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Long-term employment outcomes after epilepsy surgery in childhood

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Abstract

Objective

To analyze long-term employment outcomes in a population-based cohort of adults who underwent epilepsy surgery in childhood or adolescence and to compare the results to general population reference data.

Methods

Prospective data on epilepsy surgery procedures performed on patients <19 years of age between 1995 and 2012 were extracted from the Swedish National Epilepsy Surgery Register. Five-, 10-, 15- and 20-year follow-up data were analyzed. Patients aged ≥19 years at follow-up were eligible for inclusion. Educational attainment and employment status were analyzed in relation to seizure outcome. Education and employment outcomes of seizure-free patients with a preoperative IQ of ≥70 were compared to general population reference data.

Results

A total of 203 patients were included. The mean age at surgery was 13.6 years and 66% had IQ ≥70. Of these, a majority had attained at least high school education 5 years after surgery. Employment rates were 44%, 69%, 71%, and 77% at the 5-, 10-, 15-, and 20-year follow-ups, respectively. Seizure-free patients were significantly more likely to work full-time. Educational attainment and rates of full-time employment of seizure-free patients were similar to the general population. A majority of patients with IQ <70 had attended special education and were reliant on social benefits.

Conclusion

Long-term overall employment rates were higher compared to most previous studies on surgery in adults. Seizure-free patients with a preoperative IQ ≥70 showed rates of full-time employment similar to the general population. Further research is needed to determine whether this also applies for occupational complexity and wages.

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Glossary

CI = confidence intervals; **SNESUR** = Swedish National Epilepsy Surgery Register; **TLR** = temporal lobe resection.

For a selected group of children with medically intractable epilepsy, epilepsy surgery is an established treatment option.[1] The efficacy of epilepsy surgery in achieving seizure freedom or a worthwhile reduction in seizure frequency has been shown in several studies.[2,3] The goals of epilepsy surgery are not restricted to seizure freedom alone; professional and educational gains in the long term are also desirable, both from the patient/caregiver perspective and for health economic reasons. People with childhood-onset epilepsy show consistently lower educational attainment and rates of employment as adults compared with the general population.[4–6] There is currently limited knowledge of employment rates after epilepsy surgery in childhood. Studies on the subject intrinsically necessitate long follow-up periods as the participants must have reached an age at which self-sustaining employment is the norm in order for meaningful analyses to be possible. Previous reports have shown a great variance in employment rates (33%–81%).[7–12] The interpretation of previous studies is complicated by short follow-up times and cross-sectional study designs with widely varying follow-up periods. As a consequence, cohorts consist of individuals of varying ages ranging from early adolescence to adulthood.

The aims of this study were to report long-term population-based educational and employment outcomes in adults who underwent epilepsy surgery in childhood or adolescence, to analyze these findings in relation to postoperative seizure outcome, and to compare the results to general population reference data.

Methods

This is a population-based observational study based on prospectively collected data from the Swedish National Epilepsy Surgery Register (SNESUR). The SNESUR is a collaboration among all 6 centers performing epilepsy surgery in Sweden (Gothenburg, Lund, Uppsala, Stockholm, Linköping, and Umeå). Preoperative data, information about type of surgery and complications, and 2-year follow-up data have been reported to the register since 1990, including medical and social variables. Long-term follow-ups were initiated in 2005 for patients operated from 1995 onwards. These follow-ups consist of structured telephone interviews conducted every 5th year. As long-term follow-ups began in 2005, patients operated from 1995 to 1999 did not undergo 5-year follow-ups; the first long-term follow-up for those patients was 10 years after surgery. Patients operated in 2000 and later have had follow-ups every 5 years since surgery. The first 20-year follow-ups were done in 2015.

