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► To cite this version:

Lara Vlietstra, Ben Kirk, Gustavo Duque, Clifford Qualls, Bruno Vellas, et al.. Using minimal clinically important differences to measure long-term transitions of osteosarcopenia: The New Mexico Aging Process Study. *Experimental Gerontology*, 2023, 173, pp.112106. 10.1016/j.exger.2023.112106 . hal-04485843

HAL Id: hal-04485843

<https://hal.science/hal-04485843>

Submitted on 24 May 2024

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Using minimal clinically important differences to measure long-term transitions of osteosarcopenia: The New Mexico Aging Process Study

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ARTICLE INFO

Section Editor: Liang-Kung Chen

Keywords:

Aging
Transitions
Life course
MCID
Osteosarcopenia

ABSTRACT

Background/objective: By having a better understanding of transitions in osteosarcopenia, interventions to reduce morbidity and mortality can be better targeted. The aim of this study was to show the rationale and method of using minimal clinically important differences (MCID's) to classify transitions, and the effects of demographic variables on transitions in a 9-year follow-up data from the New Mexico Aging Process Study (NMAPS).

Methods: Transitions were identified in four aspects of osteosarcopenia: bone mineral density (BMD), appendicular skeletal muscle mass/body mass index ratio (ASM/BMI), grip strength and gait speed. Transitions were identified using a MCID score. As there is currently no available MCID for BMD and ASM/BMI, those were determined using a distribution-based and an anchor-based method. Total transitions were calculated for all four measures of osteosarcopenia in all transition categories (maintaining a health status, beneficial transition, harmful transitions). Poisson regression was used to test for effects of demographic variables, including age, sex, physical activity, medication, and health status, on transitions.

Results: Over the 9-year follow-up, a total of 2163 MCID-derived BMD transitions were reported, 1689 ASM/BMI transitions, 2339 grip strength transitions, and 2151 gait speed transitions. Additionally, some MCID-derived transition categories were associated with sex, age, and health status.

Conclusion: Use of MCID-derived transitions reflected the fluctuation and the dynamic nature of health in older adults. Future research should focus on transitions of modifiable markers in osteosarcopenia to design intervention trials.

1. Introduction

The WHO defined health in 1946, as “a state of complete physical, mental and social wellbeing and not merely the absence of disease or infirmity” (Constitution of the World Health Organization, 1946). Since this definition has been established, discussions have emerged highlighting the dynamic nature of health, which is more reflected in the

Integrated Care for Older People (ICOPE) approach (Integrated care for older people (ICOPE) implementation framework: guidance for systems and services, 2019). The dynamic nature of health is particularly evident in older adults, as their health can fluctuate between relatively good and poor health episodes over time. Eventually, there is a trajectory of declining health and frailty, but which obscures the transitions that occur along this trajectory.

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<https://doi.org/10.1016/j.exger.2023.112106>

Received 20 September 2022; Received in revised form 16 January 2023; Accepted 23 January 2023

Available online 26 January 2023

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Interest in a life course perspective on health emerged in the 1980s, and mainly focused on chronic diseases (IAG et al., 2001; Ben-Shlomo and Kuh, 2002). Health trajectories are often estimated from health measures and are used in the gerontology research area as older adults often show a steady decline in multiple organ systems given they progressively lose function and cognitive capacities (Burton-Jeangros et al., 2015). On the contrary, health transitions can be used to describe changes in health status, over both shorter or longer time frames (Burton-Jeangros et al., 2015). More importantly, these transitions can fluctuate in an unclear trend among individuals who experience periods of good and poor health.

