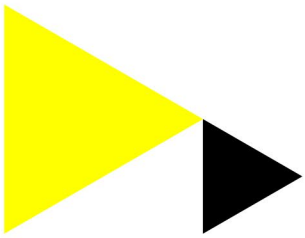
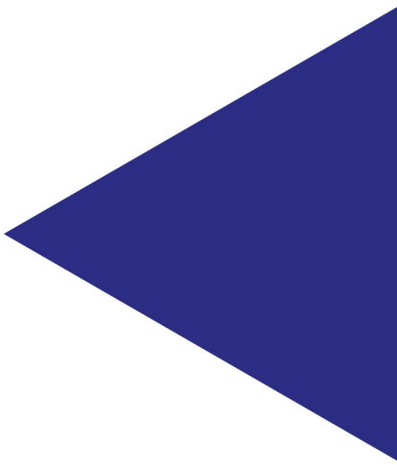
Sarcopenia predicts 5-year mortality in older adults with intellectual disabilities





JIDR Journal of Intellectual Disability Research
Published on behalf of mencap and in association with IASSID

Journal of Intellectual Disability Research doi: 10.1111/jir.13078

VOLUME 67 PART 11 pp 1161–1173 NOVEMBER 2023

Sarcopenia predicts 5-year mortality in older adults with intellectual disabilities

B. Valentin,[1,2] D. Maes-Festen,[1] J. Schoufour[2] & A. Oppewal[1]

1 *Department of General Practice, Intellectual Disability Medicine, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands*

2 *Faculty of Sports and Nutrition, Faculty of Health, Center of Expertise Urban Vitality, Amsterdam University of Applied Sciences, Amsterdam, The Netherlands*

Abstract

Background People with intellectual disabilities (ID) have a lower life expectancy than their peers without ID. A contributing factor to the lower life expectancy and early mortality could be sarcopenia: low muscle mass and low muscle function. In the general population, sarcopenia strongly predicts early mortality, but this association is unknown in people with ID. Therefore, this study aims to explore the association between sarcopenia and 5-year mortality in older adults with ID.

Methods In the Healthy Ageing and Intellectual Disabilities (HA-ID) study, the prevalence of sarcopenia was measured at baseline among 884 older adults (≥50 years) with ID. All-cause mortality was measured over a 5-year follow-up period. Univariable and multivariable Cox proportional hazard models were applied to determine the association between sarcopenia (no sarcopenia, pre-sarcopenia, sarcopenia, severe sarcopenia) and early mortality, adjusted for age, sex, level of ID, presence of Down syndrome, and co-morbidity (chronic obstructive pulmonary disease, diabetes type 2 and metabolic syndrome).

Results The unadjusted hazard ratio (HR) for sarcopenia was 2.28 [95% confidence interval (CI) 1.48–3.42], $P < 0.001$), and 2.40 (95% CI 1.40–4.10, $P = 0.001$) for severe sarcopenia. When adjusted for age, sex, level of ID, and Down syndrome, sarcopenia (HR = 1.72, 95% CI 1.08–2.75, $P = 0.022$) and severe sarcopenia (HR = 1.86, 95% CI 1.07–3.23, $P = 0.028$) were significantly associated with early mortality. When additionally adjusted for co-morbidity, the adjusted HR decreased to 1.62 (95% CI 1.02–2.59, $P = 0.043$) and 1.81 (95% CI 1.04–3.15, $P = 0.035$) for sarcopenia and severe sarcopenia, respectively.

Conclusion Sarcopenia is an independent risk factor for early mortality in older adults with ID over a 5-year follow-up period. Our results stress the need to delay the incidence and development of sarcopenia in older adults with ID.

Keywords intellectual disabilities, mortality, older adults, sarcopenia

Introduction

Over the past few decades, there has been an increase in life expectancy in adults with intellectual disabilities (ID) (Coppus, 2013; De Leeuw *et al.*, 2022). These additional years are not always spent in good health or with good quality of life (Coppus, 2013; De Leeuw *et al.*, 2022). In fact, adults

Correspondence: MSc Bas Valentin, Department of General Practice, Intellectual Disability Medicine, Erasmus MC, University Medical Center, Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands (e-mail: b.valentin@hva.nl).

with ID experience up to twice as many health problems as the general population (Van Schrojenstein Lantman-De Valk *et al.*, 2000). Observational studies show that adults with ID have frailty, physical disability, and co-morbidity more frequently and at a younger age than the general population (Haveman *et al.*, 2010; ; de Winter *et al.*, 2012; Evenhuis *et al.*, 2012; Schoufour *et al.*, 2013; De Leeuw *et al.*, 2022).