All patients who underwent epilepsy surgery in childhood or adolescence (<19 years of age) between 1995 and 2012 and were at least 19 years old at a minimum of one long-term follow-up (5, 10, 15, or 20 years after surgery) were eligible for inclusion in this study. Some patients in this study have been included in previous articles.[13,14] In cases of reoperation before 19 years of age, only follow-ups after the last operation were included in the study. Patients reoperated as adults were excluded after the reoperation. These patients are included in an earlier study on vocational outcomes after epilepsy surgery in adults.[15]

Baseline variables studied were sex, age at epilepsy onset, age at surgery, epilepsy duration (between onset and surgery), neurologic deficits, preoperative intellectual functioning dichotomized as IQ ≥70 or <70, mean monthly seizure frequency during the year preceding surgery, number of antiepileptic drugs, and type of surgery. Neurologic deficits include motor, visual, speech, and auditory deficits. Intellectual functioning was assessed by means of age-appropriate neuropsychological tests.[16]

The outcome measures were seizure outcome, educational attainment, and employment outcome at each follow-up. Seizure outcome is reported as the mean monthly seizure frequency during the year preceding each follow-up, compared to the seizure frequency reported before surgery. Complete seizure freedom since surgery (without aura) is also reported. As seizure outcome is not the main topic of this study, we chose to pool all patients with persisting seizures into one outcome category. Educational attainment (highest level of education, finished or ongoing) was classified into 4 categories: special education (adapted schooling provided up to the age of 20 for individuals with intellectual disabilities), compulsory school (9 years), high school (3 years following the compulsory 9 years), and postsecondary education (university, college, or vocational education after high school). Employment outcome was categorized into full-time employment, part-time employment, ongoing studies, or reliance on social benefits. Due to the impact of intellectual disability on the ability to work and attain higher education, patients were stratified into 2 groups according to baseline IQ with a cutoff at 70.

We compared attainment of postsecondary or high school education and rates of full-time employment of seizure-free patients with preoperative IQ ≥70 with general population data. For this purpose, patients were grouped according to age (19–24 or ≥25 years of age at follow-up). Age-matched general population reference data were acquired from Statistics Sweden. General population data on education were collected from the register Educational Attainment of the Population, which is individual-based and encompasses true figures for the

whole Swedish population. Reference data on employment were acquired from the Labour Force Surveys which, in contrast, are based on samples. Therefore, general population employment figures are estimates with confidence intervals (CIs). Yearly educational attainment and employment data for the period 2005–2017 during which the follow-ups in this study took place were analyzed and mean values for the total period were calculated. Full-time employment was defined as working ≥35 hours per week. The general population reference figures were weighted to match the sex distribution in each of the 4 follow-up cohorts.

Statistical analysis

For comparisons between 2 groups, Fisher exact test was used for dichotomous variables and the Mann-Whitney *U* test for ordered categorical variables. For the purpose of comparisons of educational and employment outcomes with general population data, 95% CIs of patient proportions were derived from the single proportion *Z* test. Univariate binary logistic regression was performed for the prediction of being employed (full- or part-time). Predictors for employment were sought based on findings in earlier studies.[15,17] Presented *p* values are 2-tailed. Missing data were treated as missing at random. Statistical analyses were made in IBM SPSS (Chicago, IL) Statistics 25 for Windows.

Standard protocol approvals, registrations, and patient consents

The study was approved by the Regional Board of Medical Ethics at the University of Gothenburg. The board considered long-term follow-up after epilepsy surgery to be a quality control measure not necessitating individual consent.

Data availability

Swedish general population employment and educational data are freely accessible via Statistics Sweden (scb.se/en/). The SNESUR is subject to personal information protection regulations and sharing of anonymized data will be considered on a case-by-case basis on request.

Results

Between 1995 and 2012, 356 children and adolescents underwent epilepsy surgery in Sweden. A total of 203 patients were included in the study. Seventy-two were followed up 5 years after surgery, 127 after 10 years, 105 after 15 years, and 42 patients 20 years after surgery (figure 1).

Baseline characteristics of the included patients are presented in table 1. A majority (61%) were male and about 1 in 3 patients had a preoperative IQ of <70. Temporal lobe resection (TLR) was the most common type of surgery. Nonresective procedures were more prevalent in patients with low IQ, as were neurologic deficits. Differences with respect to baseline variables between included patients and those lost to follow-up were tested for significance (table e-1, doi.org/10.5061/dryad.tf8440h). Except for type of surgery at the 10-year follow-up (more patients undergoing nonresective surgery were lost to follow-up, Fisher exact test: $p = 0.007$) and sex distribution at the 15-year follow-up (more men were lost to follow-up, Fisher exact test: $p = 0.031$), no statistically significant differences were found.

