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Reliability of kinetic visual field testing in children with mutation-proven retinal dystrophies: Implications for therapeutic clinical trials

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Abstract

Purpose—Kinetic visual field testing is used to monitor disease course in retinal dystrophy clinical care and treatment response in treatment trials, which are increasingly recruiting children. This study investigates Goldmann visual field (GVF) changes in young children with mutation-proven retinal dystrophies as they age and with progression of the retinal degeneration.

Methods—Retrospective review of children 17-years-old with a mutation-proven retinal dystrophy. Objective clinical disease activity was assessed by a retinal degeneration specialist masked to GVF results. Digital quantification of GVF area was performed.

Results—Twenty-nine children (58 eyes), ages 5–16, were identified. GVF area increased with age despite progression in 20 children and clinical stability in 9 children. Mean±standard error increase in GVF area/year was 333±130 mm² (I4e, p=0.012), 720±155 mm² (III4e, p<0.001) and 759±167 mm² (IV4e, p<0.001), with greater increases at earlier ages. Repeatability coefficients were 7381 mm² (I4e), 9379 mm² (III4e) and 10346 mm² (IV4e), indicating a large variability. At 2.5 years after the baseline GVF the area increased 20%, the criterion for positive treatment outcome defined in recent published therapeutic trials, in 38% (I4e), 34% (III4e) and 33% (IV4e) of eyes.

Conclusion—In a substantial proportion of children with mutation-proven retinal dystrophies, there is a significant increase in GVF area with age, particularly those <12 years, despite progression or stability of disease. These findings suggest that change in GVF area in children with retinal dystrophies can be an unreliable measure of response to treatment and on which to base appropriate counseling about visual impairment.

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DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

Keywords

Children; Goldmann visual field; kinetic visual field; retinal degeneration; retinal dystrophy; visual field testing

INTRODUCTION

The number of therapeutic clinical trials for inherited retinal dystrophies is expanding rapidly as both the genetic causes of disease and available interventions, such as gene therapy, are better understood. Visual field (VF) is often an endpoint in therapeutic clinical trials to assess the effect of treatment. As the visual defects may lie beyond the standard 30 degrees tested by the Humphrey Visual Field analyzer, the VFs of patients with retinal dystrophies are better assessed with widefield perimetry.¹ Although Goldmann visual field (GVF) testing is less frequently utilized than automated perimetry for the assessment of visual function, characteristics uniquely inherent to this test are conducive to its use in the evaluation of patients with retinal dystrophies; thus, it is often used in therapeutic clinical trials. For many of these diseases, natural history studies, which typically precede therapeutic trials, often show a variable expression of disease, highlighting the difficulty of prognostication for these patients. In the clinical setting, a variety of studies, including VF testing, are performed in pediatric patients to assess retinal and visual function, with the intent to aid in the diagnosis and monitoring of disease progression.

Since GVF area is an endpoint in some therapeutic clinical trials, its ability to serve as a reliable marker has been evaluated in some previous studies. In one such study, test-retest variability of GVF area in adults with retinitis pigmentosa was assessed by examining 2 within-visit test results.² This study reported no significant increase or decrease between the first and second GVF and an inherent test-retest variability limited to <20%. Later, Koenekoop et al³ evaluated patients with Leber congenital amaurosis treated with oral 9-cis retinoid. They defined a gain in GVF area of 20% from baseline as a positive response to therapy and, based on this criterion, they found that the majority of patients (64%) had a positive response to therapy.³ The concern with this positive finding was highlighted in the editorial by Iannaccone et al,⁴ who contended that a change as small as 1° in a constricted GVF, localized to 5–6° around fixation, can equal a 44% change in GVF area.

Therapeutic clinical trials for retinal dystrophies increasingly include children, since the therapeutic windows for these disorders are often in childhood. Unfortunately, reported VF data, including GVF, are largely lacking in the pediatric population, and there are numerous obstacles to testing. In children, learning difficulties,^{5, 6} inability to maintain fixation^{7–10} and lack of concentration¹¹ have been reported to affect the reliability of VF testing. Since GVF testing is used as a measure of treatment effect in therapeutic clinical trials in patients with retinal dystrophies, we sought to investigate changes in GVF area and variability in GVF testing in children with mutation-proven retinal dystrophies across multiple visits over an extended period of time.