In the general population, frailty and physical disability are strongly associated with sarcopenia, defined by low muscle mass (structure) and low muscle strength (function); sarcopenia is considered severe if physical performance is also impaired (Cruz-Jentoft *et al.*, 2019). The presence of sarcopenia is considered to precede physical frailty and, as such, is an important pathway through which adverse associated health outcomes of frailty develop (Landi *et al.*, 2015). The presence of sarcopenia significantly restricts the ability to perform activities of daily living (Wang *et al.*, 2020) and sarcopenia is highly prevalent in individuals with cardiovascular disease, diabetes mellitus and respiratory disease (Pacifico *et al.*, 2020). Diabetes, for instance, can cause muscle wasting through insulin resistance, inflammation and oxidative stress (Shen *et al.*, 2022). Furthermore, chronic obstructive pulmonary disease (COPD) is also associated with sarcopenia (Benz *et al.*, 2019), and can cause muscle wasting due to the increased energy demands of breathing (the body may break down muscle protein to supply amino acids for energy production) and the systemic inflammation that accompanies the disease (Wüst & Degens, 2007). The bidirectional relationship of sarcopenia suggests that it can both be influenced by and influence other health factors.

Sarcopenia is an age-related disease of involuntary loss of muscle mass and strength. People lose approximately 1–2% of muscle mass per year from the fourth decade of life (Cruz-Jentoft *et al.*, 2019). Additionally, muscle strength decreases with age in a linear association, with up to 50% lost at the age of 80 years. However, these age-related decreases do not inevitable lead to sarcopenia, because the aetiology of sarcopenia is multifactorial (Cruz-Jentoft *et al.*, 2019). The risk factors for sarcopenia include metabolic conditions, chronic inflammation, hormonal changes, oxidative stress, neurological factors, and lifestyle factors such as physical inactivity and inadequate protein and energy intake (Domingues-Faria *et al.*, 2016; Dalle *et al.*, 2017; Cruz-Jentoft *et al.*, 2019).

Unhealthy lifestyle factors are highly prevalent among the ageing population with ID. Older adults with ID generally have a sedentary lifestyle and are physically inactive (Hilgenkamp *et al.*, 2012a). They are at a higher risk of physical inactivity due to multimorbidity (Hermans & Evenhuis, 2014), physical disability at younger age, trouble accessing facilities/programs/equipment, and dependency on staff (van Schijndel-Speet *et al.*, 2014). In addition, they do not meet nutritional guidelines (Hoey *et al.*, 2017; Gast *et al.*, 2022). These unhealthy lifestyle factors put older adults with ID at risk for sarcopenia. In the Healthy Ageing and Intellectual Disabilities (HA-ID) study, the prevalence of sarcopenia was 12.7% in the age group 50–64 years and 14.3% for the entire study group (median age of 60 (IQR 55–66] years) (Bastiaanse *et al.*, 2012). This prevalence is higher than the prevalence found in the general Dutch population, in which a prevalence rate of 4.4% is found among adults who were on average 69.2 ± 9.1 years old (Trajanoska *et al.*, 2018).

In the general population, sarcopenia strongly predicts early mortality (Bachettini *et al.*, 2020; Xu *et al.*, 2021). Thus, it is important for professionals to be aware of the risk of sarcopenia and to diagnose and intervene sarcopenia. Little is known about the patterns of early mortality in adults with ID after middle age, because few studies have been conducted on the cause-specific early mortality of the ageing population with ID (Hosking *et al.*, 2016; Glover *et al.*, 2017; O'Leary *et al.*, 2018; Oppewal *et al.*, 2018; Hirvikoski *et al.*, 2021). Until now, no studies have been conducted on the association between sarcopenia and mortality in older adults with ID. Therefore, it is unknown if sarcopenia is predictive for early mortality in older adults with ID, which is important information due to the high prevalence of sarcopenia observed in older adults with ID. The results of the general population cannot be generalised to the population with ID because of the higher prevalence of multimorbidity, polypharmacy, physical inactivity, low physical fitness, metabolic conditions and unhealthy dietary habits in older adults with ID (de Leeuw *et al.*, 2022). This can alter the age-related aspect and consequences of sarcopenia for the ID population.

Insight in the consequences of sarcopenia is important, as sarcopenia is a partially modifiable disease in the general population and it can be effectively treated with nutritional and exercise interventions (Cruz-Jentoft *et al.*, 2019). To better understand how sarcopenia is associated with mortality in people with ID, our objective is to verify the 5-year association of sarcopenia with early mortality.

