QUESTION

Should a specific diet (ie: vitamins, coffee, Mediterranean, ketogenic) vs. usual diet be used for all individuals who report fatigue with Friedreich ataxia?	
POPULATION:	all individuals who report fatigue with Friedreich ataxia
INTERVENTION:	a specific diet (ie: vitamins, coffee, Mediterranean, ketogenic)
COMPARISON:	usual diet
MAIN OUTCOMES:	Reported fatigue; Reported fatigue; Reported fatigue; Improved quality of life; Improved quality of life; Improved energy levels; Improved physical capacity; Improved physical capacity; Improved capacity to participate in daily tasks; Reduced falls;

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Fatigue may be a rather frequent and often under recognized feature in individuals with FRDA (da Silva et al, 2013).	The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were interviewed on the consequences, urgency and priority of fatigue. 4/7 indicated that the problem was serious, 3/7 indicated probably serious. 3/7 indicated that the problem was urgent, 2/7 indicated probably urgent, 2/7 indicated probably not urgent. 4/7 indicated that the problem was a priority, 3/7 indicated probably a priority. (Aug 2020)

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know		

Outcomes	№ of	Certainty of	Relative	Anticipated absolute effects* (95% CI)

	participants (studies) Follow-up	the evidence (GRADE)	effect (95% CI)	Risk with usual diet	Risk difference with a specific diet (ie: vitamins, coffee, Mediterranean, ketogenic)
Reported fatigue assessed with: Neurological Fatigue Index-MS	36 (1 RCT)[1]	⊕◯◯◯ Very low[a,b,c,d,e,f]	-	36 women with multiple sclerosis were randomly assigned to follow or not follow a prescribed modified Mediterranean dietary intervention for 6 months. Exploratory analyses were used to examine whether the trajectory differed between the intervention groups over time using mixed effects models with a random intercept for the NFI-MS. Higher scores in the NFI-MS indicate worse fatigue. The non-intervention group increased by about 2.2 points, on average, over the 6-month study period (p = 0.07). The dietary intervention group exhibited a statistically significant decline in the 6-month trajectory of NFI-MSscores over time as compared to the trajectory of the non-intervention group (-4.6, p = 0.01). (Katz Sand et al 2019).	
Reported fatigue assessed with: Persian Modified Fatigue Impact Scale	101 (1 observational study)[2]	⊕◯◯◯ Very low[g,h,i,j]	-	101 patients with multiple sclerosis had their dietary intake assessed using a 3-day food record questionnaire. Association between variables was determined using Pearson Correlation Coefficient. After adjusting for daily energy intake, there were significant correlations between increasing total of MFIS, and decreasing daily intake of folate (p = 0.02) and magnesium (p= 0.03). This correlation was significant between physical subscale of MFIS and daily intake of folate (p = 0.008) and magnesium (p = 0.003). (Bitarafan et al 2014).	
Reported fatigue assessed with: Fatigue Visual Analogue	12 (1 RCT)[3]	⊕◯◯◯ Very low[c,d,f,g,j]	-	12 patients with multiple sclerosis were randomised to a high flavonoid cocoa drink (350mg gallic acid equivalents (GAE)/g) or low flavonoid cocoa drink (120mg GAE/g). Fatigue was recorded on a horizontal 100mm VAS every 30 min	

