RESEARCH ARTICLE

# Evolution of disability in spinocerebellar ataxias type 1, 2, 3, and 6

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## Abstract

**Objective**: The aim was to study the evolution of disability in spinocerebellar ataxias (SCAs) type 1, 2, 3, and 6 (SCA1, 2, 3, 6). **Methods**: We analyzed data of two longitudinal cohorts (RISCA, EUROSCA) which recruited ataxic and non-ataxic SCA1, SCA2, SCA3, and SCA6 mutation carriers. To study disability, we used a five-stage system for ataxia defined by walking ability (stages 0–3) and death (stage 4). Transitions were analyzed using a multi-state model with proportional transition hazards. Based on the hazard estimates, transition probabilities and the expected lengths of stay in each stage were calculated. We further studied the effect of sex and CAG repeat length on progression. **Results**: Data of 3138 visits in 677 participants were analyzed. Median SARA scores for SCA1, SCA2, SCA3, and SCA6 ranged from 1.5 (interquartile range [IQR] = 0.0–3.5) to 3.5 (IQR = 1.4–6.1) in stage 0, 11.5 (IQR = 9.6–14.0) to 13.8 (IQR = 11.0–16.0) in stage 1, 19.0 (IQR = 17.0–21.0) to 23.8 (IQR = 19.5–27.0) in stage 2, and 28.5 (IQR = 26.0–32.5) to 34.0 (IQR = 32.6–37.1) in stage 3. Modeling allowed to calculate the subtype-specific probability to be in a certain stage at a given age and duration of each stage. CAG repeat length was associated with faster progression in SCA1 (HR, 95% CI: 1.1, 1.1–1.2), SCA2 (1.2, 1.1–1.3), and SCA3 (1.1, 1.0–1.2). In SCA6, female sex was associated with faster progression (1.7, 1.1–2.6). **Interpretation**: Our data are important for counselling of patients, assessment of the relevance of outcome markers, and design of clinical trials.

## Introduction

The spinocerebellar ataxias (SCAs) are a genetically heterogeneous group of autosomal dominantly inherited progressive ataxia disorders. The most common, SCA1, SCA2, SCA3, and SCA6, are due to translated CAG repeat expansions that encode elongated polyglutamine tracts within the proteins associated with each subtype. SCA1, SCA2, and SCA3 mutation carriers typically develop ataxia in the fourth decade of life, whereas the onset of ataxia in SCA6 is about 20 years later.[1] Survival after ataxia onset has been reported to be about 20 years.[2,3]

A number of cohort studies assessed the progression rates of SCA1, SCA2, SCA3, and SCA6 patients by repeated administration of clinical scales. The majority of these studies used the Scale for the Assessment and Rating of Ataxia (SARA),[4-7] one of the International Cooperative Ataxia Rating Scale,[8] and another the neurological examination score for spinocerebellar ataxia (NESSCA).[9] The maximal observation times of most of these studies ranged between 1 and 3 years. EUROSCA, a European longitudinal cohort study of 526 SCA1, SCA2, SCA3, and SCA6 patients had the longest follow-up with a median observation time of 49 months.[4] The RISCA study

followed 252 risk persons for SCA1, SCA2, SCA3, and SCA6 for a median period of 53 months and observed transition to manifest ataxia in 52% of the SCA1, 59% of the SCA2, 42% of the SCA3, and 13% of SCA6 mutation carriers.[10,11] These studies provided important quantitative information on the progression and on the transition of pre-ataxic mutation carriers to manifest ataxia. However, all studies covered only a small part of the entire disease span of SCA1, SCA2, SCA3, and SCA6. In all studies, progression rates were calculated as average values of the entire study population, although study participants entered the cohorts at different times of disease development. Another shortcoming of these studies is the reliance on clinical scales, although these scales may not always adequately reflect the consequences of ataxia on the daily life of affected individuals.[12]

An alternative approach to assess disease progression in ataxia and its impact on patients´ daily life is the use of staging systems defined by walking disability. To this end, a five-stage system for ataxia including four stages related to walking ability and a final stage defined by death was proposed. This staging system was applied in a retrospective survey of 466 ataxia patients including 286 patients with an autosomal dominantly inherited ataxia that revealed disease-specific differences of progression rates and identified CAG repeat length as risk factor for faster progression in SCA2 and SCA3.[13]

In the present study, we applied a multi-state model to analyze longitudinally acquired walking disability data of 677 SCA1, SCA2, SCA3, and SCA6 mutation carriers from the RISCA and EUROSCA cohorts. Our aim was to (1) better understand the relation between disability and clinical measures, (2) define the evolution of walking disability over the entire disease span, and (3) identify factors that influence transition into higher disability stages.

# Methods

## Participants

We analyzed longitudinal data of pre-ataxic and ataxic SCA 1, 2, 3, and 6 mutation carriers from the RISCA and EUROSCA cohorts. The RISCA study enrolled non-ataxic children or siblings of patients aged 18–50 for relatives of patients with SCA1, SCA2, or SCA3 and aged 35–70 years for relatives of patients with SCA6.[10,11] In the current analysis, only mutation carriers were included. EUROSCA enrolled ataxic SCA 1, 2, 3, and 6 mutation carriers aged 18 years or older.[4,14] The data of all participants with at least one follow-up visit were considered.

To study the evolution of walking disability, we used the following staging system: stage 0 (no gait difficulties), stage 1 (gait difficulties), stage 2 (loss of independent gait, as defined by permanent use of a walking aid or reliance on a supporting arm), stage 3 (confinement to wheelchair), and stage 4 (death).[13]

At baseline, all RISCA participants were in stage 0 by definition, but in the course of the longitudinal study, a part of them converted to manifest ataxia.[11] As walking disability stages were not formally assessed in the RISCA study, we used the rating of the gait item (item 1) of SARA to infer walking disability, as follows: 0–1 points: stage 0; 2–4 points: stage 1; 5–7 points: stage 2; > 8 points: stage 3.