METHODS

Patient selection

A retrospective, consecutive analysis was conducted on data from patients seen at the Kellogg Eye Center/University of Michigan between January 1, 2004, and October 28, 2015. We included patients who were under the age of 17, had a mutation-proven retinal dystrophy and underwent GVF testing on at least 2 different visits within the almost 12 year time frame. This study adhered to the tenets of the Declaration of Helsinki for research involving human subjects, and was approved by the University of Michigan Institutional Review Board. Patients were excluded if they had insufficient follow-up, GVF testing was noted to be unreliable by the technician, they had other ocular diagnoses or if they did not have consent for participation in a research study.

Data collection

Patient files were accessed to obtain demographic and clinical characteristics, including age, sex, causal mutated gene, progression of disease, and Snellen visual acuity with correction or pinhole at each examination. Objective clinical disease status (progression, stability or improvement) was assessed by a retinal dystrophy specialist (TJ), who was masked to GVF results, by evaluation of any or a combination of the following at the initial and all follow-up visits: fundus autofluorescence, the width of the ellipsoid zone (EZ width) on macular optical coherence tomography (OCT), fundus photography and Snellen visual acuity (VA).

Visual field testing and quantification

All patients were seated upright during testing. Testing was performed with the Goldmann perimeter (Haag-Streit, Bern, Switzerland) by experienced technicians. Background illumination was 31.5 apostilbs (asb) and three isopter sizes were tested: (1) I4e, (2) III4e and (3) IV4e. All children were given the standard testing instructions recommended by the manufacturer. Significant refractive errors (≥ 8 diopters) were corrected. Manual perimetry results were scanned, and digital quantification of GVF area was performed with Adobe Photoshop CS3, using a previously described technique.¹² A scale was established for each image, with a length of 94 pixels set to 12 mm. The GVF area (mm²) was calculated by subtracting the areas of scotomata from the area of functional vision. This was performed for each isopter.¹²

Statistical analysis

Statistical analyses were conducted in R 3.2.5 (R Foundation for Statistical Computing, Vienna, Austria). Time course plots for three isopters (I4e, III4e and IV4e) by age were calculated for individual eyes and summarized by a local polynomial smoother. Linear mixed models with nested random effects for individual and eye were fit by restricted maximum likelihood estimation to estimate the average change in GVF area per year for each individual eye. An alternative model using order of test rather than age was considered and compared by Akaike Information Criterion (AIC).¹³ The reliability coefficient (RC) was computed for each isopter size, as described by Jeffrey et al.¹⁴ Bootstrap resampling was used to determine the standard error of the RC estimate.

RESULTS

We analyzed results on 58 eyes of 29 children (19 male and 10 female) and 52 eyes of 26 children were excluded based on the described exclusion criteria. Goldmann visual field measurements were taken between 5 and 16 years of age. There was a mean±standard deviation (SD) follow-up period of 4.2±2.0 years and a maximum follow-up of 7 years. The mean age at first VF measurement was 8.9±2.0 years. The mean number of VF measurements per eye was 4.1±2.0 (range 2 to 9). The mean age for all GVF measurements was 10.9±2.6 years. Refractive error correction at the time of GVF testing was made for 6 eyes of 3 patients with a mean refractive error of -12.75 diopters (D) (range -16.00 D to -10.00 D). Subjects had disease-causing mutations in the following genes (Table 1): *ABCA4* (n = 9), *RPGR* (n = 6), *CNGB3* (n = 3), *RP2* (n = 2), *CHM* (n = 2), *RPE65* (n = 1), *USH2A* (n = 1), *PDE6C* (n = 1), *RHO* (n = 1), *MYO7A* (n = 1), *KCNV2* (n = 1) and *NYX* (n = 1).