Methods

Study design and participants

This study is part of the Healthy Ageing and Intellectual Disabilities (HA-ID) study, a prospective multicentre cohort study performed within the equally named consortium of three Dutch ID care organisations and the research group of Intellectual Disability Medicine of the Erasmus MC, University Medical Center Rotterdam. The recruitment and inclusion of study participants have been described in detail elsewhere (Hilgenkamp *et al.*, 2011). In short, the HA-ID study began in 2008 and focused on the health of older adults with ID (≥50 years), with a specific focus on physical activity and fitness, nutrition and nutritional state, and mood and anxiety. From November 2008 to July 2010, all 2322 clients aged 50 years and older, who received care and support from participating care organisations, were invited to participate in the study without any exclusion criteria. Informed consent was obtained from 1050 adults with ID or their legal representatives, resulting in a near-representative sample of the total client population aged 50 years and older receiving specialised care from the providers. However, there was a slight overrepresentation of women and a slight underrepresentation of individuals living independently and those who are aged 80 years and older. Sample representativeness calculations were performed in our design and recruitment article (Hilgenkamp *et al.*, 2011). The HA-ID study has been approved by the Medical Ethics Committee of the Erasmus MC, University Medical Center Rotterdam in the Netherlands (MEC nr. 2008-234 and MEC nr. 2011-309). The study was carried out according to the principles of the Declaration of Helsinki.

Measurements

Measurement of sarcopenia

In 2010, the European Working Group on Sarcopenia in Older Adults established criteria to diagnose sarcopenia (Cruz-Jentoft *et al.*, 2010). For the current study, these criteria were used and operationalised as follow (Bastiaanse *et al.*, 2012): handgrip strength was used to indicate muscle strength, calf circumference to indicate muscle mass, and walking speed to indicate physical performance. To measure handgrip strength, participants were asked to squeeze a Jamar Hand Dynamometer (Sammons Preston Rolyan, USA) in a seated position with maximum power, three times for each hand. Of these six scores, the highest recorded handgrip strength value was used as the final score (Reijnierse *et al.*, 2017). The feasibility of measuring handgrip strength in older adults with ID is good to excellent, with good test–retest reliability (Hilgenkamp *et al.*, 2012b). In addition, handgrip strength is predictive for survival [hazard ratio (HR) = 0.97, 95% confidence interval (CI) 0.94–0.99)] in older adults with ID and significantly predicts a decline in daily functioning (Oppewal *et al.*, 2014; Oppewal & Hilgenkamp, 2019). Low muscle strength was defined as less than 30 kg for men and 20 kg for women (Cruz-Jentoft *et al.*, 2010). Cut-off values are based on the statistical analysis of risk factors for disability in old age in an epidemiological study in the general population (Cruz-Jentoft *et al.*, 2010; Lauretani *et al.*, 2003).

Calf circumference was measured using a standard anthropometric tape with the participant standing upright. The measurement was done on the non-dominant leg at the widest part to acquire the maximum width. A cut-off value of 31 cm was used as an indicator for low muscle mass because of its association with disability and self-reported physical function (Rolland *et al.*, 2003), as well as physical performance and survival in community-dwelling older adults (Landi *et al.*, 2014).

Comfortable walking speed was measured over 5 m distance on an 11 m course, with 3 m for acceleration and 3 m deceleration. The participants had to walk without physical support from others, but were allowed to use a walking aid. Three attempts were averaged to get the participant's result. Measuring comfortable walking speed in older adults with ID has been found to be feasible with good to excellent

reliability (Hilgenkamp *et al.*, 2012b). In addition, comfortable walking speed is predictive for survival (HR = 0.65 [95% CI 0.54–0.78]) in older adults with ID (Oppewal & Hilgenkamp, 2019) and significantly predicts a decline in daily functioning (Oppewal *et al.*, 2014).

A cut-off value of 0.8 m/s was used to indicate poor physical performance, as it is a predictor for adverse health outcomes in community-dwelling older adults (Abellan Van Kan *et al.*, 2009).

Based on the handgrip strength, calf circumference and walking speed measurements, sarcopenia was classified into three categories (Cruz-Jentoft *et al.*, 2010). Participants were classified as having *pre-sarcopenia* when they had low muscle mass, normal muscle strength and normal physical performance; as having *sarcopenia* when they had low muscle mass in combination with low muscle strength or low physical performance; and as having *severe sarcopenia* when they had low muscle strength, low muscle mass, and low physical performance. Table 1 provides an overview of these measurements and their cut-off values for these classifications. Participants who did not meet any of these criteria were classified as participants without sarcopenia.

Personal characteristics

Sex, age and residential status were obtained from the participating care providers for adults with ID. Residential status was divided into living with relatives, living independently, living in group homes or the community, and living in group homes in central settings. Diagnosis of Down syndrome was retrieved from medical files. Psychologists and behavioural therapists documented the levels of ID and defined as follow: borderline (IQ 70–85), mild (55–70), moderate (40–55), severe (25–40) and profound (IQ < 25).

