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RESEARCH ARTICLE

Impact of diabetes in the Friedreich ataxia clinical outcome measures study

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Abstract

Objective: Friedreich ataxia (FA) is a progressive neuromuscular disorder caused by GAA triplet repeat expansions or point mutations in the *FXN* gene. FA is associated with increased risk of diabetes mellitus (DM). This study assessed the age-specific prevalence of FA-associated DM and its impact on neurologic outcomes. **Research Design and Methods:** Participants were 811 individuals with FA from 12 international sites in a prospective natural history study (FA Clinical Outcome Measures Study, FACOMS). Physical function was assessed, using validated instruments. Multivariable regression analyses examined the independent association of DM with outcomes. **Results:** Mean age of participants was 30.1 years (SD 15.3, range: 7–82), 50% were female, and 94% were non-Hispanic white. 9% (42/459) of adults and 3% (10/352) of children had DM. Individuals with FA-associated DM were older ($P < 0.001$), had longer GAA repeat length on the least affected *FXN* allele ($P = 0.037$), and more severe FA ($P = 0.0001$). Of individuals with DM, 65% (34/52) were taking insulin. Even after accounting statistically for both age and GAA repeat length, DM was independently associated with greater FA symptom burden ($P = 0.010$), reduced capacity to perform activities of daily living ($P = 0.021$), and a decrease of 0.33 SDs on a composite performance measure (95% CI: -0.56 – 0.11 , $P = 0.004$); the relative impact of DM was most apparent in younger individuals. **Conclusions:** DM-associated FA has an independent adverse impact on well-being in affected individuals, particularly at younger ages. In future, evidence-based approaches for identification and management of FA-related DM may improve both health and function.

Introduction

Friedreich ataxia (FA) is a progressive neurodegenerative disorder affecting both children and adults¹ characterized by ataxia, gait abnormalities, loss of sensory reception,

and areflexia. In 96% of individuals with FA, disease is caused by homozygous expanded guanine-adenine-adenine (GAA) repeats in the *FXN* gene.² Pathologic GAA repeat expansions in *FXN* lead to decreased expression of the encoded gene product frataxin, a protein vital to the

assembly and function of iron–sulfur–cluster-containing enzymes and ATP production within mitochondria.^{3,4}

Individuals with FA are also at an increased risk of developing diabetes mellitus (DM). FA-associated DM affects between 5% and 40% of affected individuals, depending on the age distribution of the cohort and strategy for ascertaining DM status.^{5,6} Individuals who are older, non-ambulatory, and/or who have longer GAA repeat lengths in the *FXN* gene are more likely to develop DM.^{7,8} Additionally, there may be a modest secular increase in DM prevalence over time.⁶ However, these factors incompletely explain variation in FA-associated DM status.⁸

The objective of the present study was to investigate the role of FA-associated DM in FA progression by leveraging a large, international, prospective, physician-curated natural history study of individuals with FA. We report age-specific prevalence estimates of FA-associated DM and test the independent association between the FA-associated DM and level of function.^{9,10} Also, we describe the variation in approaches to DM management in FA.

Materials and Methods

Study design and participants

This analysis used FACOMS, a longitudinal, prospective natural history study of FA. 811 individuals with FA were enrolled between 2004 and 2015, and re-evaluated annually at 12 international sites.⁶ Information from the most recent visit was used in the present study.

The study was approved by the Institutional Review Board at the Children's Hospital of Philadelphia and other institutions, and informed consent from adult participants or the parent/guardian of participants under 18 years old was obtained prior to participation. Interim analyses of this natural history cohort have been reported previously,^{5,6,8–13} a subset of which has included assessments of glucose homeostasis.^{5,8} The present study is a cross-sectional analysis including self-reported health history and medications, physician-administered performance metrics, and neurological testing.