Clinical progression of retinal dystrophy was observed in 20/29 (69%) children and clinical stability in 9/29 (31%) children, as assessed by the retinal dystrophy specialist. No patient had improvement of retinal disease. Objective clinical disease status was assessed by evaluating the areas of hyper- and hypoautofluorescence on fundus autofluorescence in 11 eyes, Snellen VA in 9 eyes, width of the ellipsoid zone (EZ width) on macular OCT in 5 eyes, areas of atrophy and peripheral pigment deposits on fundus photography in 1 eye, fundus autofluorescence and OCT in 1 eye, fundus photography and VA in 1 eye and OCT and VA in 1 eye. There was clinical progression of disease in 9 patients with macular/cone disease (*ABCA4* and *KCNV2*), 10 patients with retinitis pigmentosa/*CHM* (*RPGR*, *RP2*, *RPE65*, *USH2A*, *RHO*, *MYO7A* and *CHM*) and 1 patient with congenital stationary disease (*CNGB3*, *PDE6C* and *NYX*). Clinical stability was seen in 1 patient with macular/cone disease, 4 patients with retinitis pigmentosa/*CHM* and 4 patients with congenital stationary disease. At the first visit mean±SD GVF area was 5229±5331 mm² (I4e), 10926±5390 mm² (III4e) and 14114±5658 mm² (IV4e) (Figure 1). The mean±standard error (SE) increase in GVF area per year, by linear mixed model analysis, was 333±130 mm² (I4e, p = 0.012), 720±155 mm² (III4e, p <0.001) and 759±167 mm² (IV4e, p <0.001) (Figure 2). For each isopter, the increase was greatest for early ages, before or at age 11 years (p = 0.015, 0.0002 and 0.001 for I4e, III4e and IV4e isopters, respectively, Table 2). The increase after age 11 was not statistically significantly different from 0 (p = 0.62, 0.16 and 0.09 for I4e, III4e and IV4e isopters, respectively). However the difference in slopes before age 11 and after age 11 was not statistically significant (p = 0.17, 0.13 and 0.31 for I4e, III4e and IV4e isopters, respectively) (Table 2 and Figure 3).

At 2.5 years after the baseline GVF, there was an increase in GVF area of 20% or more in 22 (38%), 20 (34%) and 19 (33%) eyes for the I4e, III4e and IV4e isopters, respectively. Over the entire study period there was an increase in GVF area of 20% or more in 26 (45%, I4e), 26 (45%, III4e) and 33 (38%, IV4e) eyes. There was a decrease in GVF area over time in both eyes of 5/29 (17%) patients. Four of these patients had clinical progression of the retinal dystrophy and 1 patient had stable disease. The rate of change of VF size in patients with progressive and stable disease was not statistically different (p = 0.9, 0.3 and 0.4 for I4e, III4e and IV4e, respectively). Age was found to be a better predictor of GVF size than

number of tests. For all 3 isopters, the AIC was lower (better) for the model using age (4256, 4311 and 4367 for I4e, III4e and IV4e isopters, respectively) than it was when using order of test (4262, 4325 and 4381 for I4e, III4e and IV4e isopters, respectively). Repeatability coefficients (RC)±SE were 7381±547 mm² (95% CI, 6952–8361), 9379±630 mm² (95% CI, 9041–10383) and 10346±760 mm² (95% CI, 9893–11832) for I4e, III4e and IV4e, respectively.

DISCUSSION

Widefield perimetry, either by Octopus or Goldmann visual field (GVF) testing, is integral to the evaluation of patients with retinal dystrophies. An advantage of GVF testing in children is that the operator is able to interact with the patient, allowing the operator to evaluate the child's comprehension of and ability to complete the test. Our study identified changes and variability in GVF area in children with retinal dystrophies. We found that even though there was progression or stability of retinal disease, GVF area increased as children aged. These findings allude to the possibility that, in the pediatric population, VF test-taking ability is dependent upon cognitive development and ability to cooperate and thus may not be a reliable measure of visual function. This is also important when counseling parents of children with retinal dystrophies, as VF testing may be a poor prognosticator and an inadequate indicator of true visual function, particularly for patients under the age of 12 years.

In addition to the uses of GVF in clinical care, therapeutic trials often use GVF testing to evaluate visual function and measure treatment efficacy. As we have shown that VF area increases with age in children, despite progression or stability of retinal disease, GVF testing may not accurately assess treatment effect. Koenekoop et al³ used GVF testing to measure visual function improvement in patients with Leber congenital amaurosis treated with oral 9-cis retinoid. They regarded patients as having a positive response to therapy if they had at least a 20% improvement in GVF area compared to baseline. In our study, depending upon which isopter is relied upon, 33% to 38% of eyes had increase in VF area of at least 20% at 2.5 years after the baseline GVF and 38% to 45% of eyes had an increase in VF area of at least 20% over the study period. Studies that use change in GVF area as a primary outcome measure in children may be biased, since, as we have shown, an increase in VF area may occur in children whose disease is stable or even progressing.