Although trajectories and the general decline of health in older adults are well described (Diehr et al., 2013), there is little research on health transitions in older adults. Most research on transitions to date have described transitions based on dichotomizing variables into “healthy” or “sick,” disease-states (Diehr et al., 2013; Thielke and Diehr, 2012; Thielke et al., 2012; Qualls et al., 2017; Waters et al., 2020). Thielke & Diehr described one-year transitions among health states in 12 measures of successful aging among adults, and estimated the prevalence of the healthy state and the probability of transitioning from one state to another during yearly intervals (Thielke and Diehr, 2012). Thielke et al. also characterized longitudinal patterns of musculoskeletal pain in a community sample of older adults over a 6-year period, to identify factors associated with persistence of pain (Thielke et al., 2012). Qualls et al. reported the probabilities of age-adjusted transition of worsening physical/cognitive function states, reversal to normal cognition/physical function, or maintenance of normal state (Qualls et al., 2017). Lastly, Waters et al. described sex-specific muscle and metabolic biomarkers associated with gait speed and cognitive transitions in older adults over a 9-year period (Waters et al., 2020). However, using disease-state cut-scores may not accurately reflect the fluctuation and the dynamic nature of health in older adults. In this study, we therefore propose to classify transitions based on the minimal clinical important difference (MCID).

One of the emerging ‘geriatric giants’ in health conditions, and one that is often described as a trajectory, is osteosarcopenia (Kirk et al., 2020). Osteosarcopenia is the presence of both osteopenia/osteoporosis and sarcopenia and is associated with both morbidity as well as early mortality (Kirk et al., 2020). Furthermore, the prevalence osteosarcopenia is expected to grow in both age-related as well as disease-related states, and is therefore posing a serious global health burden (Kirk et al., 2020). Age-related loss of bone density, muscle mass, strength, and function have previously been described as a linear process, or trajectories over longer periods of time (Cawthon et al., 2020). To date, there has been no research conducted on transitions in osteosarcopenia. By having a better understanding of transitions in osteosarcopenia, interventions to reduce morbidity and mortality can be better targeted.

The aim of this study was two folded: 1) to show the rationale and method of using MCID’s to classify transitions, and 2) to show the existence of transitions in osteosarcopenia and to test for effects of specific demographic characteristics.

2. Methods

2.1. Study design and participants

To be able to analyse health transitions, a minimum of two measures is needed to compute change over time and a minimum of three measures allows description of patterns in transitions. The NMAPS was a prospective cohort study of successful aging that started in 1979 and is described in detail elsewhere (Garry et al., 2007). Participants were 60 years of age or older, free of major medical conditions, and living independently. Participants were seen annually between 1979 and 2003, and for this specific study, had at least two consecutive annual assessments of gait speed, grip strength and/or body composition (lean mass and bone density) at any time between 1993 and 2001. The

NMAPS was originally approved by the University of New Mexico Health Sciences Internal Review Board and has approval for further data analyses. For a flow diagram of number of participants in the study see Fig. 1.

2.2. Outcome measures

A description of the outcome measures has been previously reported (Baumgartner et al., 1999). In brief, the following measurements were used to assess the four aspects of osteosarcopenia: body composition (bone density and appendicular lean mass (ALM)) was assessed by dual-energy x-ray absorptiometry (Lunar DPX, DXA Lunar Radiation Corp. Madison WI). Grip strength was measured for the dominant hand using a Takei (Tokyo, Japan) dynamometer. The maximum value out of three repeated trials was recorded. Gait speed was assessed over 25 ft (7.62 m) at usual pace (canes/walkers allowed). Table 1 describes the absolute and percentage change per year for all four outcome measures.

2.3. Demographic variables

The following demographic variables at baseline were tested for their effects on the number of transitions in each outcome measure: age, sex, physical activity, physical health status, and medication. The baseline variables of the year the participant entered in the study was used for physical activity, physical health status, and medication. Physical health status was ascertained using a standardized medical history questionnaire and interview, and a general physical examination by a trained research nurse. Health status was then graded on a 4-point scale of “excellent”, “good”, “frail” or “sick” (Vellas et al., 1997). Physical activity was assessed using a modification of the health insurance plan (HIP) questionnaire and produced a summary score (range 0–65) that graded individuals with regard to self-reported ‘usual’ physical activity, rather than an estimate of energy expenditure (Baumgartner et al., 1999). Medication was recorded as a binary variable (0 = no more than three different prescribed medications, 1 = more than three different prescribed medications).