## Clinical assessments

The EUROSCA and RISCA protocol included the following clinical assessments. SARA was used to assess the presence and severity of ataxia.[15] The SARA sum score ranges from 0 to 40 with 0 indicating absence of ataxia and 40 the most severe degree of ataxia. In addition, a performance-based coordination test, the SCA Functional Index (SCAFI) was applied.[16] SCAFI consists of three subtests: 8 m walk (8MW), 9-hole peg test (9HPT), and PATA rate (PATA). Each subtest is converted into a *Z*-score, the SCAFI score is generated as the arithmetic mean of all three *Z*-scores. The assessment of neurological signs other than ataxia was done using the Inventory of non-ataxia signs (INAS).[17] The INAS is a list of 30 items that are grouped into 16 non-ataxia signs, with the presence or absence of these signs resulting in a score of either 1 or 0. The INAS count denotes the number of non-ataxia signs with a range between 0 and 16. Moreover, patient-related outcome measures were assessed. As a measure of depressive symptoms, we applied the Patient's Health Questionnaire (PHQ-9).[18] The PHQ-9 sum score ranges from 0 (absence of depression) to 27 (severe depression). Health-related quality of life was assessed using the EQ-5D visual analogue scale (EQ-5D).[19] For calculation, the patient is asked to mark the present day's health status on a scale with end points of 0 and 100, indicating the "the worst" (0) and "the best health you can imagine" (100).

## Data analysis and modeling

All analyzes were performed using the R Software for Statistical Computing, version 4.0.4.[20]

To describe the relation between disability stages and clinical assessments, we calculated the median and interquartile range (IQR) of each measure of all participants who were in a certain stage at any time. For those who had multiple visits in one disease stage, the median values of the clinical assessments were used. We used the Kruskal–Wallis Rank Sum test for comparison of clinical

 

assessments (SARA, SCAFI, INAS, PHQ-9, and EQ-D5) across disability stages in a nonconfirmatory fashion, followed by post hoc procedure with Dunn's tests including Bonferroni correction to find differences in clinical assessments between the disability stages for each SCA. We did not make any further corrections to adjust *p*-values for multiple comparisons across score variables. The observational units in these tests refer to stage occupations. It is assumed that the distribution of the test statistic is not affected by possible dependencies occurring in persons occupying more than one stage.

Transitions between disability stages were analyzed using a multi-state modeling approach with proportional transition hazards.[21-23] Multi-state models describe how an individual moves between a series of states in continuous time. Each movement—referred to as transition—from one state to another state is characterized by a (possibly covariate-dependent) transition hazard describing the dynamics of the transition process between the two states. Here, we specified a separate multi-state model for each of the SCA subtypes. All models were defined by five states (stages 0–4). Age was used as time scale, and several sets of covariates were considered. Starting with a covariate-free model, we incorporated repeat length of expanded and normal allele and sex as covariates. As the exact age at conversion was not observed, we computed the time of conversion as the midpoint of the time interval defined by the visits before and after conversion. This adjustment was in line with earlier work on ataxia progression.[11] No adjustments were made if the last two (or even more) visits were observed within the same stage and no further follow-up data were available. Conversion times to stage 4 (death) were also left unadjusted, as the dates of death of deceased patients were known exactly.

Because SCA1, SCA2, SCA3, and SCA6 are progressive diseases, we restricted our analysis to conversions into higher disability stages. In a small number of visits, conversions to a lower stage were recorded (SCA1: 8, SCA2: 18, SCA3: 14, SCA6: 8). These were classified as stable. Conversions that skipped one stage were classified as conversion to the next higher stage (SCA1: 1, SCA2: 1, SCA3: 2, SCA6: 5). Due to small numbers, conversions from either stage 0 or 1 to stage 4 (death) were not included in the model (SCA1: 3, SCA2: 5, SCA3: 1, SCA6: 2). The multi-state model and the observed numbers of conversions are depicted in Figure 1.

Multi-state models were specified such that each covariate shared a common hazard ratio (HR) across all transitions, while baseline transition hazards were allowed to vary between states. To increase numerical stability, cumulative transition hazards were smoothed using shape-constrained additive models with monotone increasing P-splines.[24,25] Based on the smoothed hazard estimates, state occupation probabilities, and expected lengths of stay (starting with the smallest time point and restricted by the last observed time point) in stages were calculated.[26] Ninety-five percent confidence intervals (95% CIs) were calculated using the bias-corrected and accelerated bootstrap with 1000 samples.

Results are presented in terms of estimated transition HRs with 95% CIs. Likelihood-ratio tests were used to investigate the associations between covariates and