Scale				following drink consumption and throughout testing, every 2 hrs after testing and until 6 hrs after leaving the lab. Fatigue raw data was calculated using a fixed-effects model with two treatments adjusted using the Tukey-Kramer and comparing time and treatment interaction. A moderate effect was found in self-reported fatigue throughout the day in favour of the high flavonoid group post comsumption (Cohen's *d* 0.32, 95% non-central t CI 0.57 to 1.20). (Coe et al 2017).
Improved quality of life assessed with: Multiple Sclerosis Impact Scale-29	36 (1 RCT)[1]	⊕◯◯◯ Very low[a,b,c,d,e,f]	-	36 women with multiple sclerosis were randomly assigned to follow or not follow a prescribed modified Mediterranean dietary intervention for 6 months. Exploratory analyses were used to examine whether the trajectory differed between the intervention groups over time using mixed effects models with a random intercept for the MSIS-29. An increase in the MSIS-29 score of about 4.8 (p = 0.16), on average, over the 6-month study period was observed for the non-intervention group. The intervention group's change in score was approximately 7.4 points lower than the trajectory observed among the non-intervention group over the 6-month study period (p = 0.12). This trend was statistically significant (p = 0.023) when one outlier was removed from each group (both in the same direction). (Katz Sand et al 2019).
Improved quality of life assessed with: MSQOL-54	36 (1 RCT)[1]	⊕◯◯◯ Very low[a,b,c,d,e,f]	-	36 women with multiple sclerosis were randomly assigned to follow or not follow a prescribed modified Mediterranean dietary intervention for 6 months. Exploratory analyses were used to examine whether the trajectory differed between the intervention groups over time using mixed effects models with a random intercept for the MSQOL-54. There was no statistically significant difference between the groups with

				respect to change in MSQOL-54 physical or mental health composite score over the 6 month study period. (Katz Sand et al 2019).	
Improved energy levels - not measured	-	-	-	-	-
Improved physical capacity assessed with: Expanded Disability Status Scale	36 (1 RCT)[1]	⊕◯◯◯ Very low[a,b,c,d,e,f]	-	36 women with multiple sclerosis were randomly assigned to follow or not follow a prescribed modified Mediterranean dietary intervention for 6 months. Exploratory analyses were used to examine whether the trajectory differed between the intervention groups over time using mixed effects models with a random intercept for the MSQOL-54. A statistically significant increase of 0.6 points (p = 0.03), on average, was noted for the non-intervention group over the 6-month study period. The dietary intervention group displayed a statistically significant decrease in the trajectory of EDSS scores over the 6-month study period as compared to the trajectory of the non-intervention group (-0.98, p = 0.01). (Katz Sand et al 2019).	
Improved physical capacity assessed with: 6 min walk test	12 (1 RCT)[3]	⊕◯◯◯ Very low[c,d,e,f,g,j]	-	12 patients with multiple sclerosis were randomised to a high flavonoid cocoa drink (350mg gallic acid equivalents (GAE)/g) or low flavonoid cocoa drink (120mg GAE/g). Fatigue raw data was calculated using a fixed-effects model with two treatments adjusted using the Tukey-Kramer and comparing time and treatment interaction. The 6MWT was administered at the end of the study visit (2 hrs) and and at 24 hours. All participants completed the 6MWT on both visits. There were no changes to 6MWT distances. (Coe et al 2017).	
Improved capacity to participate in	-	-	-	-	-

daily tasks - not measured					
Reduced falls - not measured	-	-	-	-	-

1. Katz Sand I, Benn EKT Fabian M et a. Randomized-controlled trial of a modified Mediterranean dietary program for multiple sclerosis: A pilot study. Multiple Sclerosis and Related Disorders; 2019.
2. Bitarafan S., Harirchian M.-H. Nafissi S. et al. Dietary intake of nutrients and its correlation with fatigue in multiple sclerosis patients. Iranian Journal of Neurology; 2014.
3. Coe S, Axelsson E Murphy V et al. Flavonoid rich dark cocoa may improve fatigue in people with multiple sclerosis, yet has no effect on glycaemic response: An exploratory trial. Clinical Nutrition ESPEN; 2017.

a. Participants were women with Multiple Sclerosis (not participants diagnosed with FRDA).
b. Clinical scales measuring multiple domains of impairment.
c. Single study published.
d. Small sample size.
e. No confidence intervals reported with low absolute numbers of participants and events.
f. Allocation not concealment from enrolling investigator or clinicians providing intervention.
g. Participants with multiple sclerosis (no participants with a diagnosis of FRDA).
h. Confidence intervals not reported.
i. Cross sectional, observational study.
j. Self-reporting of dietary intake.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large
○ Moderate
○ Small
○ Trivial
○ Varies
● Don't know