2.4. Minimal clinically important difference transitions

To date, in health transitions research, transitions are often described in variables that are dichotomized into a “healthy” or “sick” state (Diehr et al., 2013; Thielke et al., 2012). However, this reflects a health state and does not always reflect the health fluctuations from year to year. For example, low grip strength is defined using sex-specific disease-state cut-scores as proposed by the Sarcopenia Definition and Outcomes Consortium as ≤ 35.5 kg in men and ≤ 20.0 kg in women (Bhasin et al., 2020). If an older male NMAPS participant “transitioned” from 35.4 to 34.6 kg, and maintained this lower score for the following 1–2 annual assessment, this would be classified as “maintaining a bad health state transition” even though this does not reach a minimal clinical important difference (MCID) of ≥ 2.5 kg (Bobos et al., 2020). The other side of that coin is also true, if an older female NMAPS participant “transitioned” from 21 kg to 25 kg and she maintained 25 kg at 2 subsequent annual visits, this would be classified as “maintaining a good health state transition” even though this is a clinically important difference (see Fig. 2 for a visual representation of these approaches). To represent the true clinical importance of health transitions, we therefore identified transitions using a MCID score. The following MCID’s were used to calculate transitions for grip strength (≥ 2.5 kg (Bobos et al., 2020)) and gait speed (> 0.10 m/s (Bohannon and Glenney, 2014; Kon et al., 2014)). There is currently no MCID available for change in BMD of the femoral neck or ALM/BMI. We therefore calculated the MCID using both an anchor-based and distribution-based method (Mouelhi et al., 2020; Crosby et al., 2003). For the distribution-based method we used 0.5 of the standard deviation (Mouelhi et al., 2020).

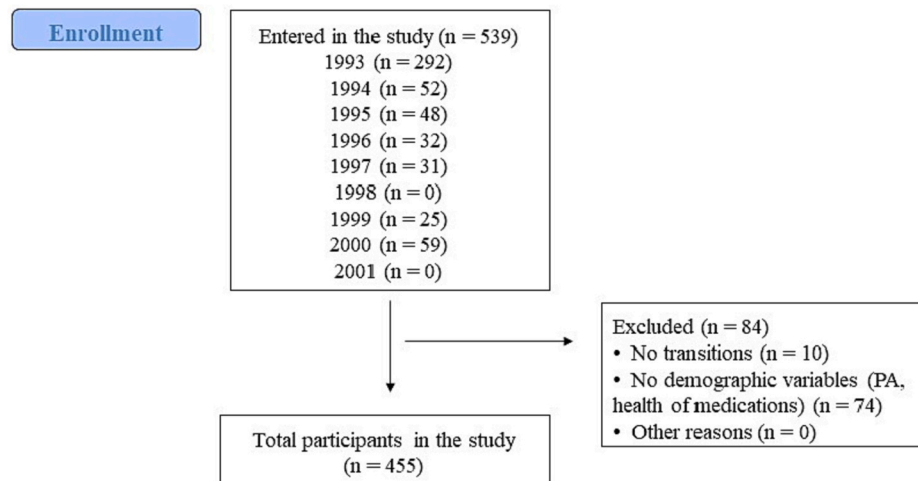


Fig. 1. Flow-chart.

Table 1
Characteristics by year of the study.

