QUESTION

Should standard BMI thresholds vs. FA-specific evaluation be used for defining undernutrition and overnutrition in adults and children with Friedreich ataxia?	
POPULATION:	defining undernutrition and overnutrition in adults and children with Friedreich ataxia
INTERVENTION:	standard BMI thresholds
COMPARISON:	FA-specific evaluation
MAIN OUTCOMES:	Disease progression; Health-related quality of life; Diabetes; Bone health; Body composition;

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Greeley et al (2014): - N=158 (109 adults, 49 children): BMI was 21.7+/- 5.2 (range 12.4-41.8) with 20% of children at or below the 5%tile (underweight by CDC guidelines). 5% of adults considered underweight (BMI < 18.5). McCormick et al (2017) - Analysis of FACOMS data: A substantial proportion (245/460 adults and 279/352 children) were missing BMI measurements. Pappa et al (2018) - Evaluation of 19 individuals with FRDA associated DM - Patients with FRDA have been assumed to be at risk for obesity. Among the 16 patients with data available, 7 had overweight and one was severely obese, whereas normal weight was present in 6 and underweight in 2. Cnop et al (2012) - Increased body fat as measured by (3)H20 contributes to insulin resistance in FRDA	The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were interviewed on the consequences, urgency and priority of nutrition. 4/7 indicated that the problem was serious, 3/7 indicated probably serious. 2/7 indicated that the problem was urgent, 3/7 indicated probably urgent, 2/7 indicated probably urgent. 3/7 indicated that the problem was a priority, 3/7 indicated probably a priority, 1/7 indicated probably not a priority. (Aug 2020)

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate	A search of four databases (CENTRAL, MEDLINE, EMBASE, CINAHL) identified no randomized, non-randomized controlled, cohort and case studies published from 2014 through to 16 July 2020. No further published evidence meeting the search criteria was identified in the Consensus Clinical	

○ Large ○ Varies ● Don't know	Management Guidelines for Friedreich's ataxia, 2014.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	A search of four databases (CENTRAL, MEDLINE, EMBASE, CINAHL) identified no randomized, non-randomized controlled, cohort and case studies published from 2014 through to 16 July 2020. No further published evidence meeting the search criteria was identified in the Consensus Clinical Management Guidelines for Friedreich's ataxia, 2014.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	No published evidence.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability		

Outcomes	Importance	Certainty of the evidence (GRADE)
Disease progression - not measured	IMPORTANT[a]	-
Health-related quality of life - not measured	IMPORTANT[b]	-
Diabetes - not measured	CRITICAL[c]	-
Bone health - not measured	IMPORTANT[d]	-
Body composition - not measured	IMPORTANT[d]	-

a. Identified as critical (1/6), important (4/6) and low importance (1/6) by people with FA and critical by expert authors on this topic.
b. Identified as critical (2/6) and important (4/6) by people with FA and important by expert authors on this topic.
c. Identified as critical (3/6), important (2/6) and low importance (1/6) by people with FA and important by expert authors on this topic.
d. Identified as critical (1/6) and important (5/6) by people with FA and important by expert authors on this topic.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	No published evidence. No published evidence therefore at this time probably favors the intervention (standard BMI thresholds) since there is nothing now to suggest different.	A survey designed to systematically collect expert-based opinions from clinicians involved in the development of these guidelines and providing clinical care for individuals with Friedreich ataxia, was conducted. Clinical experts from Australia, Europe, UK, South America, Canada and the USA were asked to consider the harms/benefits of defining undernutrition as BMI < 18.5kg/m2 in adults (or < 5%ile in children) and overnutrition as BMI >= 25kg/m2 (or >=85%ile in children) as a management strategy for people. Reflecting on the impact of defining undernutrition as BMI < 18.5kg/m2 in adults (or < 5%ile in children) and overnutrition as BMI >= 25kg/m2 (or >=85%ile in children) on disease progression, 32% (8/25) clinical experts reported a benefit (large, moderate or small), 20% (5/25) reported no effect and, 4% (1/25) reported observing a harm (large, moderate or small). 11

		clinicians could not provide any information on this outcome. Reflecting on the impact on health-related quality of life, 44% (11/25) clinical experts reported a benefit, 4% (1/25) reported no effect and, 4% (1/25) reported observing a harm. 12 expert clinicians could not provide any information on this outcome. Reflecting on the impact on Diabetes, 40% (10/25) clinical experts reported a benefit, 4% (1/25) reported no effect and, 8% (2/25) reported observing a harm. 12 expert clinicians could not provide any information on this outcome. Reflecting on the impact on Bone Health, 32% (8/25) clinical experts reported a benefit, 8% (2/25) reported no effect and, 4% (1/25) reported observing a harm. 14 expert clinicians could not provide any information on this outcome. Reflecting on the impact on Body Composition, 36% (9/25) clinical experts reported a benefit, 8% (2/25) reported no effect and, 4% (1/25) reported observing a harm. 13 expert clinicians could not provide any information on this outcome.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No published evidence. No published evidence, but likely small undesirable effects	The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were asked if using standard BMI thresholds for defining under or over nutrition was acceptable (weighing up the balance between benefits, harms and costs). 2/3 indicated the intervention was acceptable, 1/3 indicated varied or sometimes acceptable. (Aug 2020).

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty	Possibly important	Probably no important	**No important**			

	JUDGEMENT						
	or variability	uncertainty or variability	uncertainty or variability	**uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

We suggest using standard BMI thresholds to define underweight and overweight in children and adults with Friedreich ataxia.

Justification

There is no current evidence to suggest that FRDA-specific BMI thresholds are needed.

Subgroup considerations

In children, studies have shown that there is an increased prevalence of being underweight (Greeley et al, 2014) and therefore height and weight should be measured at every clinical or research visit. Standard BMI measurements are used in studies of children with other mitochondrial disorders and low BMI is prevalent (Wolney et al, 2009).

While there are limited data on adults with FRDA, studies in adults with mitochondrial disease report a high prevalence of being overweight or obese (28% overweight, 20% obese) (Apabhai et al, 2011).

Research priorities

BMI is not routinely evaluated at all visits. Initial research priorities would be to understand the prevalence of underweight or overweight individuals with FRDA but calculating at all clinical and research visits.

Further studies are needed to determine the association of these parameters with clinical co-morbidities in FRDA such as diabetes or cardiac disease.

Finally, additional research is needed to evaluate body composition, as BMI may not be the best measure of body composition. For example, Cnop et al (2012) showed increased body fat had a relationship to insulin resistance in FRDA. Studies in other diseases have showed markers of body composition such as lean body mass are associated with function (Baker et al, 2017).

References

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Baker JF, Giles JT, Weber D, Leonard MB, Zemel BS, Long J, et al. Assessment of muscle mass relative to fat mass and associations with physical functioning in rheumatoid arthritis. Rheumatology (Oxford). 2017;56(6):981-8.

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