There is a paucity of normative VF data for children. The literature to date contains disparate findings on the size and shape of the VF in children. Quinn et al¹⁵ performed kinetic perimetry in normal children and reported an increase in VF area with age, reaching a stable adult size at a mean age of 11.6 years. Patel et al¹⁶ sought to define normative GVF values in children aged 5 to 15 and reported an increase in GVF area as children aged, as well as an association between age and mean deviation until 12 years of age, after which point there was no significant association ($p = 0.526$).¹⁶ While the age cutoff over which VF testing in children is presumed to be reliable has been investigated, no conclusive data exist. It is important to note that, although automated VF testing in children can be started at age 5, there is an age-related improvement in testing.^{17, 18} Our study shows the greatest increase in

GVF area over time in patients 11 years old and only smaller increases in GVF area occur after this age.

There are a variety of reasons why VF testing in children may provide unreliable results. Difficulty maintaining concentration may contribute greatly to test-taking ability in younger children, and a learning effect may contribute to the increase in GVF with age. A learning curve has been demonstrated in adults¹⁹ and likely also affects children. Our results showed that age was a better predictor of GVF area than number of tests taken. Fatigue may also play a role and can manifest as decreased cooperation, possibly resulting in poorer responses and smaller VF area. Whiteside²⁰ suggests that the decreased peripheral sensitivity in children may be based on conceptual or attention-based difficulties rather than perceptual ones.

Cortical and ocular development may play a role in VF area increase with age. Studies have shown that performance on tests of executive ability in children increases with age until about 11 or 12 years of age.¹⁷ As children age and their ability to perform complex functions improves, their ability to perform GVF testing may also improve. Additionally, changes in facial structure and skeletal development may contribute. As children age, their upper face, lower face and orbits develop at different rates and in different proportions. Such anatomic developmental changes might play a factor in changing VF area in children, especially the possible contribution from an increasing interpupillary distance.²² These cognitive and anatomic developmental changes may contribute to the observed age-related trend in the increase in GVF area.

In this pediatric population, we calculated the RC, which is an objective measure of test-retest variability, and found considerable test-retest variability with kinetic perimetric testing. Similarly, Quinn et al⁵ reported high test-retest reliability with perimetric testing in normal children aged 4 to 10 years ($p < 0.001$). However, Bittner et al² reported that the typical variability of GVF results could be as wide as $\pm 20\%$ among adults with retinitis pigmentosa tested with 2 within-visit GVFs. In our study, the large RC values represent high test-retest variability.

In an attempt to achieve reliable VF results in children, an effort should be made to familiarize children with the testing procedure. Studies have shown improved VF assessment in children who have been familiarized with the testing protocol. For example, Nesher et al²¹ reported that 40% of children undertaking frequency-doubling technology testing required more than one demonstration of the nature of the procedure. Furthermore, as verbal instruction on testing procedures can also impact VF results, it is important to provide clear verbal instructions on what is expected of the child prior to administering the VF test. Kutzko et al²³ evaluated the importance of clear verbal instruction in their study of the effects of neutral, liberal and conservative instruction on the results of VF testing in adults and they found that the results of VF testing can be significantly altered by various perimetrist instructions. Finally, as Seiple et al²⁴ demonstrated reported estimates of patient variability of visual fields are not often representative of the variability in individual patients and, accordingly, published group data may not be a good comparative measure of treatment effect in clinical trials. The provision of adequate instruction and training and the

performance of multiple baseline assessments may improve the validity of VF results in therapeutic trials.

It is also important that refractive error is corrected, especially in patients with large errors (≥ 8 D), as this can contribute to falsely small VF areas. Additionally, ergonomics of testing may also contribute to unreliable results, since children with small stature or faces cannot rest their chin on the chinrest and their forehead does not always rest on the forehead strap. Finally, there may be a response-time delay, especially in children who are distracted or not positioned correctly, or false positives from children who enjoy pushing the response button.