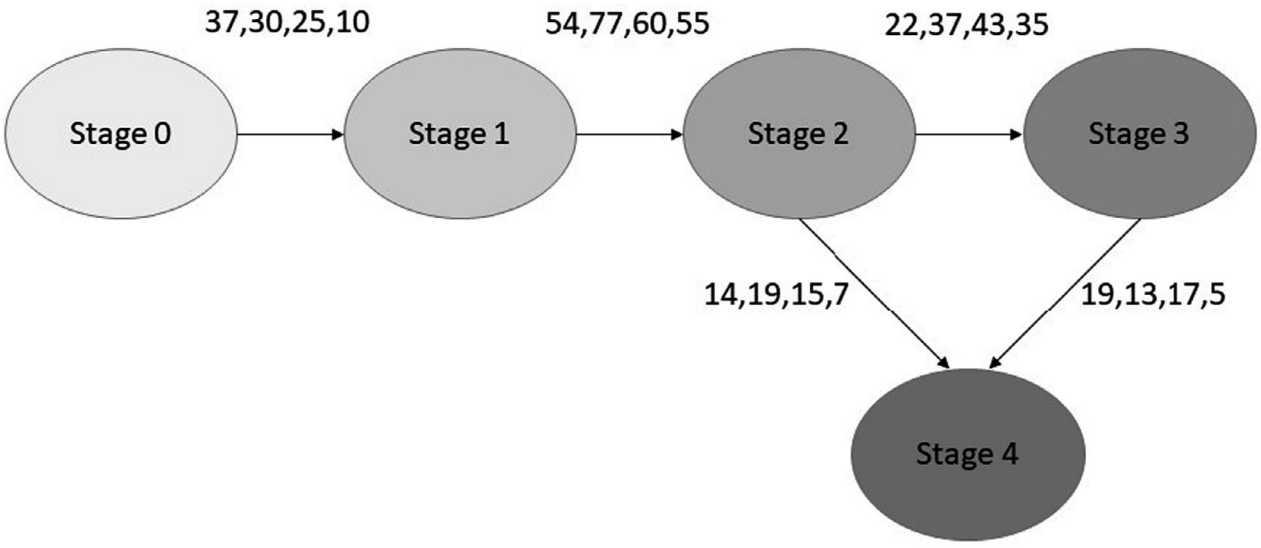


**Figure 1.** The multi-state model, describing five states from stage 0 to absorbing stage 4. The numbers next to the arrows denote the numbers of transitions from the respective to the subsequent state for SCA1, SCA2, SCA3, and SCA6. SCA, spinocerebellar ataxia.

 

transition hazards. The proportional hazards assumption was checked by a graphical analysis of Schoenfeld residuals (SSR).

## Results

Data of 3138 visits in 677 participants, 525 from the EUROSCA and 152 from the RISCA study, were analyzed. The study population included 173 SCA1 mutation carriers with 759 visits, 207 SCA2 mutation carriers with 1011 visits, 172 SCA3 mutation carriers with 783 visits and 125 SCA6 mutation carriers with 585 visits. Participants had a median of 3.0 (IQR = 2.0–4.0) visits and a median observation time of 7.6 years (IQR = 3.3–10.1). Demographic and clinical characteristics of all participants are given in Table 1 and Table S1.

At baseline, 210 subjects were in stage 0 (SCA1: 75; SCA2: 63; SCA3: 48; SCA6: 24), 290 in stage 1 (SCA1: 61; SCA2: 101; SCA3: 64; SCA6: 64), 137 in stage 2 (SCA1: 25; SCA2: 36; SCA3: 45; SCA6: 31), and 40 in stage 3 (SCA1: 12; SCA2: 7; SCA3: 15; SCA6: 6). Hundred and twenty-three participants died during the observation period (SCA1: 37; SCA2: 38; SCA3: 34; SCA6: 14).

### Relation between disability stages and clinical assessments

In all SCA subtypes, median SARA scores steadily increased with increasing disability stages, and the IQR boundaries did not overlap (Fig. 2; Table S2). Similarly, median SCAFI scores steadily decreased, but the IQR boundaries of stage 1 and stage 2 in SCA6 overlapped. All SCAFI subscores steadily decreased. Among them, 8MW and 9-HPT had the closest relation to the disease stages. The median INAS count steadily increased in all subtypes with the exception of SCA6, in which it decreased from 2.3 in stage 2 to 2.0 in stage 3. IQR boundaries overlapped between stage 1, stage 2, and stage 3 in SCA1 and SCA2, and between all stages in SCA3 and SCA6 (Fig. 2; Table S2).

In all subtypes, median scores of patient-related outcome measures, PHQ-9, EQ-5D, worsened with increasing disability stages. Exceptions were median PHQ-9 score in SCA2 that decreased from 8.0 in stage 2 to 6.0 in stage 3, median PHQ-9 score in SCA6 that decreased from 4.5 in stage 2 to 2.0 in stage 3, and median EQ-5D score in SCA6 that increased from 51.5 in stage 2 to 54.0 in stage 3. In all subtypes, the PHQ-9 and EQ-5D IQR boundaries of all stages overlapped (Fig. 2; Table S2).

We further analyzed changes of each clinical measure of all transitions (Table S3). In all exceptional changes which seemed to show improvement of clinical measures, the changes of clinical measures between the stages were not significant.

### Modeling of the evolution of disability

To determine the probability to be in a certain stage at a given age, we used multi-state modeling for each SCA subtype. The results of the covariate-free models are presented in Figure 3. In the first two decades of life, the estimated probability to be in stage 0 was 1. This result reflects the inclusion criteria of the RISCA and EUROSCA studies. In SCA1, the probability started to decrease around the age of 20 years reflecting onset of ataxia. It reached 0 at around the age of 50 years. In SCA2 and SCA3, the decrease started between 30 and 40 years, and

**Table 1.** Demographic and clinical characteristics of participants at baseline.

| | SCA1 | SCA2 | SCA3 | SCA6 |
|---|---|---|---|---|
| Number of participants | 173 | 207 | 172 | 125 |
| Men/women | 89/84 | 104/103 | 87/85 | 63/62 |
| Age (years) | 40.0 (31.0–50.0) | 43.0 (31.0–52.0) | 45.0 (38.0–53.3) | 65.0 (51.0–72.0) |
| Normal allele (repeat number) | 30.0 (29.0–31.0) | 22.0 (22.0–22.0) | 22.0 (20.0–23.0) | 12.0 (12.0–13.0) |
| Expanded allele (repeat number) | 47.0 (44.0–50.0) | 38.5 (37.0–41.0) | 69.0 (66.0–71.0) | 22.0 (22.0–22.0) |
| Disability stage (0/1/2/3) | 75/61/25/12 | 63/101/36/7 | 48/64/45/15 | 24/64/31/6 |
| SARA | 9.0 (1.5–16.0) | 12.0 (5.8–17.8) | 11.5 (4.0–18.6) | 13.0 (8.5–18.0) |
| SCAFI | − 0.2 (−0.9 to 0.6) | −0.4 (−1.0 to 0.2) | −0.1 (−0.8 to 0.8) | −0.4 (−0.9 to 0.3) |
| SCAFI – 8MW | −0.2 (−1.1 to 0.6) | −0.4 (−1.2 to 0.3) | −0.4 (−1.4 to 0.7) | −0.6 (−1.2 to 0.2) |
| SCAFI – 9HPT | −0.3 (−1.1 to 0.8) | −0.6 (−1.3 to 0.1) | −0.3 (−0.9 to 0.4) | −0.4 (−1.1 to 0.2) |
| SCAFI – PATA | −0.3 (−1.0 to 0.3) | −0.5 (−0.9 to 0.2) | 0.2 (−0.5 to 1.0) | −0.3 (−0.7 to 0.5) |
| INAS | 3.0 (1.0–5.0) | 3.0 (1.5–5.0) | 4.0 (2.0–6.0) | 2.0 (1.0–3.0) |
| PHQ-9 | 4.0 (2.0–8.0) | 4.0 (1.0–7.0) | 5.0 (2.0–9.0) | 4.0 (1.0–7.0) |
| EQ-5D | 56.0 (44.0–76.0) | 64.0 (44.0–76.0) | 59.0 (34.0–76.0) | 64.0 (44.0–76.0) |