The mean ages at follow-up were 21.7, 24.3, 26.6, and 30.9 years at the 5-, 10-, 15-, and 20-year follow-ups, respectively. A majority of patients with IQ ≥70 in each follow-up cohort were seizure-free: 40/61 (66%), 58/90 (64%), 38/61 (62%), and 14/22 (64%). In contrast, only 4/11 (36%), 5/37 (14%), 8/44 (18%), and 3/20 (15%) in the IQ <70 group were seizure-free at the 5-, 10-, 15-, and 20-year follow-ups, respectively (Fisher exact test: $p = 0.095$, <0.001, <0.001, and =0.002).

Educational outcomes

Educational outcomes are presented in table 2. In the IQ ≥70 group, a majority had achieved at least high school education 5 years after surgery. The proportion with ongoing or completed postsecondary education increased over time and was higher in seizure-free patients. The differences with respect to seizure outcome were not statistically significant except at the 5-year follow-up (table 2). A majority of the patients with IQ <70 had attended special education, as had a lesser proportion of the patients in the IQ ≥70 group.

Educational attainment in the IQ ≥70 group compared to the general population

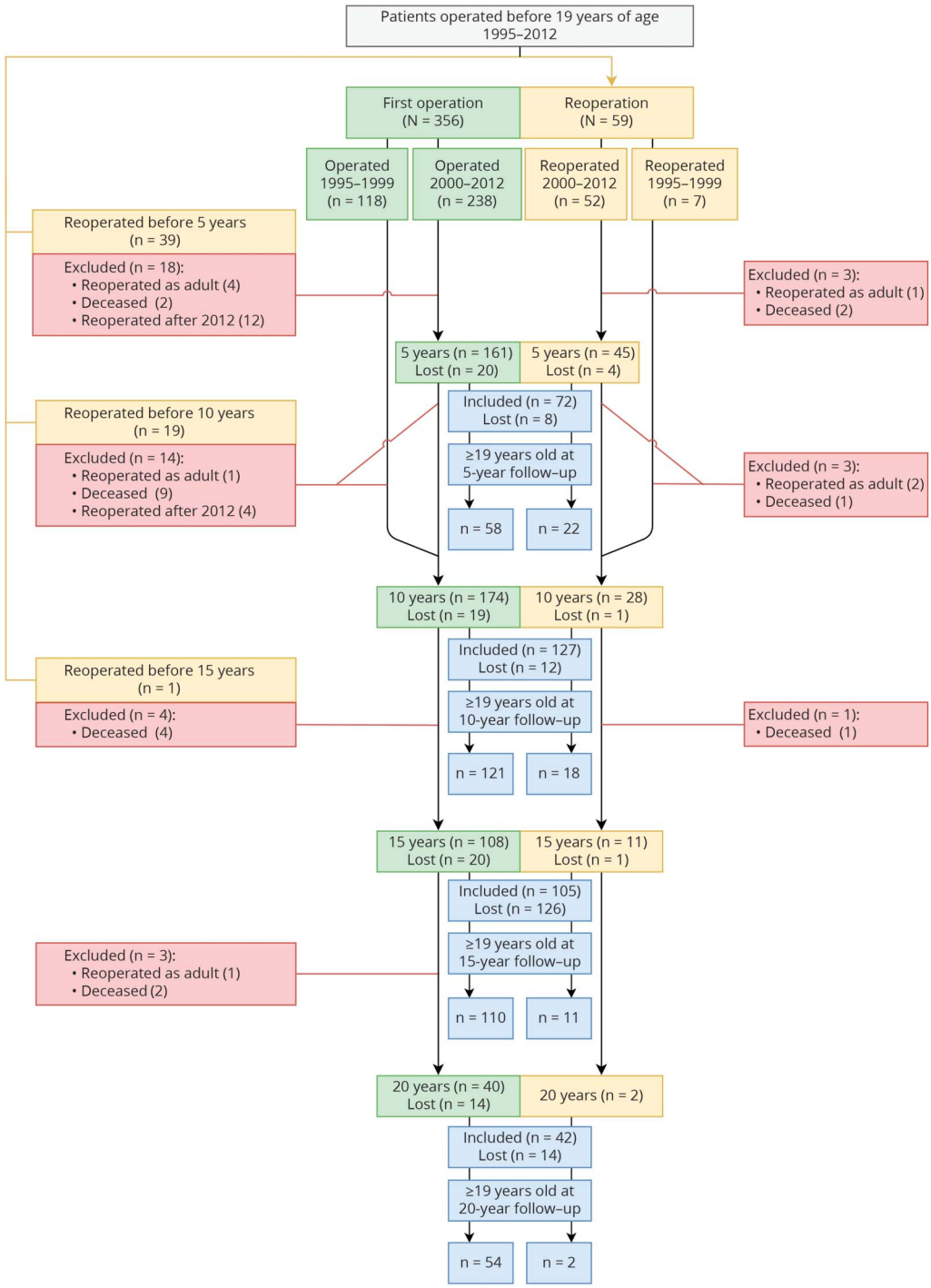
Proportions of seizure-free patients with preoperative IQ ≥70 having attained high school or postsecondary education in comparison to general population reference data are presented in figure 2. Among those aged ≥25 years, 7/25 (28%, 95% CI 10%–46%), 16/29 (55%, 95% CI 37%–73%), and 8/13 (62%, 95% CI 35%–88%) had attained postsecondary education at the 10-, 15-, and 20-year follow-ups, respectively. This can be compared with 43%, 44%, and 44% in the general population.