Cardiovascular and pulmonary health factors

Blood samples were taken after an overnight fast. The blood samples were frozen, transported, and stored at minus 80°C. Blood samples were stored and analysed at the Erasmus MC. The presence of cardiovascular and pulmonary disease was operationalised as follow (de Winter *et al.*, 2012). The diagnosis Diabetes Mellitus type 2 was retrieved from medical records (absent/present). Metabolic syndrome was defined as present (according to the NCEP-ATP III criteria) if at least three of the following five criteria were met: abdominal obesity (waist circumference for men >102 cm, women >88 cm), insulin resistance (serum fasting glucose ≥6.1 mmol/L), hypertriglyceridemia (≥1.7 mmol/L), low HDL cholesterol (<1.0 mmol/L in men, <1.3 mmol/L in women) and hypertension (blood pressure systolic ≥130 and diastolic ≥85 mmHg). The diagnosis COPD was obtained from medical records (absent/present).

All-cause mortality

Follow-up data on all-cause mortality were collected during a 5-year follow-up (range 5–6.3 years) period

Table 1 Anthropometric sarcopenia assessments

Diagnosis	Muscle mass: Calf circumference	Muscle strength: Hand grip strength	Physical performance: Walking speed
Pre-sarcopenia*	<31 cm	≥30 kg[§] ≥20 kg[‖]	≥0.8 m/s
Sarcopenia[†]	<31 cm	<30 kg[§] <20 kg[‖]	<0.8 m/s
Severe sarcopenia[‡]	<31 cm	<30 kg[§] <20 kg[‖]	<0.8 m/s

*Pre-sarcopenia was based on low muscle mass and normal muscle strength and performance.
†Sarcopenia was based on low calf circumference in combination with low hand grip strength or walking speed.
‡Severe sarcopenia was based on low muscle mass, low muscle strength and low muscle performance.
§Cut-off value for men, based on the on the 2010 EWGSOP criteria to diagnose sarcopenia (Cruz-Jentoft *et al.*, 2010).
‖Cut-off value for women, based on the on the 2010 EWGSOP criteria to diagnose sarcopenia (Cruz-Jentoft *et al.*, 2010).

from the baseline measurements up to March 2015 (Oppewal *et al.*, 2018). Administrative services within participating healthcare organisations identified the deceased participants and provided the date of death.

Analysis

Descriptive analysis

Data analysis was performed using R version 4.07(R Foundation, Core Team, Vienna, Austria) in RStudio. Assumptions for normality of numerical variables were examined using histograms and boxplots. Means and standard deviations were used to describe numerical and normally distributed data. Numerical, non-normally distributed data were presented as medians and interquartile ranges. Categorical data were reported as a numbers (*n*) and percentages (%). Personal characteristics were described for the whole sample and stratified by sarcopenia status. Differences between all categories of sarcopenia were tested using χ^2 tests for categorical data.

Missing data

Missing data were identified by tabulating missing values and creating a matrix plot. Correlations of missing values were assessed using a shadow matrix. If missing data were missing completely at random or missing at random, multiple imputations by chained equations were used to create five complete datasets from the existing dataset. Analyses were performed in each dataset and results were combined using Rubin's rules (Campion, 1989) to obtain point estimates and confidence intervals. We assumed that missing data for COPD were missing not at random, as it is likely to be reported in a participant's case file when present. The same assumption was made for the presence of Down syndrome. These conditions were therefore considered absent in case of missing. To address the remaining missing data on metabolic syndrome (28.9%) and the presence of diabetes (14.7%), we applied multiple imputations, using fully conditional specification (multiple imputations by chained equations package in R; van Buuren & Groothuis-Oudshoorn, 2011) under a missing at random assumption for diabetes and metabolic syndrome, while still classifying COPD and Down syndrome as absent in case of missing (missing not at random assumption).

Inferential analyses

The association between sarcopenia and early mortality was assessed using Cox proportional hazard models. Assumptions for proportional hazards were checked using scaled Schoenfeld residuals, and beta coefficients of the covariates were plotted against time. First, univariable Cox proportional hazard regression was conducted with early mortality as the dependent variable and sarcopenia (no sarcopenia [reference category], pre-sarcopenia, sarcopenia, and severe sarcopenia) as a categorical independent variable using all available data. The second model was adjusted for potential confounders, including age, sex, level of ID, and Down syndrome, as these are known predictors of early mortality (Ouellette-Kuntz *et al.*, 2015; Glover *et al.*, 2017; Cooper *et al.*, 2020) and are likely to be associated with sarcopenia. Because the co-morbidities COPD, diabetes, and metabolic syndrome could be argued to be either confounders or mediators, a third model was created adjusting for COPD, diabetes, and metabolic syndrome. For this third model, we pooled the analyses as performed in the five imputed datasets. The multivariable models had an event per variable ratio of 5:1 (model 2) and 3:1 (model 3), which is acceptable when adjusting for confounding (Vittinghoff & McCulloch, 2007).