Data are given as median (interquartile ranges [IQR]). SCA, spinocerebellar ataxia; SARA, Scale for the Assessment and Rating of Ataxia; SCAFI, SCA Functional Index; SCAFI – 8MW, SCAFI 8 m walk; SCAFI – 9HPT, SCAFI – 9-hole peg test; SCAFI –PATA, SCAFI – PATA rate; INAS, Inventory of Non-Ataxia Signs; PHQ-9, Patient's Health Questionnaire.

 

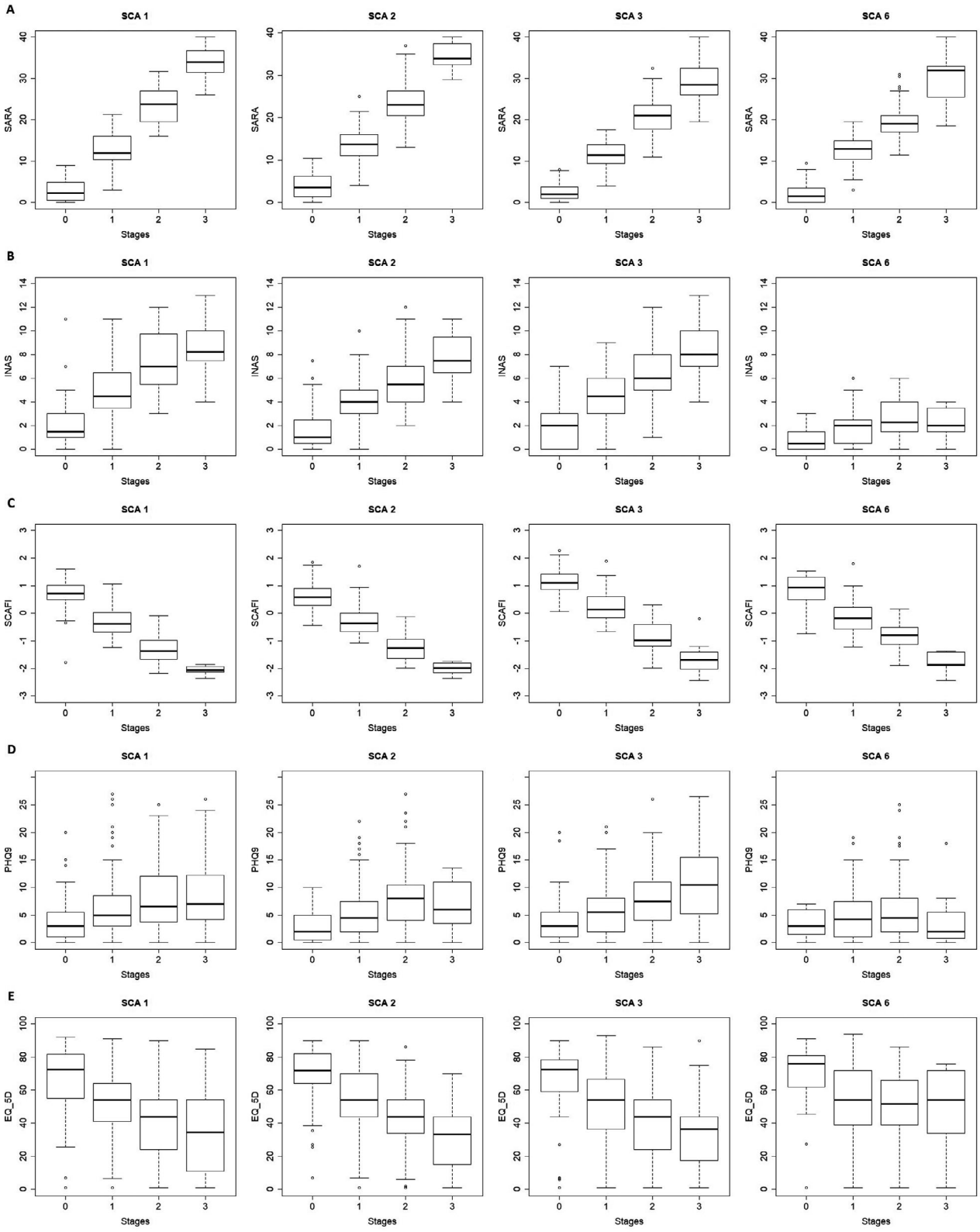


**Figure 2.** Median SARA values for each stage in SCA1, SCA2, SCA3, and SCA6. SCA, spinocerebellar ataxia. (A) SARA; (B) INAS; (C) SCAFI; (D) PHQ-9; (E) EQ-5D. SARA, Scale for the Assessment and Rating of Ataxia; INAS, Inventory of Non-Ataxia Signs; SCAFI, SCA Functional Index; PHQ-9, Patient´s Health Questionnaire; EQ-5D, EQ-5D visual analogue scale.

 

the probability to be in stage 0 reached 0 between 50 and 60 years. The corresponding age values for SCA6 were 40 years and 70–80 years. The maximum probabilities of being in stages 1, 2, and 3 increased with time, with peaks ranging between 0.1 (stage 3 in SCA2 at age 48 years) and 0.6 (stage 3 in SCA6 at age 75 years). The estimated probability to be in stage 4 (death) started to rise from 0 around the age of 25 years in SCA1, 30 years in SCA2, 40 years in SCA3, and 55 years in SCA6. The probability to be in stage 4 at the age of 80 years was estimated to be 1 in SCA1 and SCA3, 0.8 in SCA2, and 0.5 in SCA6.