Employment outcomes

Overall, 27/61 (44%), 62/90 (69%), 43/61 (71%), and 17/22 (77%) of the patients with IQ ≥70 were employed part-time or full-time compared to 6/11 (55%), 7/37 (19%), 11/44 (25%), and 2/20 (10%) in the IQ <70 group. The number of students decreased over time. Except at the 5-year follow-up, rates of both full-time employment and any employment (part-time and full-time combined) were significantly higher for patients with IQ ≥70 than for those with low IQ (Fisher exact test: $p = 1.00$, =0.001, =0.002, and <0.001 at 5-, 10-, 15-, and 20-year follow-ups for full-time employment and $p = 0.744$, <0.001, <0.001, and <0.001 for any employment). A majority of the patients with IQ <70 were reliant on social benefits at all time points except the 5-year follow-up.

Employment outcomes stratified by seizure outcome 5, 10, 15, and 20 years after surgery are shown in table 3. In the IQ ≥70 group, 10-, 15-, and 20-year full-time employment rates were significantly higher for seizure-free patients compared to those who still had seizures (table 3).

Figure 1 Flowchart of patients undergoing epilepsy surgery in Sweden before 19 years of age, 1995–2012



Long-term follow-ups (≥5 years after surgery) began in 2005. Therefore, patients operated in 1995–1999 did not undergo a 5-year follow-up and had their first long-term follow-up 10 years after surgery. In cases of reoperation, only outcomes at follow-up after the last operation were included. Only patients aged ≥19 years were included at each follow-up. 5y = 5-year follow-up; 10y = 10-year follow-up; 15y = 15-year follow-up; 20y = 20-year follow-up.

Full-time employment in the IQ ≥70 group compared to the general population

A comparison between full-time employment rates of patients with IQ ≥70 and general population reference data is shown in figure 3. At the 10-, 15-, and 20-year follow-ups, 17/25 (68%, 95% CI 50%–86%), 22/29 (76%, 95% CI 60%–91%), and 8/13 (62%, 95% CI 35%–88%) of the seizure-free patients aged ≥25 years worked full-time. In the general population, the corresponding weighted figures were 66% (95% CI 65%–67%), 66% (95% CI 65%–67%), and 68% (95% CI 67%–69%). No patients had reached the age of 25 at the 5-year follow-up. Of the younger seizure-free patients aged

Table 1 Baseline characteristics of included patients grouped according to preoperative IQ