Clinical characteristics

The following were abstracted: sex, population ancestry, age at assessment, age of FA-onset, medications, and comorbidities, including DM and hypertrophic cardiomyopathy.¹⁴

Genetic diagnosis and modeling of genetic information

All participants underwent confirmatory genetic testing to verify FA diagnosis prior to participating in FACOMS. For testing

the effect of GAA repeat length on outcomes, the length of the shorter GAA repeat (or single GAA repeat length, if present in combination with a point mutation) was used.¹⁵

Presence of DM, treatment characteristics (Fig. S1)

First, participant-reported DM status was recorded. For participants who answered “no” or did not answer, review of the medications was performed; taking a glucose-lowering medication was also considered consistent with having DM.¹⁶

Medications

Medications were assessed at each visit. Glucose-lowering agents for treatment of DM were assigned a therapeutic class according to the American Diabetes Association Standards of Medical Care's (2016).¹⁶

Anthropometrics

Standing height was measured to the nearest centimeter (cm) using a stadiometer, and weight was recorded in light clothing using a digital scale. BMI was calculated as weight in kilograms (kg) divided by height in meters-squared (m²). In order to measure the effect of excess adiposity across a wide range of ages, BMI values were transformed into sex- and age-specific Z-scores.¹⁷ BMI values were also categorized into four groups (underweight, normal weight, overweight, obese) based on pediatric- and adult-specific reference values.¹⁷ To permit analyses of a continuous metric of excess adiposity across children and adults, BMI Z-scores were also assigned to adults, using metrics for adult age (i.e., age of 20 years).

Measurements of FA disease severity

These included: Friedreich's Ataxia Rating Scale (FARS), Activities of Daily Living (ADL) questionnaire, and FA stage.^{6,18} Performance measures were also assessed, including: 25-Foot Walk (T25FW),^{6,9,18} 9-Hole Peg Test (9HPT),^{6,13} and Contrast Letter Acuity (vision score).^{6,9,19}

Composite performance measure

The 9HPT, T25FW, and vision score were transformed into Z-scores for each participant to create a composite performance measure score (Z3) as previously described.^{6,9,18}

Statistical analyses

Summary statistics were generated for each clinical variable for the entire sample, as well as stratified by DM

status. Wilcoxon rank sum tests or Fisher's exact test were performed to test for differences in clinical factors between individuals with and without DM. We examined bivariate relationships between DM status and clinical characteristics including age at assessment, age of FA-onset, GAA repeat length, sex, BMI z-score, and presence or absence to point mutation. Clinical characteristics were included as covariates in the multivariable regression analyses if they were found to have a statistically significant association with DM status in bivariate analyses. Age of FA-onset and GAA repeat length are known to be highly associated with each other. To avoid collinearity, we included GAA repeat length and not age of FA onset in our final multivariable regression analyses because age of FA-onset may be subject to recall bias by study participants.²⁰ Summary statistics were generated for FARS scores and performance measures, including ADL and Z3 composite scores, first for the entire cohort, and then stratified by presence or absence of DM. Wilcoxon rank sum tests or two-sample t-tests were performed, as appropriate given variable distributions, to assess for differences between individuals with and without DM. The independent effect of DM status on FA disease-specific outcomes (FARS, ADL, Z3 composite scores), accounting statistically for other clinical covariates (age at assessment, GAA repeat length), was assessed using multivariable regression analysis. We tested separate models that included interaction terms to determine if the effect of DM depended on either age and/or GAA repeat length. In separate models, we also tested for the independent effects of insulin requirement on these outcomes. Analyses were performed using STATA v11.2 (StataCorp LP, College Station, TX), and R v3.2.2. A two-sided $P < 0.05$ was considered statistically significant.

Mediation analysis

We performed a causal mediation analysis ("Mediate" package implemented in R) to estimate both the direct effect of GAA repeat length on outcomes of interest, as well as the proportion of the effect of GAA repeat length that is indirect, that is, mediated by DM.

Burden of self-reported comorbidities

We hypothesized that DM may exert adverse effects on physical function and quality of life in FA by increasing the burden of DM-related comorbidities. In this database focused primarily on neurological outcomes, individuals reported any other comorbidities present; as a result, DM-specific comorbidities were not collected systematically but may have been reported. We identified the comorbidities that were reported by least 10% of

individuals with DM, and then compared the prevalence of these conditions in individuals with versus without DM using a chi-squared or Fisher's exact test, as appropriate, depending on the sample size.