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with usual diet	Risk difference with a specific diet (ie: vitamins, coffee, Mediterranean, ketogenic)
Reported fatigue assessed with: Neurological Fatigue Index-MS	36 (1 RCT)[1]	⊕◯◯◯ Very low[a,b,c,d,e,f]	-	36 women with multiple sclerosis were randomly assigned to follow or not follow a prescribed modified Mediterranean dietary intervention for 6 months. Exploratory analyses were used to examine whether the trajectory differed between the intervention groups over time using mixed effects models with a random intercept for the NFI-MS. Higher scores in the NFI-MS indicate worse fatigue. The non-intervention group increased by about 2.2 points, on average, over the 6-month study period (p = 0.07). The dietary intervention group exhibited a statistically significant decline in the 6-month trajectory of NFI-MSscores over time as compared to the trajectory of the non-intervention group (-4.6, p = 0.01). (Katz Sand et al 2019).	
Reported fatigue assessed with: Persian Modified Fatigue Impact Scale	101 (1 observational study)[2]	⊕◯◯◯ Very low[g,h,i,j]	-	101 patients with multiple sclerosis had their dietary intake assessed using a 3-day food record questionnaire. Association between variables was determined using Pearson Correlation Coefficient. After adjusting for daily energy intake, there were significant correlations between increasing total of MFIS, and decreasing daily intake of folate (p = 0.02) and magnesium (p= 0.03). This correlation was significant	

				between physical subscale of MFIS and daily intake of folate (p = 0.008) and magnesium (p = 0.003). (Bitarafan et al 2014).
Reported fatigue assessed with: Fatigue Visual Analogue Scale	12 (1 RCT)[3]	⊕◯◯◯ Very low[c,d,f,g,j]	-	12 patients with multiple sclerosis were randomised to a high flavonoid cocoa drink (350mg gallic acid equivalents (GAE)/g) or low flavonoid cocoa drink (120mg GAE/g). Fatigue was recorded on a horizontal 100mm VAS every 30 min following drink consumption and throughout testing, every 2 hrs after testing and until 6 hrs after leaving the lab. Fatigue raw data was calculated using a fixed-effects model with two treatments adjusted using the Tukey-Kramer and comparing time and treatment interaction. A moderate effect was found in self-reported fatigue throughout the day in favour of the high flavonoid group post comsumption (Cohen's d 0.32, 95% non-central t CI 0.57 to 1.20). (Coe et al 2017).
Improved quality of life assessed with: Multiple Sclerosis Impact Scale-29	36 (1 RCT)[1]	⊕◯◯◯ Very low[a,b,c,d,e,f]	-	36 women with multiple sclerosis were randomly assigned to follow or not follow a prescribed modified Mediterranean dietary intervention for 6 months. Exploratory analyses were used to examine whether the trajectory differed between the intervention groups over time using mixed effects models with a random intercept for the MSIS-29. An increase in the MSIS-29 score of about 4.8 (p = 0.16), on average, over the 6-month study period was observed for the non-intervention group. The intervention group's change in score was approximately 7.4 points lower than the trajectory observed among the non-intervention group over the 6-month study period (p = 0.12). This trend was statistically significant (p = 0.023) when one outlier was removed from each group (both in the same direction). (Katz Sand et al 2019).