Results

Participants

Valid calf circumference results were obtained for 929 of the in total 1050 participants of the HA-ID study. Of these 929 participants, 45 participants could not be included because of missing data on grip strength or walking speed. Data on walking speed were missing for a total 103 participants due to physical impairments, and data on grip strength were missing for 173 participants due to limited understanding or non-cooperation. This resulted in a sample of 884 participants with complete sarcopenia data available for the current study.

Baseline characteristics

At baseline, the median age was 60 (IQR = 55–66) years, and 50.9% of the study population was male (Table 2). Sarcopenia was present in a total of 126 participants (14.3%), of which 46 (5.2%) participants had severe sarcopenia. Twenty-four (2.7%) participants were classified as pre-sarcopenia. Participants with severe sarcopenia were on average older and more often had moderate, profound, or severe ID, than the other sarcopenia groups. Participants with sarcopenia or severe sarcopenia more often lived in a central setting, and COPD was more prevalent in participants with sarcopenia and severe sarcopenia compared with participant with pre-sarcopenia or no sarcopenia (Table 2).

The association between sarcopenia and early mortality

Overall, of the 884 participants, 162 (18.3%) died over the 5-year follow-up period. During the 5-year follow-up, 6 (25%) participants with pre-sarcopenia died, 25 (31.3%) participants with sarcopenia, and 15 (32.6%)

Table 2 Comparison of participants: sarcopenia stage

	No sarcopenia (*n* = 734)	**Pre-sarcopenia (*n* = 24)**	**Sarcopenia (*n* = 80)**	**Severe sarcopenia (*n* = 46)**	χ^2	***P*-value**	**Overall (*n* = 884)**
Gender					0.281	0.964	
Male	374 (51.0%)	13 (54.2%)	39 (48.8%)	24 (52.2%)			450 (50.9%)
Female	360 (49.0%)	11 (45.8%)	41 (51.3%)	22 (47.8%)			434 (49.1%)
Age (years)					20.901	0.013	
50–59	352 (48.0%)	8 (33.3%)	33 (41.3%)	18 (39.1%)			411 (46.5%)
60–69	258 (35.1%)	13 (54.2%)	29 (36.3%)	11 (23.9%			311 (35.2%)
70–79	110 (15.0%)	3 (12.5%)	14 (17.5%)	16 (34.8%)			143 (16.2%)
>80	14 (1.9%)	0 (0%)	4 (5.0%)	1 (2.2%)			19 (2.1%)
Level of ID					92.868	<0.001	
Borderline	27 (3.7%)	1 (4.2%)	1 (1.3%)	1 (2.2%)			30 (3.4%)
Mild	176 (24.0%)	10 (41.7%)	11 (13.8%)	4 (8.7%)			201 (22.7%)
Moderate	364 (49.6%)	12 (50.0%)	32 (40.0%	29 (63.0%)			437 (49.4%)
Severe	112 (15.3%)	0 (0%)	11 (13.8%)	9 (19.6%)			132 (14.9%)
Profound	35 (4.8%)	0 (0%)	25 (31.3%)	2 (4.3%)			62 (7.0%)
Missing	20 (2.7%)	1 (4.2%)	0 (0%)	1 (2.2%)			22 (2.5%)
Down syndrome					5.478	0.140	
Absent	644 (87.7%)	24 (100%)	67 (83.8%)	38 (82.6%)			773 (87.4%)
Present	90 (12.3%)	0 (0%)	13 (16.3%)	8 (17.4%)			111 (12.6%)
Residential status					42.806	<0.001	
Central	341 (46.5%)	7 (29.2%)	60 (75.0%)	33 (71.7%)			441 (49.9%)
Community	348 (47.4%)	14 (58.3%)	19 (23.8%)	12 (26.1%)			393 (44.5%)
Independent	40 (5.4%)	2 (8.3%)	1 (1.3%)	0 (0%)			43 (4.9%)
Relatives	5 (0.7%)	1 (4.2%)	0 (0%)	1 (2.2%)			7 (0.8%)
Diabetes					1.188	0.756	
Absent	568 (77.4%)	17 (70.8%)	71 (88.8%)	36 (78.3%)			692 (78.3%)
Present	54 (7.4%)	1 (4.2%)	4 (5.0%)	3 (6.5%)			62 (7.0%)
Missing	112 (15.3%)	6 (25.0%)	5 (6.3%)	7 (15.2%)			130 (14.7%)
Metabolic syndrome					7.877	0.049	
Absent	408 (55.6%)	6 (25.0%)	41 (51.3.5%)	21 (45.7%)			476 (53.8.%)
Present	136 (18.5%)	6 (25.0%)	6 (7.5%)	6 (13.0%)			154 (17.4%)
Missing	190 (25.9%)	12 (50.0%)	33 (41.3%)	19 (41.3.%)			254 (28.7%)
COPD					1.286	0.732	
Absent	681 (92.8%)	23 (95.8%)	72 (90.0%)	42 (91.3%)			818 (92.5%)
Present	53 (7.2%)	1 (4.2%)	8 (10.0%)	4 (8.7%)			66 (7.5%)