Results

At their initial study visit, 811 subjects from 12 international sites had a mean age of 30.1 ± 15 (mean \pm SD) years (range:7–82) (Table 1). 33 subjects (4%) carried a single GAA expansion on one *FXN* allele along with a point mutation on the other *FXN* allele; all other subjects were homozygous for GAA expansions. Mean length of the GAA repeat expansion on the least affected allele was 642 ± 243 base pairs (in contrast, unaffected individuals have between 8 and 22 GAA repeats)²¹, and mean age of FA-onset was 13.7 ± 10 years (SD), both similar to values reported in previous natural history studies of FA.¹ The mean Functional Disability Score, which ranges from 0 to 6, with higher values indicating worse function, was 4.0 ± 1.3 (SD), a score that is reflective of a participant having difficulty ambulating independently, with moderate-to-severe ataxia, requiring the use of a walker or canine-assistant.¹

A substantial proportion (245/460 adults and 279/352 children) were missing BMI measurements. We did not identify any systematic differences between individuals with and without anthropometric measurements, but since the presence of severe ataxia may make accurate height measurement more difficult, thus there is a risk for associated bias.

In total, 6.4% (52/811) of participants in the cohort had DM; DM was present in 3% (10/352) of children and 9% (42/459) of adults (Table 1). The point-prevalence of DM, stratified by age and tertile of GAA repeat length, is shown in Figure 1. Clinical characteristics of the cohort stratified by DM status are shown in Table 1. Individuals with DM were older at assessment (by 8.6 years, $P \leq 0.001$), had longer GAA repeat length in the least affected allele (by 75 nucleotides, $P = 0.037$), and had a worse FA stage (by 0.9, $P \leq 0.001$). There were no statistically differences in self-reported history of cardiomyopathy, sex, or presence of genetically confirmed point mutation.

With respect to management, out of 52 cases of DM, 48% ($n = 25$) reported using insulin alone, and 17% ($n = 9$) received a combination of insulin and an oral agent (Table S1). An additional 23% ($n = 12$) reported taking oral agents alone, and 12% ($n = 6$) patients reported having DM but denied taking any glucose-lowering medications. To determine the extent to which adverse effects commonly associated with glucose-lowering agents²² might impact outcomes in FA, we tabulated

Table 1. Clinical characteristics of FACOMS participants, with stratification by DM status.

	All participants (<i>n</i> = 811)		Participants without DM (<i>n</i> = 759)		Participants with DM (<i>n</i> = 52) <i>P</i> -value for association with DM (if <0.05)	
Age at assessment, in years (mean, SD)	30.1 (15.3)		29.6 (15.2)		38.2 (13.6) <i>P</i> = 0.0001	
Proportion in each age group in years, % (<i>n</i>); <i>P</i> = 0.001 for association of age category with DM status						
0–<21	34.7 (281)		36.7 (278)		5.8 (3)	
21–<45	46.9 (379)		46.0 (348)		59.6 (31)	
45+	18.4 (149)		17.3 (131)		34.6 (18)	
Sex, % female (<i>n</i>)	50 (405)		49 (375)		58 (30)	
Age of onset of FA in year mean (SD)	13.7 (10.0)		13.7 (9.9)		13.2 (10.5)	
Length of shorter GAA repeat, in nucleotides, mean (SD)	642 (243)		638 (241)		712 (260) <i>P</i> = 0.037	
Point mutation present or absent, % (<i>n</i>) & length of shorter GAA repeat, in nucleotides, mean (SD)	Present:	Absent:	Present:	Absent:	Present:	Absent:
	4.3	95.7	4.4	95.6	2.0	96.0
	(<i>n</i> = 33)	(<i>n</i> = 740)	(<i>n</i> = 32)	(<i>n</i> = 691)	(<i>n</i> = 1)	(<i>n</i> = 48)
	736 (259)	638 (242)	730 (260)	633 (239)	933 (0)	713 (265)
FA Stage, 0–6, higher value is worse severity,mean (SD)	4.0 (1.3)		4.0 (1.3)		4.9 (1.1) <i>P</i> = 0.0001	
HCMP, % (<i>n</i>)	56% (385/693)		55% (356/646)		61% (29/47)	
Body Mass Index (BMI)						
Adults (<i>n</i>)	215		198		17	
Z-score, mean (SD)	0.07 (1.54)		0.11 (1.48)		−0.37 (2.04)	
Classification, % (<i>n</i>)						
Underweight	13.8 (30)		13.0 (26)		23.5 (4)	
Normal	48.4 (105)		49.0 (98)		41.3 (7)	
Overweight or Obese	37.8 (82)		38.0 (76)		35.4 (6)	
Children (<i>n</i>)	73		73		0	
Z-score, mean (SD)	0.46 (1.46)		0.46 (1.46)		—	
Classification, % (<i>n</i>)						
Underweight	9.6 (7)		9.6 (7)		—	
Normal	52.1 (38)		52.1 (38)		—	
Overweight or Obese	38.4 (28)		38.4 (28)		—	