	Preoperative IQ ≥ 70	Preoperative IQ < 70
No.	134	69
Sex, male/female (% male)	79/55 (59)	45/24 (65)
Age at epilepsy onset, y, mean (SD); median (range)	7.1 (4.6); 7.0 (0.0–17.4)	1.8 (2.1); 0.7 (0.0–9.0)
Age at surgery, y, mean (SD); median (range)	13.6 (4.0); 14.5 (0.2–18.9)	10.6 (4.2); 10.7 (2.5–17.5)
Epilepsy duration,[a] y, mean (SD); median (range)	6.5 (4.4); 6.0 (0.1–17.8)	8.8 (3.8); 8.6 (1.6–16.1)
Monthly seizure frequency at baseline, mean (SD); median (range)	111 (285); 20 (0.2–2,000)	313 (538); 100 (2–3,300)
No. of AEDs at baseline, median (range)	2 (1–5)	2 (1–4)
Neurologic deficit,[b] n (%)	23 (17)	38 (55)
Type of surgery,[c] n (%)		
TLR	68 (51)	24 (35)
FLR	28 (21)	9 (13)
P/OLR	19 (14)	4 (6)
MLR	4 (3)	4 (6)
HE	8 (6)	7 (10)
CC	3 (2)	16 (23)
HH	—	2 (3)
Other	4 (3)	3 (4)
Reoperation, n (%)	22 (16)	10 (15)

Abbreviations: AED = antiepileptic drug; CC = corpus callosotomy; FLR = frontal lobe resection; HE = hemispherotomy; HH = disconnection of hypothalamic hamartoma; MLR = multilobe resection; Other = stereotactic procedures, multiple subpial transections; P/OLR = parietal or occipital lobe resection; TLR = temporal lobe resection.
[a] Time between epilepsy onset and first operation.
[b] Including motor, visual, speech, and auditory deficits.
[c] Last operation.

19–24 years at follow-up, 13/40 (33%, 95% CI 18%–47%) and 15/33 (45%, 95% CI 28%–62%) were in full-time employment 5 and 10 years after surgery, whereas the general population full-time employment rates were 39% (95% CI 38%–40%) and 38% (95% CI 37%–39%). Only a few patients were under 25 years of age at the 15- and 20-year follow-ups.

Predictors of employment

Univariate binary logistic regression analyses of potential predictors of employment (full-time or part-time) are shown in table 4. Higher age at surgery was associated with greater chances of employment at the 10- and 15-year follow-ups. At the 20-year follow-up, seizure freedom was a positive predictor of employment, whereas >30 seizures/mo at baseline was negatively associated with employment at the 15-year follow-up. Due to the small number of significant associations found in the univariate analyses, we chose not to perform further multivariable analyses.

Discussion

In this prospective, population-based study on long-term employment outcomes after paediatric epilepsy surgery, we found that a majority of patients with a preoperative IQ ≥70 were employed 10 years after epilepsy surgery and that employment rates continued to rise through the 20-year follow-up. At the 5-year follow-up, when the patients were still young adults, the rates of full-time and part-time employment were lower (44% combined), whereas more patients were students (33%). Previous studies have yielded widely varying results; employment rates in the literature range from 33% to 81%.[7–12] Outcomes with respect to employment and educational attainment are for obvious reasons dependent on the patients' age at follow-up, and thus on the length of follow-up. This is of particular importance in studies of paediatric populations as early adulthood is an age of transition when individuals attain vocational education and enter the labor market. Consequently, cross-sectional studies with mean ages at follow-up in this age span may be difficult to interpret. Three previous studies focusing on outcomes in young adults after surgery in childhood or adolescence have shown that most are either working or engaged in studies, findings that are confirmed by our results.[7,10,11] Studies with longer follow-up suggest that employment rates increase with higher age at follow-up; figures ranging from 48% to 81% have been reported.[8,9,12] This pattern is in line with our findings.