COPD, chronic obstructive pulmonary disease; ID, intellectual disability.

participants with severe sarcopenia died. Of the participants without sarcopenia, 116 (15.8%) died. Kaplan–Meier curves were visually different for all sarcopenia categories compared with those without sarcopenia (see Figure 1). In the univariable Cox-regression analysis (Table 3, model 1), sarcopenia and severe sarcopenia were significantly associated with early mortality; the unadjusted HR for sarcopenia was 2.28 (95% CI 1.48–3.42), $P < 0.001$) and 2.40 (95% CI 1.40–4.10, $P = 0.001$) for severe sarcopenia. After adjusting, for age, sex, level of ID, and Down syndrome (model 2), sarcopenia (HR 1.72, 95% CI 1.08–2.75, $P = 0.022$) and severe sarcopenia (HR 1.86; 95% CI 1.07–3.23, $P = 0.028$) were significantly associated with early mortality. After additionally adjusting for COPD, diabetes, and metabolic syndrome in the third model, sarcopenia (HR 1.62, 95% CI 1.02–2.59, $P = 0.043$) and severe sarcopenia (HR 1.81, 95% CI 1.04–3.15, $P = 0.035$), remained significantly associated with early mortality. The HR and 95% CI for models 2 and 3 changed minimally, indicating a direct pathway between sarcopenia and early mortality, accounting for confounders, mediators, and missing data.

Discussion

This is the first study to assess the association between sarcopenia and mortality over a 5-year follow-up period in older adults with ID. Sarcopenia and severe sarcopenia were independently associated with early mortality in older adults with ID.

Our finding that sarcopenia is a risk factor for early mortality in older adults with ID is in line with the association found in the general population (Zhang *et al.*, 2018; Bachettini *et al.*, 2020; Xu *et al.*, 2021). Similar HR's (1.18 [95% CI 0.53–2.65, $P = 0.005$] for sarcopenia and severe sarcopenia 3.15 [95% CI 1.44–6.90, $P = 0.005$]) were found in community-dwelling older adults using the same EWGSOP composite definition and an anthropometric measure of muscle mass (Bachettini *et al.*, 2020). A recent systematic review and meta-analysis found a pooled HR of 1.89 (95% CI 1.59–2.25, $P \leq 0.001$ in community-dwelling older adults (Xu *et al.*, 2021), in line with our results, even though different composite measurements for sarcopenia were used. A fairly recent but small systematic review and meta-analysis of six cohort

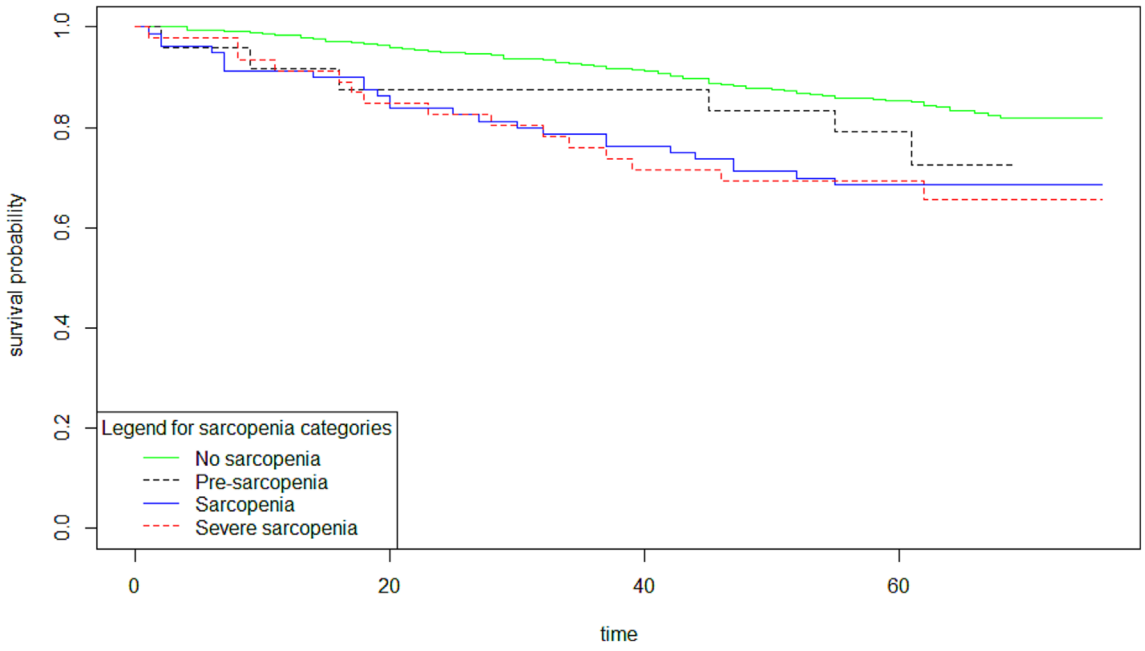


Figure 1. Kaplan–Meier survival curve. The Kaplan–Meier survival defines the probability of survival in a given length of time while considering time in many small intervals. On the *y*-axis, the survival probability varies from 0 to 1, and a time interval of 0 to 60 months on the *x*-axis. The log-rank test showed a significant difference in survival for the different sarcopenia categories with a *P*-value < 0.001.