Except where noted, mean values are presented. Values in bold text indicate a statistically significant difference (*P* < 0.05) between individuals without DM versus with DM. Age of onset is available in 792/811 (cohort), 740/759 (non-DM), 52/52 (with DM). GAA repeat length on the shorter *FXN* allele is available in 771/811 (cohort), 721/759 (non-DM), 50/52 (with DM). Point mutation status is known in 773/811 (cohort), 723/759 (non-DM), 49/52 (DM). FA stage is known in 783/811 (cohort), 731/759 (without DM), 52/52 (with DM).

SD, standard deviation; *n*, total number of participants; GAA, repeat length of the shorter *FXN* allele; HCMP, history of cardiomyopathy (self-reported by participants).

the number of participants taking these medications who reported commonly associated adverse effects. No patients reported hypoglycemia. Four participants taking biguanides also reported having gastrointestinal symptoms. None of the other commonly reported symptoms were reported, however, we note that no systematic collection was performed.

Both older age at assessment OR 1.06, (95% CI: 1.04–1.08; *P* < 0.001) and longer GAA repeat length OR 1.34 (95% CI: 1.18–1.52; *P* < 0.001) were independently associated with increased odds of having DM (Model 1, Table 2). There was no apparent association with sex. Adding BMI z-score to the model (sensitivity analysis,

Model 2, Table 2) did not substantially alter the main results, although missing measurements reduced the number of observations in this model.

Participants with DM had significantly worse FARS scores (DM: 86 ± 21; non-DM: 68 ± 21; *P* < 0.001, with scores out of a possible 125, and higher scores indicating more severe disease) (Table S2). Participants with DM also had more disability as assessed by the ADL scale (DM: 22 ± 7.2; non-DM: 16 ± 7.1; *P* < 0.001, with scores out of a possible 36, higher scores indicating more disability). Participants with DM also performed collectively worse on the summary performance measure (a lower Z3 composite score) containing the 9HPT, T25FW,