	Baseline	1993	1994	1995	1996	1997	1998	1999	2000	2001
	N = 455	N = 292	N = 329	N = 347	N = 335	N = 359	N = 315	N = 319	N = 353	N = 331
Age (years)	76.5 (6.9)	-	-	-	-	-	-	-	-	-
BMI (kg/m ²)	25.2 (3.9)	-	-	-	-	-	-	-	-	-
Years in study (#)	6.1 (2.1)	-	-	-	-	-	-	-	-	-
Physical activity (#)	18.1 (6.4)	-	-	-	-	-	-	-	-	-
Health status		-	-	-	-	-	-	-	-	-
Excellent (n (%))	137 (30 %)	-	-	-	-	-	-	-	-	-
Good (n (%))	217 (47 %)	-	-	-	-	-	-	-	-	-
Frail (n (%))	77 (17 %)	-	-	-	-	-	-	-	-	-
Sick (n (%))	26 (6 %)	-	-	-	-	-	-	-	-	-
Medication		-	-	-	-	-	-	-	-	-
<3 medications	354 (77 %)	-	-	-	-	-	-	-	-	-
≥3 medications	104 (23 %)	-	-	-	-	-	-	-	-	-
BMD										
BMD (g/m ²)	-	0.79 (0.14)	0.79 (0.14)	0.79 (0.14)	0.79 (0.13)	0.78 (0.13)	0.79 (0.14)	0.80 (0.13)	0.80 (0.14)	0.81 (0.13)
Absolute Δ BMD	-	-	0.004	0.005	0.006	0.013	0.000	-0.002	-0.003	-0.001
Percentage Δ BMD	-	-	-0.39 %	-0.55 %	-0.68 %	-1.56 %	0.05 %	0.43 %	0.42 %	0.34 %
ASM/BMI										
ASM/BMI	-	0.72 (0.21)	0.74 (0.22)	0.74 (0.22)	0.73 (0.22)	0.73 (0.23)	0.74 (0.22)	0.71 (0.22)	0.71 (0.22)	0.72 (0.22)
Absolute Δ ASM/BMI	-	-	-0.002	-0.004	-0.009	0.010	0.007	-0.024	-0.009	-0.027
Percentage Δ ASM/BMI	-	-	-0.15 %	-0.25 %	-1.15 %	1.30 %	1.04 %	-2.99 %	-1.07 %	-3.69 %
Grip strength										
Grip strength (kg)	-	26.59 (9.4)	25.17 (9.6)	25.81 (9.7)	26.15 (10.13)	27.08 (10.08)	27.77 (9.72)	27.85 (9.77)	27.85 (10.01)	27.29 (9.93)
Absolute Δ grip strength	-	-	-1.259	0.109	-0.319	0.634	-0.329	-0.290	-0.697	-0.724
Percentage Δ grip strength	-	-	-4.57 %	1.16 %	-0.89 %	3.27 %	-0.34 %	0.18 %	-1.88 %	-1.99 %
Gait speed										
Gait speed (m/s)	-	0.74 (0.17)	0.85 (0.19)	0.87 (0.23)	0.86 (0.22)	0.94 (0.19)	0.93 (0.22)	0.90 (0.21)	0.89 (0.21)	0.88 (0.19)
Absolute Δ gait speed	-	-	0.109	0.006	-0.025	0.010	-0.014	-0.033	-0.042	-0.012
Percentage Δ gait speed	-	-	1.71 %	1.36 %	1.64 %	2.26 %	-0.28 %	-1.19 %	-3.11 %	0.39 %

Note: Data is presented as mean (SD) unless stated otherwise. BMI = body mass index, kg/m² = kilogram per square meter, # = absolute score, BMD = bone mineral density, g/m² = grams per square meter, Δ = change, ASM/BMI = appendicular skeletal muscle/body mass index, kg = kilogram, m/s = meter per second.

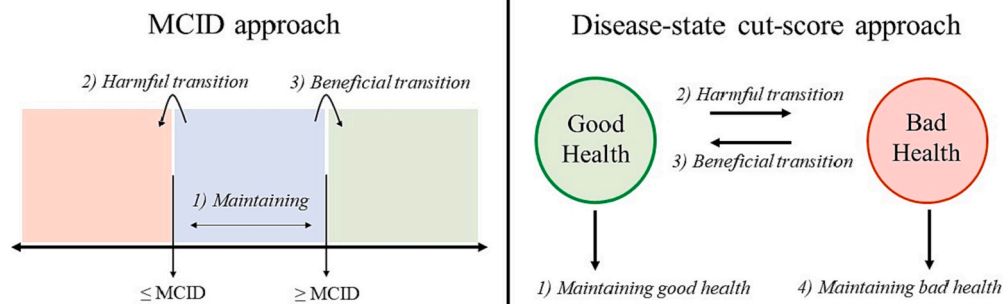


Fig. 2. Transition diagram.

Note: MCID = minimal clinically important difference.

