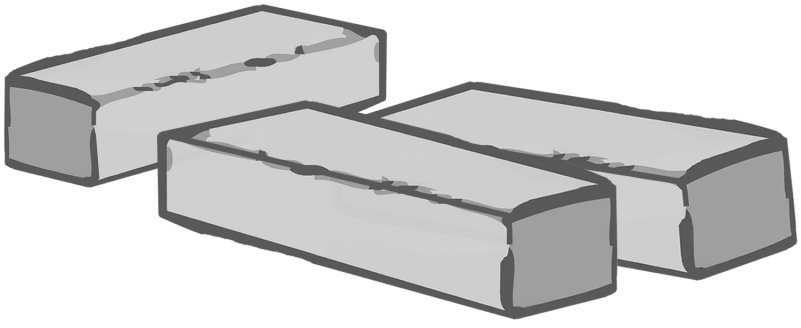
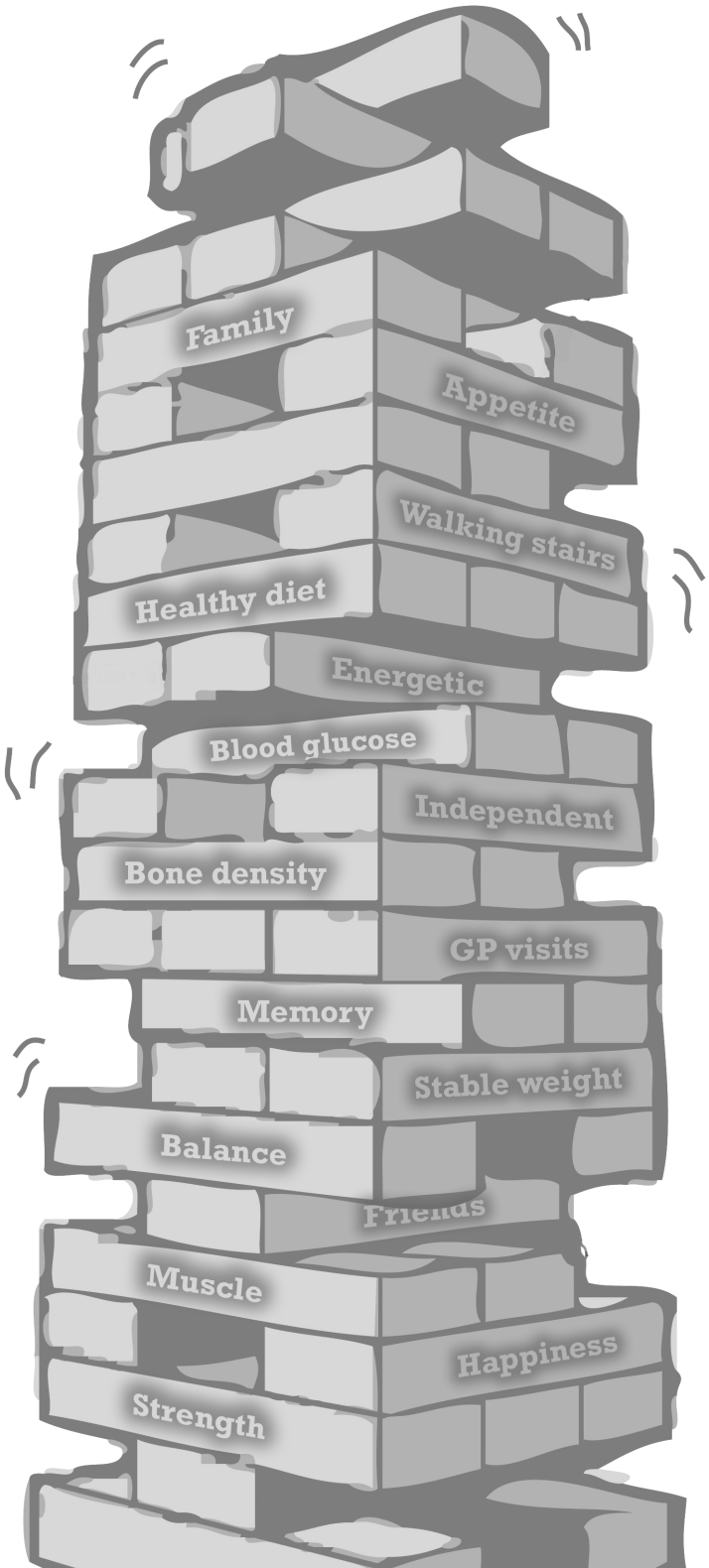
PhD portfolio