Table 3 Cox regression results

Model 1 (*n* = 884)*			**Model 2 (*n* = 884)†**			**Model 3 (*n* = 884)‡**		
Covariates	**HR (95% CI)[§]**	***P*-value**	**Covariates**	**HR (95% CI)[§]**	***P*-value**	**Covariates**	**HR (95% CI)[§]**	***P*-value**
No sarcopenia (reference)			No sarcopenia (reference)			No sarcopenia (reference)		
Pre-sarcopenia	1.67 (0.73–3.79)	0.222	Pre-sarcopenia	1.66 (0.72–3.84)	0.232	Pre-sarcopenia	1.83 (0.79–4.23)	0.159
Sarcopenia	2.28 (1.48–3.52)	<0.001	Sarcopenia	1.72 (1.08–2.75)	0.022	Sarcopenia	1.62 (1.02–2.59)	0.043
Severe sarcopenia	2.40 (1.40–4.10)	0.001	Severe sarcopenia	1.86 (1.07–3.23)	0.028	Severe sarcopenia	1.81 (1.04–3.15)	0.035

*Model 1: Univariable Cox proportional hazard model.

†Model 2: Multivariable Cox proportional hazard model, adjusted for age, sex, level of ID, and Down syndrome.

‡Model 3: Multivariable Cox proportional hazard model, adjusted for age, sex, level of ID, Down syndrome, COPD, diabetes (five imputations) and metabolic syndrome (five imputations).

§HR, hazard ratio; 95% CI, confidence interval.

studies in nursing homes found a pooled HR of 1.86 (95% CI 1.41–2.45, $P \leq 0.001$) (Bachettini *et al.*, 2020). Although risk factors and the pathophysiology in people with ID may be different than in the general population, we observed similar findings with regard to the association between sarcopenia and early mortality.

In the general population, muscle mass relative to body height is inversely associated with all-cause mortality (Srikanthan & Karlamangla, 2014). Skeletal muscle is an important organ, as muscle tissue releases myokines during exercise. These myokines act as signalling molecules that can influence various physiological processes in the body. Myokines have been associated with anti-inflammatory effects, improved insulin sensitivity, and positive effects on metabolism, cardiovascular health, and brain function (Fiuza-Luces *et al.*, 2018). Thus, a decline in muscle mass can lead to adverse health outcomes. Furthermore, older adults with ID are particularly vulnerable to sarcopenia-related mortality risks, influenced by several key factors. Reduced physical activity is as a primary risk factor, increasing the loss of muscle mass and increasing the risk of mortality due to low physical fitness (Oppewal & Hilgenkamp, 2019). Furthermore, the ID population experiences a higher prevalence of co-morbidity, including cardiovascular diseases and respiratory disorders (de Winter *et al.*, 2012), which contribute to muscle wasting and further elevate mortality risks. Dietary challenges compound these risks, as difficulties in maintaining a balanced diet arise from factors such as swallowing difficulties (Manduchi *et al.*, 2020) or inadequate support (Chadwick *et al.*, 2006). These challenges can result in a suboptimal protein intake and distribution, adversely affecting protein synthesis and degradation (Cruz-Jentoft *et al.*, 2017), negatively affecting muscle mass and increasing the likelihood of mortality (Deutz *et al.*, 2019).

Strengths and limitations

The strengths of this study are the large sample size and the near-representative study population. Therefore, the findings of this study can be generalised to the older ID population receiving specialised care in the Netherlands. Also, our use of a standard global definition (Cruz-Jentoft *et al.*, 2010) to diagnose sarcopenia allows comparing prevalence and mortality rates with those in other populations. Another strength of our study is the long follow-up period, as well as the careful handling of missing data, accounting for several confounders and mediators, and analysing different models. The found HRs and 95% CI for models 2 and 3 changed minimally, indicating a direct pathway between sarcopenia and early mortality.