Multi-state modeling allowed to estimate the age of entering stages 1, 2, 3, and 4 and the expected duration of each stage, that is, duration for each SCA subtype. The expected age of entering stage 1—corresponding to ataxia onset—was 30.1 (95% CI: 25.9–34.9) years in SCA1, 37.1 (95% CI: 32.7–43.2) years in SCA2, 38.1 (95% CI: 26.5–43.0) years in SCA3, and 47.9 (95% CI: 41.0–67.7) years in SCA6. The expected duration of staying in stage 1 was estimated to be 7.0 (95% CI: 4.2–9.5) years in SCA1, 7.6 (95% CI: 5.7–9.7) years in SCA2, 6.5 (95% CI: 3.9–9.5) years in SCA3, and 6.0 (95% CI: 3.5–12.5) years in SCA6. The corresponding durations for stage 2 were 7.7 (95% CI: 5.0–11.1) years in SCA1, 8.3 (95% CI: 6.2–10.3) years in SCA2, 6.0 (95% CI: 4.9–11.0) years in SCA3, and 11.2 (95% CI: 4.6–20.6) years in SCA6. The expected duration to stay in stage 3 was estimated to be 3.4 (95% CI: 1.7–7.7) years in SCA1, 6.6 (95% CI: 3.5–12.9) years in SCA2, 7.1 (95% CI: 4.1–12.1) years in SCA3, and 17.5 (95% CI: 5.6–31.8) years in SCA6. Estimated survival times after onset of ataxia were 18.1 years in SCA1, 22.4 years in

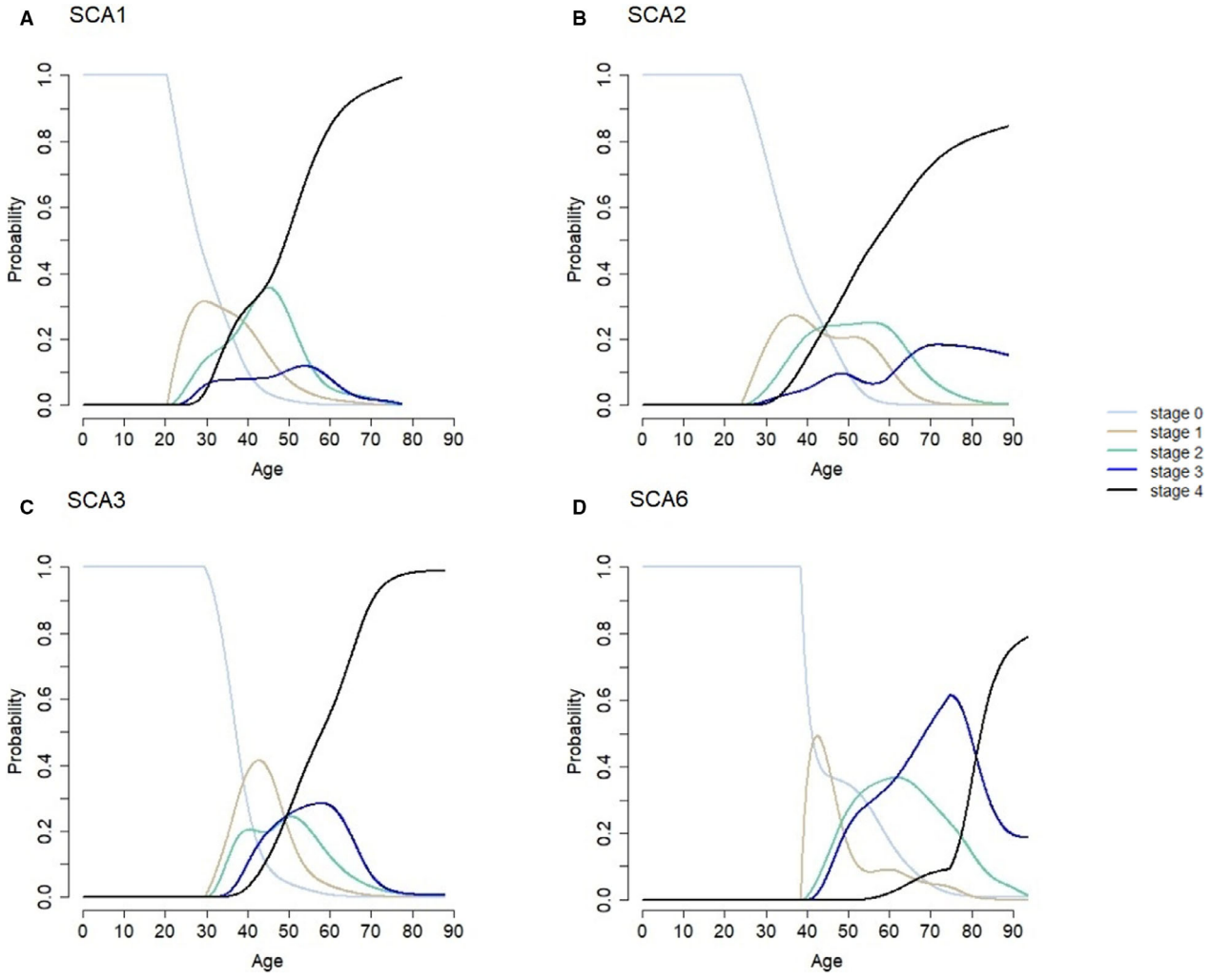


**Figure 3.** Estimated probabilities of being in stages 0–4, as obtained from the covariate-free multi-state model. (A) SCA1, (B) SCA2, (C) SCA3, (D) SCA6. SCA, spinocerebellar ataxia.