Name PhD student: Josje Schoufour
Erasmus MC Department: Department of General Practice (Intellectual Disability Medicine)

PhD period: 2011-2015
Promotor: Prof. Dr. HM. Evenhuis
Supervisor: Dr. MA. Echteld

	year	Workload (ECTS)
1. PhD training		
General Courses		
BROK (basiscursus Regelgeving Klinisch Onderzoek)	2012	1.0
Biomedical English Writing and Communication	2013	4.0
Systematic Literature Retrieval	2014	0.5
Specific courses (NIHES Research School)		
Biostatistics for Clinicians (EWP22)	2012	1.0
Regression Analysis for Clinicians (EWP23)	2012	1.8
Survival Analysis for Clinicians (EWP24)	2013	1.9
Seminars, presentations and workshops		
Department presentations (oral presentation)	2011-2015	3.0
Follow-up study HA-ID study introduction presentations (management, personal care givers, team leaders)	2011-2012	5.0
Workshop AVG AIOS science day	2011	1.0
Workshop GOUD symposium	2013	1.0
Workshop AVG AIOS science day	2014	1.0
NPO (Nationaal Programma Ouderenzorg), 2 workshops	2014	1.0
(inter)national conferences		
The 8th IAGG-ER congress, Dublin (oral presentation)	2015	2.0
The 10th congress of the EUGMS, Rotterdam (poster presentation)	2014	1.0
The 9th congress of the EUGMS, Venice (poster presentation)	2013	1.0
The IASSID world congress, Halifax (oral presentation)	2012	2.0
Congress 'Focus on Research', Utrecht (oral presentation)	2011	1.0
NPO (Nationaal Programma Ouderenzorg), Rotterdam (poster presentation)	2011	0.6
2. Teaching		
Supervising Master's theses		
4 Master Medical Science students research projects	2011-2015	8.0
Other		
Supervising student sessions 'how to judge a paper'	2011-2014	0.5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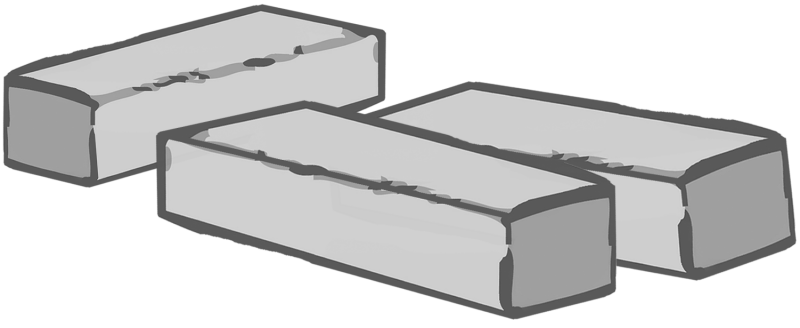
List of publications