Improved quality of life assessed with: MSQOL-54	36 (1 RCT)[1]	⊕◯◯◯ Very low[a,b,c,d,e,f]	-	36 women with multiple sclerosis were randomly assigned to follow or not follow a prescribed modified Mediterranean dietary intervention for 6 months. Exploratory analyses were used to examine whether the trajectory differed between the intervention groups over time using mixed effects models with a random intercept for the MSQOL-54. There was no statistically significant difference between the groups with respect to change in MSQOL-54 physical or mental health composite score over the 6 month study period. (Katz Sand et al 2019).
Improved energy levels - not measured	-	-	-	- -
Improved physical capacity assessed with: Expanded Disability Status Scale	36 (1 RCT)[1]	⊕◯◯◯ Very low[a,b,c,d,e,f]	-	36 women with multiple sclerosis were randomly assigned to follow or not follow a prescribed modified Mediterranean dietary intervention for 6 months. Exploratory analyses were used to examine whether the trajectory differed between the intervention groups over time using mixed effects models with a random intercept for the MSQOL-54. A statistically significant increase of 0.6 points (p = 0.03), on average, was noted for the non-intervention group over the 6-month study period. The dietary intervention group displayed a statistically significant decrease in the trajectory of EDSS scores over the 6-month study period as compared to the trajectory of the non-intervention group (-0.98, p = 0.01). (Katz Sand et al 2019).
Improved physical capacity assessed with: 6 min walk test	12 (1 RCT)[3]	⊕◯◯◯ Very low[c,d,e,f,g,j]	-	12 patients with multiple sclerosis were randomised to a high flavonoid cocoa drink (350mg gallic acid equivalents (GAE)/g) or low flavonoid cocoa drink (120mg GAE/g). Fatigue raw data was calculated using a fixed-effects model with two treatments adjusted using the

				Tukey-Kramer and comparing time and treatment interaction. The 6MWT was administered at the end of the study visit (2 hrs) and and at 24 hours. All participants completed the 6MWT on both visits. There were no changes to 6MWT distances. (Coe et al 2017).	
Improved capacity to participate in daily tasks - not measured	-	-	-	-	-
Reduced falls - not measured	-	-	-	-	-

1. Katz Sand I, Benn EKT Fabian M et a. Randomized-controlled trial of a modified Mediterranean dietary program for multiple sclerosis: A pilot study. Multiple Sclerosis and Related Disorders; 2019.
2. Bitarafan S., Harirchian M.-H. Nafissi S. et al. Dietary intake of nutrients and its correlation with fatigue in multiple sclerosis patients. Iranian Journal of Neurology; 2014.
3. Coe S, Axelsson E Murphy V et al. Flavonoid rich dark cocoa may improve fatigue in people with multiple sclerosis, yet has no effect on glycaemic response: An exploratory trial. Clinical Nutrition ESPEN; 2017.

a. Participants were women with Multiple Sclerosis (not participants diagnosed with FRDA).
b. Clinical scales measuring multiple domains of impairment.
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e. No confidence intervals reported with low absolute numbers of participants and events.
f. Allocation not concealment from enrolling investigator or clinicians providing intervention.
g. Participants with multiple sclerosis (no participants with a diagnosis of FRDA).
h. Confidence intervals not reported.
i. Cross sectional, observational study.
j. Self-reporting of dietary intake.

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	Very low certainty of the evidence of effects as per the evidence profile table.	

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)
Reported fatigue assessed with: Neurological Fatigue Index-MS	IMPORTANT[a]	⊕◯◯◯ VERY LOW[b,c,d,e,f,g]
Reported fatigue assessed with: Persian Modified Fatigue Impact Scale	IMPORTANT[a]	⊕◯◯◯ VERY LOW[h,i,j,k]
Reported fatigue assessed with: Fatigue Visual Analogue Scale	IMPORTANT[a]	⊕◯◯◯ VERY LOW[d,e,g,h,k]
Improved quality of life assessed with: Multiple Sclerosis Impact Scale-29	IMPORTANT[l]	⊕◯◯◯ VERY LOW[b,c,d,e,f,g]
Improved quality of life assessed with: MSQOL-54	IMPORTANT[l]	⊕◯◯◯ VERY LOW[b,c,d,e,f,g]
Improved energy levels - not measured	IMPORTANT[m]	-