 

**Table 2.** Expected duration of each stage and corresponding age of entering each stage in years.

| | Stage 0 | Stage 1 | | Stage 2 | | Stage 3 | | Stage 4 |
|---|---|---|---|---|---|---|---|---|
| | Duration [years] | Age [years] | Duration [years] | Age [years] | Duration [years] | Age [years] | Duration [years] | Age [years] |
| SCA1 | 30.1 [25.9, 34.9] | 30.1 [25.9, 34.9] | 7.0 [4.2, 9.5] | 37.1 [30.1, 44.4] | 7.7 [5.0, 11.1] | 44.8 [35.1, 55.6] | 3.4 [1.7, 7.7] | 48.2 [36.8, 63.3] |
| SCA2 | 37.1 [32.7, 43.2] | 37.1 [32.7, 43.2] | 7.6 [5.7, 9.7] | 44.7 [38.4, 52.9] | 8.3 [6.2, 10.3] | 53.0 [44.6, 63.1] | 6.6 [3.5, 12.9] | 59.6 [48.0, 76.1] |
| SCA3 | 38.1 [26.5, 43.0] | 38.1 [26.5, 43.0] | 6.5 [3.9, 9.5] | 44.7 [30.5, 52.5] | 6.0 [4.9, 11.0] | 50.7 [35.3, 63.5] | 7.1 [4.1, 12.1] | 57.8 [39.4, 75.6] |
| SCA6 | 47.9 [41.0, 67.7] | 47.9 [41.0, 67.7] | 6.0 [3.5, 12.5] | 53.9 [44.1, 80.1] | 11.2 [4.6, 20.6] | 65.2 [49.1, >90] | 17.5 [5.6, 31.8] | 82.7 [54.7, >90] |

Based on the hazard estimates and the state occupation probabilities, the expected lengths of stay in each of the stages were computed until the corresponding last observed time point. Data are given in years with 95% confidence intervals [95% CIs]. Ninety-five percent CIs were calculated using the bias-corrected and accelerated bootstrap with 1000 samples, as obtained from the covariate-free multi-state model. SCA, spinocerebellar ataxia.

SCA2, 19.7 years in SCA3, and 34.8 years in SCA6. Complete data are given in Table 2.

In multi-state modeling, we further studied the effect of sex, CAG repeat length of the expanded allele, and CAG repeat length of the normal allele on progression of walking disability in each SCA subtype. Analysis of SSR did not indicate major violations of proportional hazards assumption (Fig. S1).

In SCA6, female sex was associated with faster progression (HR: 1.63, 95% CI: 1.0–2.5), whereas sex was not found to have an effect on progression in the other subtypes (Table 3). CAG repeat length of the expanded allele was associated with faster progression in SCA1 (HR: 1.1, 95% CI: 1.1–1.2), SCA2 (1.2, 95% CI: 1.1–1.2), and SCA3 (1.1, 95% CI: 1.0–1.2). The CAG repeat length of the normal allele was not found to have an effect on progression in any SCA subtype (Table 3).

## Discussion

This study provides a quantitative account of the disease evolution in SCA1, SCA2, SCA3, and SCA6. Our analysis is based on longitudinal data of the RISCA and EUROSCA cohorts, which recruited SCA1, SCA2, SCA3, and SCA6 mutation carriers in different stages of the disease development.[4,11,14] Whereas RISCA is a cohort of risk persons about half of whom were pre-ataxic mutation carriers at baseline, EUROSCA included patients over the entire spectrum of disease severity. Thus, two cohorts were merged that represent complementary aspects of the disease spectrum. Median observation times in these cohorts were longer than those of other SCA cohorts, but nevertheless cover only a small part of the entire disease span. To account for this, we modeled disease progression according to five disease stages defined by walking ability (stages 0–3) and death (stage 4).[13] As gait problems in SCAs result in limited mobility, this staging system provides information that is directly meaningful for the real life of patients.

To model the transitions between stages, we used a multi-state approach that was defined by a set of proportional transition hazards. This approach extends the well-established Cox regression model to a more general sequence of outcome events also referred to as states. In case of a covariate-free model, it has the advantage of resulting in non-parametric and thus fairly general estimates of the probabilities and expected duration of each stage. When including covariates such as sex and CAG repeat length, the model additionally requires the proportional hazards assumption to hold for all transitions. Analysis of SSR did not indicate major violations of this assumption. Furthermore, all models require the assumption of independent entry times and drop-outs, ensuring that the study population is consistently representative of the full, non-truncated, and uncensored population.[27] Regarding entry times, the independence assumption is likely to be met by the design of the RISCA and EUROSCA studies. Regarding drop-outs, the multi-state model allows for stage-dependent censoring.

The expected duration of stay and corresponding age of entering each stage refer to the characteristics of the study population enrolled for RISCA and EUROSCA. This population, which has been recruited at ataxia referral centers, is likely to be skewed toward milder disease stages, as SCA patients in advanced stages are often not able to take the journey to a distant study center. This explains why the relative variability of stage duration is greater for stage 3 compared to the other stages. Although our study population may thus not be representative for the entire population of SCA1, SCA2, SCA3, and SCA6

 

**Table 3.** Risk factors for entering into a higher stage.

| | Risk factor | HR | 95% CI | *p*-value |
|---|---|---|---|---|
| SCA1 | Sex (f) | 1.1 | 0.7, 1.6 | 0.794 |
| | Normal allele (repeat number)[1] | 1.0 | 0.9, 1.1 | 0.545 |
| | Expanded allele (repeat number)[1] | 1.1 | 1.1, 1.2 | <0.001 |
| SCA2 | Sex (f) | 0.9 | 0.6, 1.3 | 0.576 |
| | Normal allele (repeat number)[1] | 1.0 | 0.9, 1.1 | 0.819 |
| | Expanded allele (repeat number)[1] | 1.2 | 1.1, 1.2 | <0.001 |
| SCA3 | Sex (f) | 0.9 | 0.6, 1.3 | 0.634 |
| | Normal allele (repeat number)[1] | 1.0 | 1.0, 1.0 | 0.964 |
| | Expanded allele (repeat number)[1] | 1.1 | 1.0, 1.2 | 0.014 |
| SCA6 | Sex (f) | 1.6 | 1.0, 2.5 | 0.032 |
| | Normal allele (repeat number)[1] | 0.1 | 0.9, 1.3 | 0.231 |
| | Expanded allele (repeat number)[1] | 1.1 | 0.8, 1.4 | 0.601 |

SCA, spinocerebellar ataxia; HR, transition hazard ratio; 95% CI, 95% confidence interval.
[1]HR is given per additional repeat.

patients, the study population is a representative target population for future clinical trials, which will preferentially be performed with patients in early disease stages.