1. **Schoufour JD**, Mitnitski A, Rockwood K, Boonstra A, Groothuismink ZMA, Evenhuis HM, Echteld MA. *Biochemical measured and frailty* in people with intellectual disabilities. Submitted
2. **Schoufour JD**, Mitnitski A, Rockwood K, Evenhuis HM, Echteld MA. *Comparing two frailty measures in their ability to predict mortality among older people with intellectual disabilities.* Submitted
3. Oppewal A, Hilgenkamp TI, van Wijck R, **Schoufour JD**, Evenhuis HM. *Physical fitness is predictive for decline in instrumental activities of daily living in older adults with intellectual disabilities.* Submitted
4. **Schoufour JD**, Mitnitski A, Rockwood K, Evenhuis, HM, Echteld MA. *Predicting 3-year survival in older people with intellectual disabilities using a frailty index.* Journal of the American Geriatrics Society, 2015 Mar;63(3):531-6 (IF 4.22, rank: 2/30 geriatrics (social), 6/49 geriatrics & gerontology)
5. **Schoufour JD**, Evenhuis HM, Mitnitski A, Rockwood K, Echteld MA. *The benefits of a frailty index for people with intellectual disabilities.* Journal of Policy and Practice in Intellectual Disabilities, accepted for publication (IF 0.63. rank: 57/69 rehabilitation, 64/70 health policy & services)
6. **Schoufour JD**, Bastiaanse LP, Mitnitski A, Rockwood K, Evenhuis HM, Echteld MA. *The use of a frailty index to predict adverse health outcomes in people with intellectual disabilities*. Research in Developmental Disabilities, 2015 Jan;7(38C):39-47 (IF 2.48, rank: 2/69 rehabilitation, 1/37 special education)
7. **Schoufour JD**, Evenhuis HM, Echteld MA. *Kwetsbaarheid bij ouderen met een verstandelijke handicap: operationalisering, risico en opsporing.* Tijdschrift voor Gerontologie en Geriatrie, 2015.
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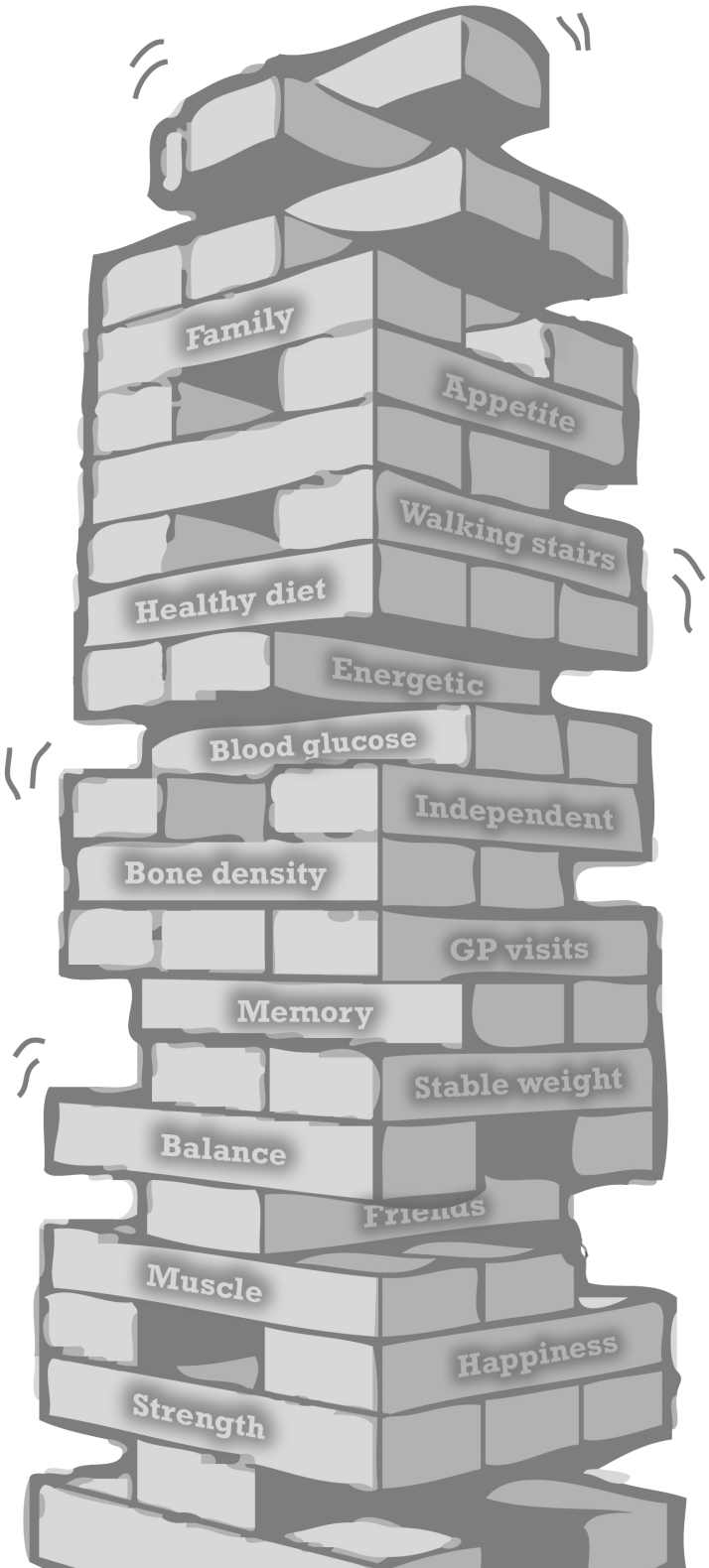