Improved physical capacity assessed with: Expanded Disability Status Scale	IMPORTANT[a]	⊕◯◯◯ VERY LOW[b,c,d,e,f,g]
Improved physical capacity assessed with: 6 min walk test	IMPORTANT[a]	⊕◯◯◯ VERY LOW[d,e,f,g,h,k]
Improved capacity to participate in daily tasks - not measured	IMPORTANT[a]	-
Reduced falls - not measured	CRITICAL[n]	-

a. Identified as important (6/6) by people with FA and critical by expert authors on this topic.
b. Participants were women with Multiple Sclerosis (not participants diagnosed with FRDA).
c. Clinical scales measuring multiple domains of impairment.
d. Single study published.
e. Small sample size.
f. No confidence intervals reported with low absolute numbers of participants and events.
g. Allocation not concealment from enrolling investigator or clinicians providing intervention.
h. Participants with multiple sclerosis (no participants with a diagnosis of FRDA).
i. Confidence intervals not reported.
j. Cross sectional, observational study.
k. Self-reporting of dietary intake.
l. Identified as critical (1/6) and important (5/6) by people with FA and important by expert authors on this topic
m. Identified as important (6/6) by people with Fa and important by expert authors on this topic.
n. Identified as critical (3/6) and important (3/6) by people with FA and critical 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		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 specific diet (i.e. Vitamins, coffee, mediterranean, ketogenic) as a management strategy for all individuals who report fatigue. Reflecting on the impact of specific diet (i.e. Vitamins, coffee, mediterranean, ketogenic) on Reported fatigue, 26.09% (6/23) clinical experts reported a benefit (large, moderate or small), 17.39% (4/23) reported no effect and, 4.35% (1/23) reported observing a harm (large, moderate or small). 12 clinicians could not provide any information on this outcome. Reflecting on the impact on quality of life, 34.78% (8/23) clinical experts reported a benefit, 13.04% (3/23) reported no effect and, 0% (0/23) reported observing a harm. 12 expert clinicians could not provide any information on this outcome. Reflecting on the impact on energy levels, 34.78% (8/23) clinical experts reported a benefit, 13.04% (3/23) reported no effect and, 0% (0/23) reported observing a harm. 12 expert clinicians could not provide any information on this outcome. Reflecting on the impact on physical capacity, 17.39% (4/23) clinical experts reported a benefit, 30.43% (7/23) reported no effect and, 0% (0/23) reported observing a harm. 12 expert clinicians could not provide any information on this outcome. Reflecting on the impact on capacity to participate in daily tasks, 21.74% (5/23) clinical experts reported a benefit, 26.09% (6/23) reported no effect and, 0% (0/23) reported observing a harm. 12 expert clinicians could not provide any information on this outcome. Reflecting on the impact on falls, 4.35% (1/23) clinical experts reported a benefit, 43.48% (10/23) reported no effect and, 0% (0/23) reported observing a harm. 12 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	No published evidence.	The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were asked if using a specific diet in people who report fatigue was acceptable (weighing up the

○ Varies ○ Don't know		balance between benefits, harms and costs). 2/4 indicated the intervention was probably not acceptable, 1/4 indicated varied or sometimes acceptable, 1/4 indicated more information on the benefits and potential harms was required. (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 or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important 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 cannot recommend any specific diet over usual diet to assist in managing fatigue in individuals with FRDA.

Justification

There is insufficient evidence and clinical experience to support the use of specific diets to manage fatigue in individuals with FRDA.

Subgroup considerations

This recommendation is for individuals with Friedreich ataxia who report fatigue.

Research priorities

Exploration of specific diets in managing fatigue in FRDA.

Reference

da Silva CB, Chevis CF, D'Abreu A, Lopes-Cendes I, Franca MC, Jr. Fatigue is frequent and multifactorial in Friedreich's ataxia. Parkinsonism Relat Disord. 2013;19(8):766-7.