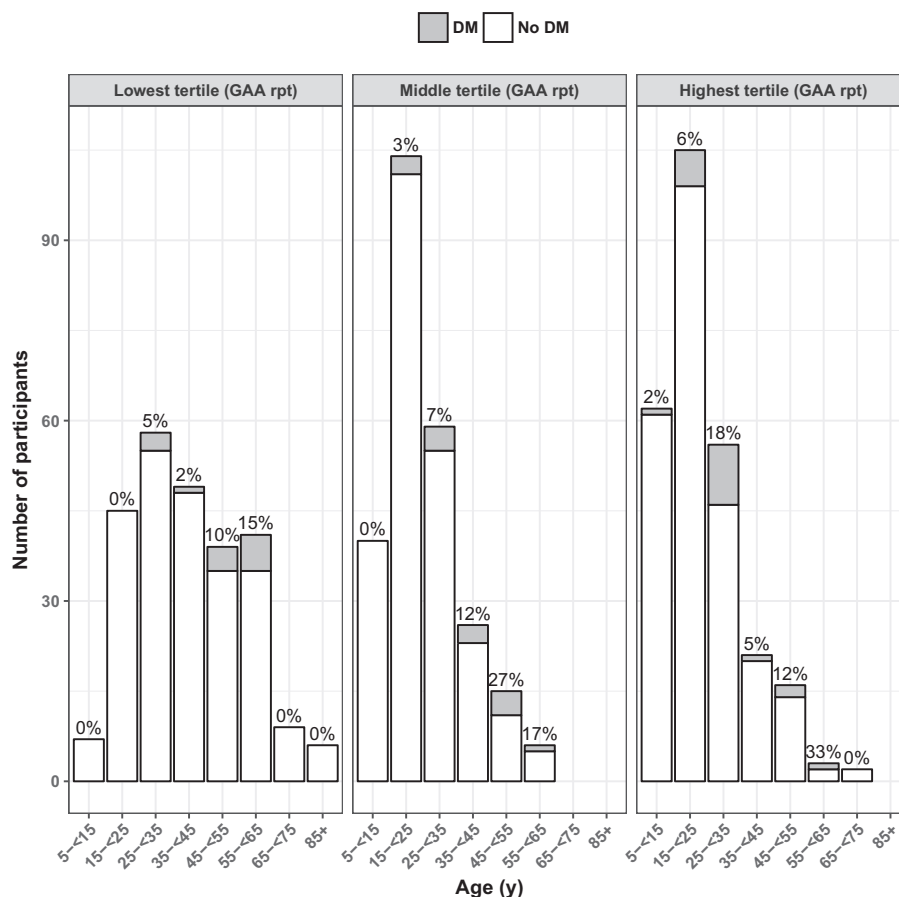


Figure 1. Point-prevalence of FA-associated DM, by age group (by 10-year increments) and GAA repeat length in the least affected allele (by tertile, from shortest to longest). Each panel represents a tertile of GAA repeat length on the least affected allele, from lowest (i.e., shortest) to highest (i.e., longest). On the x-axis, age group is shown, divided into 10-year increments. The number of individuals in each group is shown on the y-axis; the number of individuals with DM is shown, and the % with DM is indicated above each bar.

Table 2. Odds of having FA-associated DM, related to clinical factors.

Clinical factor	Model 1: Odds of having DM Odds ratio (95% CI) <i>P</i> -value (if <0.05)	Model 2: Odds of having DM Odds ratio (95% CI) <i>P</i> -value (if <0.05)
Age at assessment (years)	1.06 (1.04, 1.08) <i>P</i> < 0.001	1.05 (1.02, 1.09) <i>P</i> = 0.006
GAA repeat length	1.34 (1.18, 1.52) <i>P</i> < 0.001	1.39 (1.13, 1.70) <i>P</i> = 0.002
Sex	1.31 (0.72, 2.38)	0.90 (0.31, 2.61)
BMIz	—	0.89 (0.63, 1.26)
<i>n</i>	769	267
Pseudo- <i>R</i> ²	0.10	0.11

This table shows the odds ratio and the 95% confidence interval (CI) associated with each of the clinical factors included in the models, as well as the associated *R*² and total number of observations (*n*) included in each model. GAA repeat length is reported per 100 nucleotides for ease of presentation. Statistically significant associations for the particular clinical factor (*P* < 0.05) are indicated in bold text. BMIz, BMI z-score.

and vision testing compared to those without DM (-0.76 ± 0.83 vs. -0.018 ± 0.83 , respectively; *P* < 0.001, with scores reflecting the number of standard deviations different from to the cohort mean).

Having DM was independently associated with a worse FARS score, by 6.8 points (95% CI: 1.6, 12.1; *P* = 0.01) out of a possible 125, even after accounting statistically for both age and GAA repeat length (Table 3, Fig. S2). We also detected an independent association of DM with worsening capacity to perform ADLs, by 2.2 points on the 36-point scale (95% CI: 0.33, 4.1; *P* = 0.021), and lower score on a composite measure of performance, by 0.33 SDs (95% CI: -0.56 , -0.11 ; *P* = 0.004), again after accounting statistically for age and GAA repeat length. With respect to other clinical covariates included in the models, as expected, both older age at assessment and longer GAA repeat length were also associated with worse outcomes on all measures. There was a statistically significant interaction between DM status and age, reflecting

Table 3. Multivariable linear regression analysis of the association of DM status with performance measures, accounting for age at assessment and GAA repeat length on the least affected allele.