12. **Schoufour JD**, Wijngaarden van J, Mitnitski A, Rockwood R, Evenhuis HM, Echteld MA. *Characteristics of the least frail adults with intellectual disabilities: A positive biology perspective*. Research in Developmental Disabilities, 2013 Jan;35(1):127-36 (IF 3.41, rank: 2/69 rehabilitation, 1/37 special education)
13. Evenhuis HM, **Schoufour JD**, Echteld MA. *Frailty and intellectual disability: a different operationalization?* Developmental Disabilities Research Reviews, 2013 Aug;18(1):17-21 (IF 4.04, rank: 15/122 paediatrics, 51/135 psychiatry, 67/193 clinical neurology, 132/252 neurosciences)
14. **Schoufour JD**, Mitnitski A, Rockwood K, Evenhuis HM, Echteld MA. *Development of a frailty index for older people with intellectual disabilities: results from the HA-ID study.* Research in Developmental Disabilities, 2013 May;34(5):1541-55 (IF 3.41, rank: 2/69 rehabilitation, 1/37 special education)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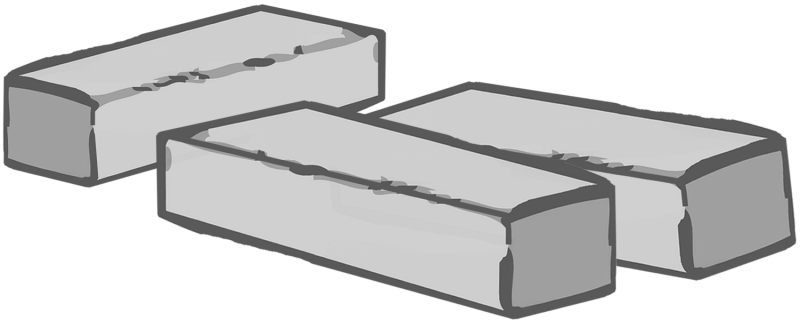

Dit proefschrift is het resultaat van 3.5 jaar data verzamelen, analyseren, schrijven en samenwerken. Er op terugkijkend waren het mooie en leerzame jaren. Maar zonder hulp van veel mensen had ik dit onderzoek nooit tot een einde kunnen brengen. Daarom wil ik op deze plaats een aantal mensen bedanken.

Allereerst wil ik graag iedereen bedanken die betrokken is geweest bij het onderzoek 'Gezond Ouder met een Verstandelijke Beperking' (GOUD). Alle cliënten van Abrona, Amarant en Ipse de Bruggen die hebben deelgenomen aan het GOUD onderzoek, familieleden, begeleiders, en medewerkers die geholpen hebben met de metingen en de logistiek, jullie hebben allemaal een enorm belangrijke bijdrage geleverd aan het in kaart brengen van de gezondheid van ouderen met een verstandelijke beperking. Zonder jullie inzet, tijd en betrokkenheid had het GOUD onderzoek nooit kunnen plaatsvinden, hartelijk dank hiervoor.

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Walking speed