Table 2 Educational attainment in relation to seizure outcome

Seizure outcome	Educational attainment, n (%)				*p* Value (postsecondary education)[a]
	Postsecondary education	High school	Compulsory school	Special education	
IQ ≥70					
5-y follow-up, n = 61					
Seizure-free, total n = 40	9 (22.5)	23 (57.5)	1 (2.5)	7 (17.5)	0.021[b]
Since surgery, n = 28	7 (25.0)	16 (57.1)	1 (3.6)	4 (14.3)	
≥1 y before follow-up, n = 12	2 (16.7)	7 (58.3)	0	3 (25.0)	
Seizures, n = 21	0	16 (76.2)	1 (4.8)	4 (19.0)	
10-y follow-up, n = 90					
Seizure-free, total n = 58	18 (31.0)	37 (63.8)	1 (1.7)	2 (3.4)	0.072
Since surgery, n = 33	10 (30.3)	21 (63.6)	0	2 (6.1)	
≥1 y before follow-up, n = 25	8 (32.0)	16 (64.0)	1 (4.0)	0	
Seizures, n = 32	4 (12.5)	17 (53.1)	2 (6.3)	9 (28.1)	
15-y follow-up, n = 61					
Seizure-free, total n = 38	19 (50.0)	15 (39.5)	0	4 (10.5)	0.106
Since surgery, n = 24	15 (58.3)	7 (29.2)	0	3 (12.5)	
≥1 y before follow-up, n = 14	5 (35.7)	8 (57.1)	0	1 (7.1)	
Seizures, n = 23	6 (26.1)	11 (47.8)	0	6 (26.1)	
20-y follow-up, n = 22					
Seizure-free, total n = 14	8 (57.1)	6 (42.9)	0	0	0.204
Since surgery, n = 8	4 (50.0)	4 (50.0)	0	0	
≥1 y before follow-up, n = 6	4 (66.7)	2 (33.3)	0	0	
Seizures, n = 8	2 (25.0)	2 (25.0)	1 (12.5)	3 (37.5)	
IQ <70					
5-y follow-up, n = 11					
Seizure-free, total n = 4	0	1 (25.0)	0	3 (75.0)	
Since surgery, n = 1	0	0	0	1 (100)	
≥1 y before follow-up, n = 3	0	1 (33.3)	0	2 (66.7)	
Seizures, n = 7	0	0	1 (14.3)	6 (85.7)	
10-y follow-up, n = 37					
Seizure-free, total n = 5	0	1 (20.0)	0	4 (80.0)	
Since surgery, n = 3	0	0	0	3 (100)	
≥1 y before follow-up, n = 2	0	1 (50.0)	0	1 (50.0)	
Seizures, n = 32	0	1 (3.1)	1 (3.1)	30 (93.8)	
15-y follow-up, n = 44					
Seizure-free, total n = 8	0	3 (37.5)	1 (12.5)	4 (50.0)	

Continued

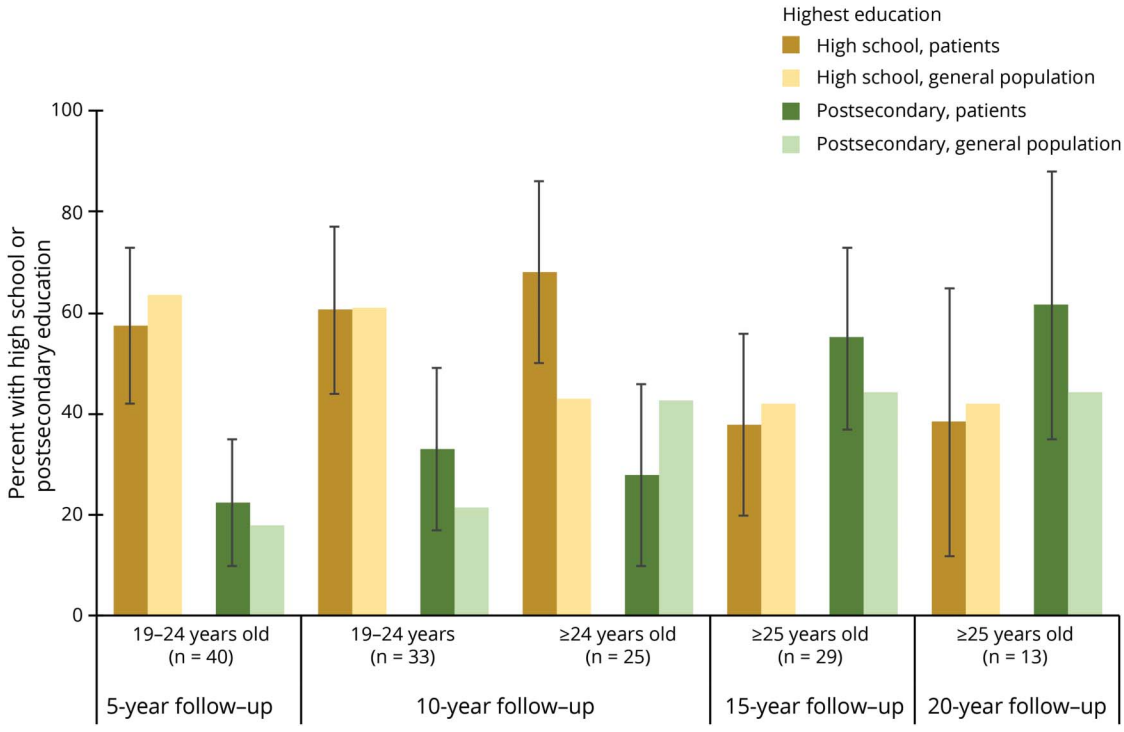
Table 2 Educational attainment in relation to seizure outcome *(continued)*