Limitations of this study include small study population and retrospective study design. As such, there is limited control over data collection and an inability to measure certain variables. In an ideal study setting, the same test operator would perform the test to minimize operator-driven variability, but this requirement is impractical in a busy retinal dystrophy practice setting. However, we were able to obtain more than seven years of data for some subjects, which would not have been as feasible in a prospective natural history study.

This study evaluated the change and variability in GVF area in children with mutation-proven retinal dystrophies. We found a significant correlation between age and area of GVF, whereby VF area expanded as children aged, despite disease progression or stability in these individuals. These findings suggest that GVF testing in children with retinal dystrophies should be evaluated along with other measures of disease burden when counseling patients and parents about the severity and progression of visual impairment. If the reliability of these GVF tests in a young child is not carefully considered, parents may be given a worse prognosis of visual function than is warranted. In addition, in the context of clinical trials, it is important to consider that GVF results may be an unreliable measure of response to treatment, and other methods of treatment response assessment should be considered.

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Figure 1. Goldmann visual field (GVF) area. Boxplots display medians, interquartile ranges, and ranges of GVF area for each isopter (I4e, III4e and IV4e) among all children at baseline.

Figure 2. Goldmann visual field (GVF) area versus age. Change in GVF area for isopters (A) I4e, (B) III4e and (C) IV4e demonstrates an increase in area with age that is greater at younger ages for all isopters. Plot includes line traces for measurements of individual eyes and a lowess summary of the mean isopter area by age.

Figure 3.

Goldmann visual field of the right eye of one patient at (A) presentation at 8 years of age, (B) 10 years of age and (C) 14 years of age. There is an increase in all 3 isopters over time (14e—black line, III4e—green line and IV4e—red line) despite progression of disease.

Table 1

Patient demographics and clinical characteristics.

Patient	Gender	Age at onset (years)	Presenting phenotype	Gene involved	Mutation	Disease status	Visual acuity*				Electroretinography			
							Presentation		Most recent visit		Scotopic (%)		Photopic (%)	
							OD	OS	OD	OS	OD	OS	OD	OS
1	Male	8.75	Stargardt	ABCA4	p.Leu541Pro; p.Ala1038Val; p.Arg1108Cys	Progression	20/100	20/200	20/250	20/200	100	100	100	100
2	Male	8.00	RP	RPGR	p.Glu1014Glyfs	Stable	20/50	20/50	20/50	20/40	41	46	13	19
3	Male	Birth	RP	RPE65	p.Gly40Ser; p.Tyr368His	Progression	20/60	20/50	20/70	20/50	NR	Not tested	16%	Not tested
4	Female	9.25	Achromatopsia	CNGB3	p.Thr383Ilefs; p.Gln701His	Progression	20/50	20/70	20/70	20/100	100	100	16	21
5	Male	2.00	RP	RPGR	p.Glu903Argfs	Progression	20/40	20/25	20/40	20/40	NR	NR	9	7
6	Male	8.00	RP	RP2	p.Ser172Argfs	Progression	20/40	20/80	20/40	20/70	6	NR	17	11
7	Male	Birth	RP	RPGR	p.Glu991Lysfs	Progression	20/25	20/30	20/40	20/40	NR	NR	NR	9
8	Female	10.75	Usher	USH2A	p.Gly1132Asp; p.Gly4516Ala	Progression	20/20	20/20	20/40	20/50	20	50	89	79
9	Female	7.00	Stargardt	ABCA4	p.Cys1488Arg; p.Leu296Cysfs	Progression	20/200	20/200	20/200	20/150	92	62	80	65
10	Female	7.00	Stargardt	ABCA4	p.Cys1488Arg; p.Leu296Cysfs	Progression	20/200	20/100	20/150	20/100	100	100	100	91
11	Male	6.25	RP	RPGR	p.Glu905Glyfs	Progression	20/100	20/70	20/60	20/70	NR	NR	16	13
12	Male	7.00	Stargardt	ABCA4	c.5461-10T>C; p.Ala1773Val	Progression	20/100	20/125	20/250	20/150	100	Not tested	Not tested	28
13	Male	7.25	Stargardt	ABCA4	c.5461-10T>C; p.Ala1773Val	Progression	20/300	20/200	20/400	20/250	34	18	5	9
14	Female	10.00	Stargardt	ABCA4	c.5461-10T>C; p.Ala1773Val	Progression	20/200	20/200	20/300	20/250	100	65	60	45
15	Female	--	Achromatopsia	PDE6C	p.Glu71X; p.Arg527X	Stable	20/200	20/200	20/200	20/200	71	36	61	48
16	Male	9.75	RP	RHO	p.Cys187Arg	Progression	20/30	20/30	20/30	20/30	NR	NR	13	7
17	Female	Birth	Usher	MYO7A	p.Cys153Tyr; c.132+5G>A	Stable	20/40	20/40	20/50	20/40	NR	NR	5	27
18	Male	6.75	Stargardt	ABCA4	p.Arg681X; p.Asn965Ser	Progression	20/100	20/80	20/300	20/250	45	83	41	86
19	Male	7.00	Stargardt	ABCA4	c.5312+1G>A; c.3051-(35_17)del19	Progression	20/200	20/200	20/250	20/200	10	10	25	9
20	Male	7.75	Choroideremia	CHM	p.Phe9Serfs	Progression	20/25	20/25	20/30	20/25	NR	Not tested	51	Not tested
21	Male	Birth	CSNB	NYX	Deletion of exon 3	Stable	20/60	20/80	20/60	20/80	3	10	43	45
22	Female	6.25	Cone dystrophy	KCNV2	p.Glu148X; p.Gly461Arg	Stable	20/200	20/200	20/150	20/150	40	16	36	27
23	Male	5.00	RP	RP2	p.Arg118His	Stable	20/100	20/100	20/125	20/100	7	4	25	32
24	Male	9.00	RP	RPGR	p.Glu863Argfs	Stable	20/40	20/50	20/50	20/50	NR	NR	10	NR