This study has a number of limitations: The staging system used is rather rough. Perhaps the use of the slightly finer grained Friedreich's Ataxia Rating Scale (FARS) Functional Staging of Ataxia would have given more detailed information, but this was not available when initiating the EUROSCA study.[28] Furthermore, despite the high number of participants, the number of transitions between stages, particularly between higher stages were limited.

Another limitation is that walking disability stages were not formally assessed in the RISCA study. Therefore, we used the rating of the gait item (item 1) of SARA to infer walking disability. We focused on the modelling of the evolution of gait disability and overall survival. Further analysis of other parameters including oculomotor abnormalities would have been desirable,[29] but were outside the scope of the present paper. In addition, the available RISCA and EUROSCA data are limited with respect to oculomotor dysfunction, as SARA, that does not include oculomotor items, was used as the primary outcome.

In general, all clinical and patient-related measures worsened with increasing disability. Exceptions occurred mainly in SCA6. In this subtype, INAS, PHQ-9, and EQ-5D, which are measures of general neurological involvement, depression, and health-related quality of life, did not further deteriorate with progression to stage 3, which may be due to the small number of participants in stage 3. This is best explained by the milder degree of ataxia and the later ataxia onset of SCA6 compared to SCA1, SCA2, and SCA3.[1,30] As a result, walking disability due to ataxia is only one among several health problems in older SCA6 patients, which blurs the relationship between ataxia stages and these measures.

Among all clinical measures, the clinical scale, SARA,[15] had the closest relation to the disease stages underscoring the clinical relevance of SARA. SARA scores steadily worsened with increasing disease stage in all SCA subtypes. Further, SARA scores had no overlap between stages. This cannot be explained solely by the fact that gait is one of the eight SARA items and contributes up to eight of the maximally 40 SARA points. Although gait is one of the three timed tests of SCAFI,[16] we observed overlap of SCAFI scores and its gait subscore, 8MW, between disease stages.

Patient-related outcome measures have been little studied so far in SCAs, and most studies were cross-sectional or covered only short periods of the entire disease span.[31-34] As ataxia-specific patient-related outcome instruments were not available during the conduct of the RISCA and EUROSCA studies, we have used generic measures for depression, PHQ-9, and health-related quality of life, EQ-5D.[18,19] In SCA1, SCA2, and SCA3, these patient-related outcome measures deteriorated with increasing disease stages indicating that the degree of walking disability is a major determinant of limitations in the daily life of patients with these diseases. Recently, an ataxia-specific patient-reported outcome measure, PROM Ataxia has become available.[12] Properties of this new measure have to be determined in future longitudinal studies. In addition to clinical scales and patient-reported outcome measures instrumented assessments could help to quantify ataxia and disease progression.[35]

The multi-state modeling approach allowed to determine the likelihood to be in a certain disease stage at a given age and to calculate the length of each stage. The age of onset in SCA6 was higher than that of SCA1, SCA2, and SCA3, but the difference was smaller than that reported in the majority of previous cross-sectional studies that determined the age of onset based on patient report.[36,37] Whereas the median survival times in SCA1, SCA2, and

 

SCA3 ranged between 18.1 and 22.4 years, which is in line with previous studies, we found a survival time of 34.8 years in SCA6 resulting an estimated age at death of 82.7 years.[2,3] Compared to the other SCAs, SCA6 patients stayed longer in disease stages 2 and 3, that is, in a state in which they required walking aids or a wheelchair. CAG repeat length had a modest effect on disease progression in SCA1, SCA2, and SCA3, but not SCA6. In SCA3, previous analyzes of the EUROSCA data and a Brazilian study did not show an accelerating effect of CAG repeat length on the progression of ataxia severity, whereas another study that use the NESSCA scale that assesses both ataxia and non-ataxia signs showed an effect.[8,9]

Our study provides a comprehensive account of disease evolution in SCA1, 2, 3, and 6 based on prospective assessment of disability stages which are of immediate relevance for affected individuals. Our data are important for counselling of patients, for the assessment of the relevance of outcome markers, and for the design of clinical trials.

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## Conflict of Interest

No conflict of interest related to the manuscript.

## Author Contributions

(1) Conception and design of the study; (2) Acquisition and analysis of data; (3) Drafting a significant proportion of the manuscript or Figures.