2.5. Statistical analysis

2.5.1. Minimal clinically important difference calculations

Data from 1993 and 1994 was used to calculate the MCID for BMD and ASM/BMI. In the current study, as described above, a change of >2.5 kg in grip strength (Bobos et al., 2020) and >0.10 m/s in gait speed (Bohannon and Glenney, 2014; Kon et al., 2014) were considered clinically significant changes. These anchors were used to calculate the MCID for BMD and ASM/BMI. The MCID of the BMD and ASM/BMI were estimated by calculating the mean change in BMD and ASM/BMI in those achieving the MCID for grip strength (≥ 2.5 kg change) and gait speed (>0.10 m/s change). In addition, we used a distribution-based method to calculate the MCID for which we calculated half the standard deviation (SD) (0.5 SD). An average of the two methods was used as the MCID. The use of the MCID criteria counts important differences and eliminates chance differences due to small fluctuations in the measurements.

2.5.2. Transition calculations

Total transitions were calculated for all four measurements (bone density, ASM/BMI, grip strength and gait speed). Using the MCID scores, transitions were calculated yearly, in three different categories (Fig. 1): 1) maintaining a health status, 2) harmful transition (negative change \geq MCID score), 3) beneficial transition (positive change \geq MCID score). This resulted in twelve transition categories (maintaining bone density, harmful bone density transitions, beneficial bone density transition etc.). Furthermore, descriptive statistical analyses were used to describe the sample and the transitions.

2.5.3. Effects of demographic variables on transitions

Lastly, Poisson regression analysis was performed to explore the individual relationship of each demographic variable with the number of transitions in all twelve transition categories separately. All analyses were adjusted for the total number of years people were in the study, and where appropriate for sex and age. Poisson regression coefficients were exponentiated in order to interpret the results (Bohannon and Glenney, 2014). Exponentiation obtains the incident rate ratios (IRR) and their 95 % CI (Bohannon and Glenney, 2014). Each category of transition is a binary outcome allowing interpretation of an IRR to be analogous to the interpretation of an odds ratio (Bohannon and Glenney, 2014).

3. Results

3.1. Demographic characteristics

See Table 1 for participant characteristics by year. The mean age at baseline was 73.7 years (SD 7.4 years). For two people, their sex was unrecorded, and they were removed from further analysis. In total, 36 % of the participants in the current analyses were male.

3.2. Minimal clinically important difference

Using the anchor-based method, the mean change of the BMD and ASM/BMI ratio for participants with a significant change in grip strength and gait speed from 1993 to 1994 was calculated. For BMD, the anchor based MCID was 0.005 g/m² and for ASM/BMI ratio the MCID was 0.006. Using the 1993 data ($n = 257$), we used half the standard deviation (SD) (0.5 SD) as a method for the distribution-based methods of deriving the MCID. The MCID using 0.5 SD for BMD was 0.018 g/m². Using 0.5 SD, the MCID for ASM/BMI ratio was 0.024. To calculate the transitions, we used an average of the two methods, and therefore used an MCID score of 0.0115 g/m² for BMD and 0.015 for ASM/BMI ratio.

3.3. Transitions

Over the 9-year follow-up, a total of 2068 BMD transitions were reported (685 maintaining, 742 beneficial, and 641 harmful transitions), 1588 ASM/BMI transitions (626 maintaining, 387 beneficial, and 575 harmful transitions), 2239 grip strength transitions (1296 maintaining, 407 beneficial, and 536 harmful transitions), and 2060 gait speed transitions (835 maintaining, 630 beneficial, and 595 harmful transitions).

3.4. Effects of demographic characteristics on transitions

The results for the univariate Poisson analyses can be found in Table 2. In short, we found that being female was associated with more fluctuating (beneficial/harmful) transitions, including beneficial BMD transitions (IRR 0.84, 95 % CI 0.72–0.97) and both beneficial as well as harmful transition categories for grip strength (IRR 0.76, 95 % CI 0.62–0.93, IRR 0.72, 95 % CI 0.61–0.86, respectively). Additionally, we found that younger age was associated with all transition categories except for harmful grip strength transitions (e.g. decreasing grip strength) and maintaining gait speed (IRR ranging from 0.96 to 0.99), suggesting that people of a younger age are more adaptable/susceptible to changes in body composition and physical function. Being frail was associated with maintaining and beneficial transitions BMD transitions (IRR 0.72, 95 % CI 0.56–0.92). Lastly, medications and physical activity were not associated with any transition category.