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Patient	Gender	Age at onset (years)	Presenting phenotype	Gene involved	Mutation	Disease status	Visual acuity*				Electroretinography			
							Presentation		Most recent visit		Scotopic (%)		Photopic (%)	
							OD	OS	OD	OS	OD	OS	OD	OS
25	Male	4.50	RP	RPGR	p.Glu839Glyfs	Progression	20/60	20/60	20/40	20/40	Not tested	Not tested	Not tested	Not tested
26	Male	0.5	Achromatopsia	CNGB3	p.Thr383Ilefs (homozygous)	Stable	20/200	20/200	20/200	20/200	100	100	NR	NR
27	Male	Birth	Choroideremia	CHM	p.Try103X	Progression	20/25	20/25	20/40	20/50	8	NR	29	19
28	Female	0.5	Achromatopsia	CNGB3	p.Thr383Ilefs (homozygous)	Stable	20/200	20/200	20/125	20/150	40	69	32	19
29	Female	11.25	Stargardt	ABCA4	c. 4253+5 G>T; p.Ala595Thr	Progression	20/125	20/100	20/150	20/150	47	100	69	100

* Visual acuity assessed at the time of the Goldmann visual field test.

International Society of Clinical Electrophysiology of Vision (ISCEV) testing protocol. Scotopic flash b-wave and Photopic flash b-wave are presented as a percentage compared to normal.

RP = retinitis pigmentosa; NR = non-recordable.

Table 2

Change in visual field (VF) size per year. Slope (mm²/year) estimates given for all ages, age 11 years and > 11 years.

Isopter	Age (years)	Age slope (mm ² /year)	Standard error	95% CI	p-value ^{*τ}	p-value ^{*F}
I4e	All	332.6	129.7	78.7 – 592.3	0.012	
	11	623.4	251.1	133.3 – 1122.4	0.015	
	>11	105.3	213.6	–313.6 – 523.8	0.623	0.17
III4e	All	720.3	155.2	405.5 – 1053.4	<.001	
	11	1122.3	296.4	515.2 – 1759.8	<.001	
	>11	394.5	276.7	–151.1 – 935.6	0.157	0.13
IV4e	All	759.0	167.4	413.3 – 1129.5	<0.001	
	11	1060.0	320.7	379.4 – 1794.4	0.001	
	>11	526.6	304.2	–75.9 – 1120.6	0.087	0.31

* $p < 0.05$ is significant.

^τ Slope compared to zero (no change).

^F Between 11 years and > 11 years.

CI = confidence interval.