H. J. 1,2,3; T. S. 1,3; J. B. 1; S. T. M. 1,3, M. S. 1,3; T. K. 1,2,3; EUROSCA and RISCA study groups 2.

### References

1. Klockgether T, Mariotti C, Paulson HL. Spinocerebellar ataxia. Nat Rev Dis Primers. 2019;5(1):24.
2. Monin ML, Tezenas du Montcel S, Marelli C, et al. Survival and severity in dominant cerebellar ataxias. Ann Clin Transl Neurol. 2015;2(2):202-207.
3. Kieling C, Prestes PR, Saraiva-Pereira ML, Jardim LB. Survival estimates for patients with Machado-Joseph disease (SCA3). Clin Genet. 2007;72:543-545.
4. Jacobi H, du Montcel ST, Bauer P, et al. Long-term disease progression in spinocerebellar ataxia types 1, 2, 3, and 6: a longitudinal cohort study. Lancet Neurol. 2015;14(11):1101-1108.
5. Ashizawa T, Figueroa KP, Perlman SL, et al. Clinical characteristics of patients with spinocerebellar ataxias 1, 2, 3 and 6 in the US; a prospective observational study. Orphanet J Rare Dis. 2013;8:177.
6. Lee YC, Liao YC, Wang PS, Lee IH, et al. Comparison of cerebellar ataxias: a three-year prospective longitudinal assessment. Mov Disord. 2011;26:2081-2087.
7. Yasui K, Yabe I, Yoshida K, et al. A 3-year cohort study of the natural history of spinocerebellar ataxia type 6 in Japan. Orphanet J Rare Dis. 2014;9:118.
8. França MC Jr, D'Abreu A, Nucci A, et al. Progression of ataxia in patients with Machado-Joseph disease. Mov Disord. 2009;24:1387-1390.
9. Jardim LB, Hauser L, Kieling C, et al. Progression rate of neurological deficits in a 10-year cohort of SCA3 patients. Cerebellum. 2010;9:419-428.
10. Jacobi H, Reetz K, du Montcel ST, et al. Biological and clinical characteristics of individuals at risk for spinocerebellar ataxia types 1, 2, 3, and 6 in the longitudinal RISCA study: analysis of baseline data. Lancet Neurol. 2013;12(7):650-658.
11. Jacobi H, du Montcel ST, Romanzetti S, et al. Conversion of individuals at risk for spinocerebellar ataxia types 1, 2, 3, and 6 to manifest ataxia (RISCA): a longitudinal cohort study. Lancet Neurol. 2020;19(9):738-747.
12. Schmahmann JD, Pierce S, MacMore J, L'Italien GJ. Development and validation of a patient-reported outcome measure of ataxia. Mov Disord. 2021;36:2367-2377.
13. Klockgether T, Lüdtke R, Kramer B, et al. The natural history of degenerative ataxia: a retrospective study in 466 patients. Brain. 1998;121(Pt 4):589-600.
14. Diallo A, Jacobi H, Cook A, et al. Prediction of survival with long-term disease progression in Most common spinocerebellar ataxia. Mov Disord. 2019;34(8):1220-1227.
15. Schmitz-Hubsch T, du Montcel ST, Baliko L, et al. Scale for the assessment and rating of ataxia: development of a new clinical scale. Neurology. 2006;66(11):1717-1720.
16. Schmitz-Hübsch T, Giunti P, Stephenson DA, et al. SCA functional index: a useful compound performance measure for spinocerebellar ataxia. Neurology. 2008;71:486-492.
17. Jacobi H, Rakowicz M, Rola R, et al. Inventory of non-ataxia signs (INAS): validation of a new clinical assessment instrument. Cerebellum. 2013;12(3):418-428.
18. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary care evaluation of mental disorders. Patient health questionnaire. JAMA. 1999;282(18):1737-1744.

 

19. EuroQol—a new facility for the measurement of health-related quality of life. The EuroQol Group. Health Policy. 1990;16(3):199-208.
20. R Core Team. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing; 2021. https://www.R-project.org/. Accessed March 1, 2021.
21. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Stat Med. 2007;26 (11):2389-2430.
22. de Wreede LC, Fiocco M, Putter H. The mstate package for estimation and prediction in non- and semi-parametric multi-state and competing risks models. Comput Methods Programs Biomed. 2010;99(3):261-274.
23. de Wreede LC, Fiocco M, Putter H. mstate: an R package for the analysis of competing risks and multi-state models. J Stat Softw. 2011;38(7):1-30.
24. Pya N, Wood SN. Shape constrained additive models. Stat Comput. 2015;25(3):543-559.
25. Pya N. Scam: shape constrained additive models. R Package version 1.2-11. 2021. https://cran.r-project.org/web/packages/scam. Accessed May 12, 2021.
26. Beyersmann J, Puttner H. A note on computing average state occupation times. Demogr Res. 2014;30(62):1681-1696.
27. Betensky RA, Mandel M. Recognizing the problem of delayed entry in time-to event studies: better late than never for clinical neuroscientists. Ann Neurol. 2015;78 (6):839-844.
28. Subramony SH, May W, Lynch D, et al. Measuring Friedreich ataxia: interrater reliability of a neurologic rating scale. Neurology. 2005;64(7):1261-1262.
29. Moscovich M, Okun MS, Favilla C, et al. Clinical evaluation of eye movements in spinocerebellar ataxias: a prospective multicenter study. J Neuroophthalmol. 2015;35(1):16-21.
30. Geschwind DH, Perlman S, Figueroa KP, et al. Spinocerebellar ataxia type 6. Frequency of the mutation and genotype-phenotype correlations. Neurology. 1997;49:1247-1251.
31. Schmitz-Hübsch T, Coudert M, Giunti P, et al. Self-rated health status in spinocerebellar ataxia—results from a European multicenter study. Mov Disord. 2010;25(5):587-595.
32. Schmitz-Hübsch T, Coudert M, Tezenas du Montcel S, et al. Depression comorbidity in spinocerebellar ataxia. Mov Disord. 2011;26(5):870-876.
33. Lo RY, Figueroa KP, Pulst SM, et al. Depression and clinical progression in spinocerebellar ataxias. Parkinsonism Relat Disord. 2016;22:87-92.
34. Jacobi H, du Montcel ST, Bauer P, et al. Long-term evolution of patient-reported outcome measures in spinocerebellar ataxias. J Neurol. 2018;265(9):2040-2051.
35. Kashyap B, Phan D, Pathirana PN, Horne M, Power L, Szmulewicz D. Objective assessment of cerebellar ataxia: a comprehensive and refined approach. Sci Rep. 2020;10 (1):9493.
36. Schöls L, Krüger R, Amoiridis G, et al. Spinocerebellar ataxia type 6: genotype and phenotype in German kindreds. J Neurol Neurosurg Psychiatry. 1998;64:67-73.
37. Matsumura R, Futamura N, Fujimoto Y, et al. Spinocerebellar ataxia type 6 - molecular and clinical features of 35 Japanese patients including one homozygous for the CAG repeat expansion. Neurology. 1997;49:1238-1243.

## Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Figure S1.** Graphical checks of the proportional hazards assumption.
**Table S1.** Demographic and clinical characteristics of RISCA and EUROSCA participants at baseline.
**Table S2.** Outcome measures stratified by stage.
**Table S3.** Changes of outcome measures between the stages.

 