Clinical factor	FARS (higher = more severe disease) Coefficient (95% CI) P-value (if <0.05)	FARS (higher = more severe disease) Coefficient (95% CI) P-value (if <0.05)	ADL (higher = more impairment) Coefficient (95% CI) P-value (if <0.05)	ADL (higher = more impairment) Coefficient (95% CI) P-value (if <0.05)	Z3 (lower = worse performance) Coefficient (95% CI) P-value (if <0.05)	Z3 (lower = worse performance) Coefficient (95% CI) P-value (if <0.05)
DM status	6.9 (1.6,12.1) P = 0.010	35.1 (6.7,63.5) P = 0.016	2.2 (0.3,4.1) P = 0.022	13.8 (3.6,24.0) P = 0.008	-0.3 (-0.6, -0.1) P = 0.003	-1.3 (-2.6, -0.1) P = 0.035
Age at assessment (years)	0.73 (0.63,0.83) P < 0.001	0.40 (0.20,0.60) P < 0.001	0.26 (0.22,0.30) P < 0.001	0.19 (0.11,0.26) P < 0.001	-0.03(-0.03,-0.03) P < 0.001	-0.02 (-0.03,-0.02) P < 0.001
GAA repeat length	5.4 (4.8,6.1) P < 0.001	3.3 (2.0,4.6) P < 0.001	1.4 (1.2,1.7) P < 0.001	0.9 (0.5,1.4) P < 0.001	-0.18 (-0.21,-0.16) P < 0.001	-0.14 (-0.20,-0.08) P < 0.001
Sex	-0.6 (-3.1,2.0)	-0.6 (-3.1,1.9)	0.2 (-3.3,1.3)	0.1 (-0.8,1.0)	0.1 (0,0.2)	0.1 (0,0.2)
DM × Age	—	-0.43 (-0.85,-0.07) P = 0.046	—	-0.20 (-0.35, -0.05) P = 0.009	—	0.02 (0,0.04) P = 0.05
DM × GAA repeat length	—	-1.8 (-4.1, 0.5)	—	-0.6 (-1.4,0.2)	—	0.04 (-0.06,0.14)
Age × GAA repeat length	—	0.06 (0.03, 0.09) P < 0.001)	—	0.02 (0.004,0.03) P = 0.009	—	-0.001 (-0.003,0.001)
n	732	732	700	700	631	631
R ²	0.34	0.36	0.27	0.29	0.31	0.31

Coefficients and 95% confidence intervals (CI) are shown, along with respective R² and total number (n) of values for each relationship. GAA repeat length is reported per 100 nucleotides for ease of presentation. Values in bold text indicate a statistically significant difference ($P < 0.05$) related to the particular clinical factor. Interaction terms are indicated.

that the impact of DM depends on participant age (Figs. S2, S3a, b, and c). Specifically, in individuals with FA-associated DM, clinical outcomes were worse at younger ages, so appeared to be less of a decline in performance with increasing age.

To assess whether DM exerts independent effects on outcomes or alternatively, is simply a reflection of disease severity, we conducted a mediation analysis (Table S3). We found that DM status does mediate a small proportion of the effect of GAA repeat length on FARS (3%; 95% CI: 1–5%; $P < 0.001$), ADL (by 3%; 95% CI: 1–7%; $P < 0.001$), and Z3 (by 3%; 95% CI: 1–6%; $P < 0.001$) scores. We also analyzed the extent to which DM may adversely affect function and quality of life in FA by increasing the burden of comorbidities (Figure S4). We found that both depression and neuropathy were more common in DM (both $P < 0.001$); rates of GERD and urinary frequency were not statistically different.

In addition, after accounting for the effects of clinical covariates, an insulin requirement is associated with 7.2 worse score on the FARS scale, 3.1 points worse with respect to ADL, and 0.33 SDs worse on their Z3 composite score (Table S4). Of note, participants who reported

taking insulin were diagnosed with FA at younger age (median of 8 years, IQR: 6–12, $n = 34$) than those participants with DM who were not using insulin (median of 14.5 years, IQR: 10–32, $n = 18$), a statistically significant difference ($P = 0.004$, by Wilcoxon rank sum test).