4. Discussion

Using transitions in osteosarcopenia, the current study aimed to show the rationale and method of using MCID's to classify transitions. Using MCID-derived transitions reflects the fluctuation and the dynamic nature of health in older adults. Additionally, some MCID-derived transitions categories were associated with demographic characteristics including sex, age, and health status.

Although clinical relevance is not easy to define and quantify (Ranganathan et al., 2015), using MCID's to classify transitions could result

Table 2
Univariate Poisson regression results for each MCID-derived transition category.

	BMD maintaining (n = 455)		BMD beneficial (n = 455)		BMD harmful (n = 455)		ASM/BMI maintaining (n = 455)		ASM/BMI beneficial (n = 455)		ASM/BMI harmful (n = 455)	
	IRR	95 % CI	IRR	95 % CI	IRR	95 % CI	IRR	95 % CI	IRR	95 % CI	IRR	95 % CI
Sex												
Male	Base	Base	Base	Base	Base	Base	Base	Base	Base	Base	Base	Base
Female	0.97	0.83–1.13	0.84	0.72–0.97	0.97	0.82–1.14	0.83	0.71–0.97	0.90	0.73–1.09	0.91	0.77–1.08
Age (years)	0.98	0.97–0.99	0.99	0.97–0.99	0.98	0.96–0.99	0.96	0.95–0.97	0.98	0.97–0.99	0.98	0.96–0.99
Physical activity (#)	1.01	0.99–1.02	1.00	0.99–1.02	1.01	0.99–1.02	0.99	0.98–1.01	1.00	0.99–1.02	1.01	0.99–1.03
Health status												
Excellent	1.04	0.88–1.23	1.01	0.86–1.19	1.06	0.89–1.26	0.89	0.75–1.07	1.00	0.80–1.26	1.12	0.94–1.35
Good	Base	Base	Base	Base	Base	Base	Base	Base	Base	Base	Base	Base
Frail	0.79	0.62–1.02	0.72	0.56–0.92	0.85	0.66–1.09	0.96	0.75–1.23	0.78	0.56–1.09	0.85	0.65–1.11
Sick	0.82	0.54–1.26	0.84	0.56–1.24	1.01	0.67–1.52	0.96	0.62–1.47	0.79	0.45–1.40	0.81	0.49–1.31
Medication												
<3 medication	Base	Base	Base	Base	Base	Base	Base	Base	Base	Base	Base	Base
≥3 medication	0.99	0.83–1.20	0.94	0.78–1.12	0.98	0.81–1.19	0.88	0.72–1.07	1.24	0.98–1.56	1.05	0.86–1.28
	Grip maintaining (n = 455)		Grip beneficial (n = 455)		Grip harmful (n = 455)		Gait maintaining (n = 455)		Gait beneficial (n = 455)		Gait harmful (n = 455)	
	IRR	95 % CI	IRR	95 % CI	IRR	95 % CI	IRR	95 % CI	IRR	95 % CI	IRR	95 % CI
Sex												
Male	Base	Base	Base	Base	Base	Base	Base	Base	Base	Base	Base	Base
Female	1.15	1.02–1.29	0.76	0.62–0.93	0.72	0.61–0.86	1.02	0.88–1.18	0.90	0.77–1.06	0.93	0.79–1.10
Age (years)	0.99	0.98–0.99	0.98	0.96–0.99	1.00	0.99–1.01	1.00	0.99–1.01	0.98	0.97–0.99	0.99	0.97–0.99
Physical activity (#)	1.01	0.99–1.01	1.00	0.98–1.02	0.99	0.99–1.01	1.00	0.99–1.01	1.00	0.99–1.01	1.00	0.99–1.02
Health status												
Excellent	0.99	0.88–1.12	1.11	0.89–1.38	0.96	0.79–1.16	0.96	0.83–1.13	1.03	0.87–1.23	1.07	0.89–1.29
Good	Base	Base	Base	Base	Base	Base	Base	Base	Base	Base	Base	Base
Frail	0.86	0.73–1.03	0.85	0.62–1.17	1.07	0.83–1.37	0.92	0.75–1.13	0.88	0.68–1.13	0.93	0.72–1.20
Sick	0.88	0.65–1.19	0.66	0.36–1.21	1.07	0.71–1.60	0.72	0.49–1.08	0.97	0.64–1.46	0.96	0.63–1.48
Medication												
<3 medication	Base	Base	Base	Base	Base	Base	Base	Base	Base	Base	Base	Base
≥3 medication	0.99	0.86–1.13	1.08	0.86–1.37	1.12	0.91–1.38	0.99	0.84–1.18	0.90	0.74–1.10	1.04	0.86–1.27