There are also limitations of this study. First, the use of calf circumference to estimate muscle mass is susceptible to inaccuracy, due to changes in fat distribution and loss of skin elasticity (Cruz-Jentoft *et al.*, 2010, 2019). Our measurement of muscle mass may therefore be less reliable, and may negatively impact the validity of our results. Instead, other methods such as bioelectrical impedance analysis, and dual-energy X-ray absorptiometry to represent muscle mass are recommended (Cruz-Jentoft *et al.*, 2019). However, because all measurements for this study were performed at the locations of the care organisations, we did not have the option to use a bioelectrical impedance analysis or dual-energy X-ray absorptiometry, and therefore chose for the calf circumference. The use of such a proxy is in line with the revised European consensus on the definition and measurement of sarcopenia in older adults (Cruz-Jentoft *et al.*, 2019).

Second, functional impairments commonly seen in adults with ID, may have made it difficult to accurately measure handgrip strength and walking speed to identify sarcopenia in some participants. Information on comfortable walking speed was missing in 173 participants, mainly due to physical limitations, and information on grip strength was missing in 103 participants, primarily due to limited understanding or non-cooperation. Consequently, we may have missed (severe) cases of sarcopenia, as sarcopenia is known to influence mobility (Cruz-Jentoft *et al.*, 2010, 2019).

Finally, only baseline prevalence of sarcopenia was available. However, it is known that the health status of a population changes over time which might also be the case for sarcopenia status. Health status may improve due to treatment, for example, a nutrition or exercise intervention. Vice versa, the health status can worsen. Therefore, our results must be interpreted with caution.

Future research on sarcopenia in older adults with ID would benefit from more frequent measurements

of health status and covariates, as more frequent measurements allow for accounting for changes in health status over time, shedding more light on the causality of the relationship.

Clinical implications

Our result that sarcopenia is not only prevalent in older adults with ID, but also strongly associated with early mortality, underscores the importance for approaches to prevent the onset or worsening of sarcopenia in older adults with ID. Literature from the general population suggests that sarcopenia is a disease that can be effectively treated and/or delayed with a combination of nutritional and exercise interventions (Cruz-Jentoft *et al.*, 2019). Interventions in specialised care settings are a challenging task (Kuijken *et al.*, 2016) and the absence of generic screening programmes indicate that the health needs of people with ID are often unrecognised (van Schrojenstein Lantman-de Valk & Walsh, 2008). These results stress that awareness among professionals for identifying and treating sarcopenia is needed. Identifying sarcopenia is relatively simple using our methods. With regards to treatment, lifestyle support for people with ID is known to be complex. It is necessary to adopt an integrated approach when developing a nutrition and exercise intervention according to the systemic approach of the socioecological model for health promotion (Steenbergen *et al.*, 2017). Unfortunately, existing nutrition and exercise interventions are often targeted separately (Willems *et al.*, 2018), whereas when they are combined, they both stimulate an anabolic response through for example resistance exercise and an adequate protein intake (Trouwborst *et al.*, 2018). Additionally, because of the high prevalence of obesity among people with ID, weight loss is often the goal of lifestyle support. However, a serious disadvantage of intentional weight loss when performed without adequate support from professionals is a decline in muscle mass that comprises up to a third of the total weight loss (Trouwborst *et al.*, 2018). The loss of muscle mass could negatively impact sarcopenia and physical fitness (Oppewal & Hilgenkamp, 2019), which are both independently associated with mortality in older adults with ID. Therefore, a combined nutrition and exercise intervention is essential. A multidisciplinary lifestyle intervention should involve a nutritional and exercise expert to provide evidence-based strategies for achieving optimal health outcomes through dietary modifications, targeted exercise prescription, and behavioural coaching.

In conclusion, sarcopenia and severe sarcopenia predict early mortality in older adults with ID. This emphasises the importance of identifying sarcopenia in people with ID, and treatment and prevention by maintaining a good level of physical fitness while eating a healthy diet. Nutrition and exercise must be key components of the care and assistance of older adults with ID. Awareness for sarcopenia is needed as health needs are often unnoticed and unmet.

Acknowledgements

The authors thank the management and professionals of the care organisations, Abrona (Huis ter Heide), Amarant (Tilburg) and Ipse deBruggen (Zoetermeer), involved in the HA-ID consortium for financing the data collection of this study and for their collaboration and support. We also thank the participants, their family and caregivers for their collaboration. Finally, we thank Martijn Stuiver for his advice.

Source of funding

This study was carried out with the financial support of the participating care organisations and the Netherlands Organization for Health Research and Development (ZonMw, No. 57,000,003 and No. 314,030,302). The sponsors had no further role in the study.

Conflict of interest

All authors declare no conflict of interest.

Ethics statement

The HA-ID study has been approved by the Medical Ethics Committee of the Erasmus MC, University Medical Center Rotterdam, in the Netherlands (MEC nr. 2008-234 and MEC nr. 2011-309).

Data availability statement

The data that support the findings of this study are available on reasonable request from the corresponding author, Oppewal, A. The data are not publicly available due to restrictions, for example, their containing information that could compromise the privacy of research participants.

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Accepted 25 July 2023