Discussion

In this prospective, observational study of individuals with FA, having DM was associated with having more severe FA, worse functional status, and diminished capacity for self-care, as assessed using objective and validated measures, even after accounting for other important clinical covariates. In addition, we have attempted to understand more about the pathophysiology of the observed association between adverse clinical outcomes and longer GAA repeat length. In a causal mediation analysis, we estimated that ~3% of the effect of GAA repeat length on these outcomes is mediated by DM status. Taken together, our results suggest that DM status both partly mediates the effects of GAA repeat length and also exerts independent adverse effects on clinical outcomes in FA. The relative adverse impact of DM was evident in

multiple functional domains,^{6,9} and was most pronounced in the youngest affected individuals.

This work builds on previous studies in FACOMS⁶ and in smaller cohorts that did not detect an independent effect of DM on FA-related performance measures;⁵ our DM prevalence estimates are modestly higher than previous reported in this cohort,⁶ likely because of the additional steps taken to ensure all DM cases were captured. We focused on DM because it is a comorbidity of FA that is amenable to specific treatment. However, there are not currently evidence-supported guidelines for screening and/or hemoglobin A1c treatment goals in FA-associated DM. Our findings have at least three implications that warrant further investigation. First, in individuals with FA, early detection and optimal management of abnormal glucose metabolism may produce clinical benefit. Second, observational studies and clinical trials in FA should consider the potentially important role that abnormal glucose metabolism has on other relevant outcomes. Finally, glucose metabolism may itself be an important prognostic biomarker in FA.

Little is known about the optimal strategy to treat FA-associated DM. It is reasonable that the choice of glucose-lowering therapy should take into account potential interactions between medications and the multi-system comorbidities that can occur in FA. For example, several investigators have suggested that patients with disorders that affect the mitochondria, as FA does,^{3,4} exercise caution when using biguanides such as Metformin.²³

This caution regarding Metformin use is for at least two reasons. First, although extremely rare, with one estimate of reported incidence of 5 cases per 100,000 patients/year²⁴, Metformin may carry a risk of lactic acidosis.²⁵ Importantly, these episodes occurred in patients who were already at increased risk for lactic acidosis, making the role of Metformin as a precipitant less clear.²⁴ In addition, in some of these studies the concentration of Metformin was likely supra-therapeutic. In addition, in particular in individuals where some degree of mitochondrial impairment may already be present, there may be an association between Metformin and increased plasma lactate concentrations.^{26,27} However, Metformin has clear efficacy in DM, and may have benefit in other conditions as well.²⁸ Thus, additional studies are clearly needed to address both the safety and overall efficacy of Metformin (for both DM and overall health) in populations that may be at higher risk for lactic acidosis. A second theoretical reason for caution in the use of biguanides is that, *in vitro*, Metformin (and also TZDs) may inhibit of complex I of the mitochondrial respiratory chain; it is not clear whether the doses used in these studies are similar to those experienced by humans on Metformin

therapy.^{23,29} Metformin also inhibits mitochondrial glycerophosphate dehydrogenase.³⁰

With respect to other oral glucose-lowering agents, some TZDs may be linked to congestive heart failure;³¹ in individuals with FA who also have cardiomyopathy, TZD-specific risks of cardiac dysfunction should also be considered in the choice of therapy. In FACOMS, six individuals reported taking Metformin, and one, a TZD.

In FACOMS, we also found that insulin therapy was independently associated with worse performance on clinical assessments. Having an insulin requirement likely reflects duration and/or age of onset of FA, since younger children with FA may be more likely to have DM requiring insulin, *e.g.*, presenting with ketoacidosis.³² Indeed, our results show that participants with DM who require insulin were diagnosed with FA approximately 3.8 years earlier than those participants in the cohort with DM who did not report using insulin. We also found a larger impact of DM on functional status in younger participants. In adults, worse functional performance in individuals who take insulin may reflect an association with more severe DM, since adults may begin insulin therapy after oral hypoglycemic agents fail to control glucose levels adequately.^{32,33}

While some therapies for DM pose a risk for exacerbation of FA-related comorbidities, other DM therapies may actually be synergistic and/or have ancillary benefits in FA. For example, incretin analogs such as Glucagon-Like Peptide-1 (GLP1) agonists currently in clinical use for treatment of DM may have neuroprotective effects in FA.³¹ Five of the FACOMS participants with DM reported using incretin-based therapy. Also, it has been proposed that peroxisome proliferator-activated receptor- γ agonists such as TZDs could have neuroprotective effects in FA by promoting mitochondrial biogenesis and reducing mitochondrial oxidant burden.³⁴ However, as noted, the risk of cardiac dysfunction with some TZDs is cause for caution.³⁵ In future studies, we can leverage the longitudinal nature of FACOMS to examine long-term safety and efficacy considerations related to the choice of diabetes therapy in FA.