Note: all univariate analyses accounted for the total number of years people were entered in the study. BMD = bone mineral density, # = absolute score, ASM/BMI = appendicular skeletal muscle/body mass index, IRR = incident rate ratios, 95 % CI = 95 % confidence interval.

Bold values indicate statistically significant at $p < 0.05$.

in a more realistic representation of the fluctuations in health measurements among older adults. Additionally, this is clinically more relevant and more often used in medical research, resulting in a more meaningful way of measuring change and difference in health-related outcomes (Ranganathan et al., 2015). The MCID, however, is a variable concept and there can be multiple MCID values for a given measure (Engel et al., 2018). Distribution-based methods have been questioned because of the lack of valuation of the importance of that change (Engel et al., 2018) and is therefore ought not to be used as a sole method for MCID derivation (Engel et al., 2018). However, we still included this method and results in the current paper to show a comparison with the MCID's derived using an anchor-based method, as anchor-based methods have been criticized for their variability, depending on multiple factors, including the type of anchor used. To the best of our knowledge, the current manuscript is the first describing MCID's for BMD and ASM/BMI.

The current manuscript showed that transitions were apparent in all variables associated with osteosarcopenia. These transitions were similar to previously described one-year transitions, in cognitive and gait speed transitions (Qualls et al., 2017; Waters et al., 2020). However, in the current study, we found a higher percentage of transitions in the harmful and beneficial categories, compared to previous research. This is most likely because previous research used the dichotomization of the variables to categorize transitions (Thielke and Diehr, 2012; Qualls et al., 2017; Waters et al., 2020). However, we should highlight that the transitions in ASM/BMI need to be interpreted cautiously, given the limitations of DXA-derived ASM, including the indirect determination of soft tissue mass, susceptibility to body fluid changes and lack of assessing muscle quality (Albano et al., 2020; Schweighofer et al., 2022;

Guglielmi et al., 2016).

We found that being female was associated with beneficial BMD transitions, maintaining ASM/BMI transitions, as well as all grip strength transitions. Additionally, we found that people of a younger age were more susceptible/adaptable to changes in body composition and physical function. Although the previous research on factors influencing transitions and trajectories is conflicting (Diehr et al., 2013; Thielke and Diehr, 2012; Cawthon et al., 2020) and often has used disease-specific cut-scores, Thielke and Diehr found similar results and showed that females between 65 and 74 who were healthy had a very high probability of remaining healthy (Thielke and Diehr, 2012). Thielke and Diehr also reported that men seem to be healthier than females because they were less likely to transition into sick states. They also reported that with increasing age, the probability of staying healthy is lower, which is similar to our results (Thielke and Diehr, 2012).

The current study has some limitations. The NMAPS cohort was relatively healthy, which could have underestimated the number of transitions to poorer health. Additionally, the NMAPS participants were also primarily Caucasians from higher socio-economic status and were more highly educated, thus limiting generalizations to other groups (Garry et al., 2007). However, a strength of this study is the long-term longitudinal data collection with annual follow-up, including gold-standard measurements for BMD, grip strength and gait speed. Another strength was the use of well-defined and widely used cut-scores of grip strength and gait speed for the anchor-based method of determining the MCID in BMD and ASM/BMI, rather than relying on a self-identified anchor, such as a rating scale or a distribution-based method. However,

In conclusion, using MCID derived transitions reflect the fluctuation

and the dynamic nature of health in older adults. In addition, beneficial and harmful transitions were found in all variables associated with osteosarcopenia, including BMD, ASM/BMI, grip strength and gait speed. Future research should focus on the modifiable transition markers of osteosarcopenia to better target intervention trials.

Data availability

Data will be made available on request.

Acknowledgements

This research was funded by National Institutes of Health grants RO1 AG02049 and AG10149.

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