The population of individuals with FA-associated DM is of particular interest because they also have increased rates of certain comorbidities. Specifically, we found that individuals with both FA and DM have a higher burden of both depression and neuropathy. This difference provides a plausible explanation for DM-related differences in physical function, especially since the neurological burden represented by FARS score captures mostly ataxia, with minimal FA-associated neuropathy. In contrast to DM-related neuropathy, the neuropathy related to FA is static, and typically has already reached maximal severity at presentation in individuals with FA.^{6,9,36} One limitation of

this analysis is that self-reported comorbidities were not verified, and some participants may have comorbidities of which they are unaware and/or were not inclined to report. These analyses also do not account for either age or GAA repeat length; these factors are included in the previously reported multivariable regression analyses. It may be that the lower burden of self-reported neuropathy in individuals with FA without DM reflects a lower prevalence of neuropathy in individuals with milder, adult-onset FA.

We also investigated risk factors for FA-related DM in our cohort, and noted that both advancing age and GAA repeat length were associated with higher odds of having DM. It is plausible that the mitochondrial dysfunction that occurs in FA makes DM apparent at younger ages than in the general population.³⁷ Aging is also accompanied by changes in body composition that may hasten onset of DM (increased fat mass, particularly visceral), and individuals with FA may also demonstrate these changes at comparatively younger ages.³⁸ It has also been previously reported that the presence of a point mutation in the *frataxin* gene also is associated with increased likelihood of DM,³⁹ although we did not detect a statistically significant association in this analysis.

There were a number of additional limitations to the present study. Firstly, FA is an orphan disease that is clinically heterogeneous. Despite the large sample size, our results may not be representative of the entire population of individuals with FA. In addition, FACOMS is focused on neurological course, so there is some missing information on other outcomes; to mitigate this, we reviewed medications and electronic medical records to verify DM status. Clinical practice guidelines currently recommend annual screening for DM in FA,⁴⁰ thus we anticipate that there is a high degree of accurate DM ascertainment in these individuals receiving care at FACOMS sites, but some cases may be missed, thus these estimates represent lower bounds.

In summary, having DM is independently associated with worse functional status in FA, in particular in younger individuals. Our findings suggest that prompt diagnosis and optimization of DM status may be one way to improve overall health in FA. Future studies should generate additional evidence to support standardized screening or treatment practices for FA-related abnormalities in glucose homeostasis. In the future, it would also be useful to consistently assess both DM status and the presence of DM-related comorbidities that could adversely affect health in FA.

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Author Contributions

AM and SEM designed the study and performed analysis and interpretation of data, as well as interpretation, preparing the first draft of the manuscript, and revised the manuscript. Also, JF, SP, MD, GW, KM, GY, CH, SHS, TZ, and DRL performed FACOMS, and participated in data interpretation and edited the manuscript.

Conflicts of Interest

The authors have no conflicts of interest to disclose.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Figure S1. Algorithm for assessing and determining DM status within FACOMS.

Figure S2. FA-associated DM, age, and mean FA-related clinical outcomes.

Figure S3. (A) Statistical interaction between FA-associated DM and age in FA-related clinical outcomes. Age is on the *x*-axis, and the distribution of ages in the cohort is shown by the small vertical lines.

Figure S4. Self-reported co-morbidity burden in individuals with versus without DM in FACOMS. On the *x*-axis, each of the co-morbidities is shown.

Table S1. Management of FA-related DM.

Table S2. Disease severity and performance measures in FA, and their association with DM.

Table S3. Causal mediation analysis to estimate the direct effect of genetic severity as well as the indirect effect of genetic severity that is mediated by DM on FARS, ADL, and Z3 outcome measures.

Table S4. Multivariable linear regression analysis of the association of insulin use with performance measures, accounting for age at assessment and GAA repeat length on the least affected allele.