Seizure outcome	Educational attainment, n (%)				*p* Value (postsecondary education)[a]
	Postsecondary education	High school	Compulsory school	Special education	
Since surgery, n = 5	0	2 (40.0)	0	3 (60.0)	
≥1 y before follow-up, n = 3	0	1 (33.3)	1 (33.3)	1 (33.3)	
Seizures, n = 36	0	3 (8.3)	1 (2.8)	32 (88.9)	
20-y follow-up, n = 20					
Seizure-free, total n = 3	1 (33.3)	0	0	2 (66.7)	
Since surgery, n = 2	1 (50.0)	0	0	1 (50.0)	
≥1 y before follow-up, n = 1	0	0	0	1 (100)	
Seizures, n = 17	0	1 (5.9)	0	16 (94.1)	

[a] *p* Values represent results from Fisher exact test comparing attainment of postsecondary education between seizure-free patients (since surgery or during the year before follow-up) and patients with persisting seizures.
[b] $p < 0.05$.

It is reasonable to believe that successful surgical intervention in childhood would allow patients to enter adulthood less hindered by their epilepsy, even though associated adverse cognitive, psychiatric, and social factors may still have an influence. As a consequence, pediatric patients could be expected to fare better in terms of long-term employment compared to patients operated later in life who in many cases have had intractable epilepsy all through adolescence and

Figure 2 Educational attainment of seizure-free patients with preoperative IQ ≥70 compared to general population reference data



Proportion of seizure-free patients with preoperative IQ ≥70 with high school or postsecondary education at each follow-up compared to corresponding age- and sex-matched general population mean values (2005–2017). Error bars represent 95% confidence intervals. Numbers in the x-axis labels represent the total number of seizure-free patients with preoperative IQ ≥70 in each age group.

Table 3 Employment outcome in relation to seizure outcome

Seizure outcome	Employment outcome, n (%)				*p* Value (full-time work)[a]	*p* Value (full-time or part-time work)[a]
	Full-time work	Part-time work	Student	On benefits		
IQ ≥70						
5-y follow-up, n = 61						
Seizure-free, total n = 40	13 (32.5)	7 (17.5)	14 (35.0)	6 (15.0)	0.063	0.281
Since surgery, n = 28	8 (28.6)	6 (21.4)	10 (35.7)	4 (14.3)		
≥1 y before follow-up, n = 12	5 (41.7)	1 (8.3)	4 (33.3)	2 (16.7)		
Seizures, n = 21	2 (9.5)	5 (23.8)	6 (28.6)	8 (38.1)		
10-y follow-up, n = 90						
Seizure-free, total n = 58	32 (55.2)	11 (19.0)	11 (19.0)	4 (6.9)	0.001[b]	0.162
Since surgery, n = 33	16 (48.5)	10 (30.3)	7 (21.2)	0		
≥1 y before follow-up, n = 25	16 (64.0)	1 (4.0)	4 (16.0)	4 (16.0)		
Seizures, n = 32	6 (18.8)	13 (40.6)	2 (6.3)	11 (34.4)		
15-y follow-up, n = 61						
Seizure-free, total n = 38	24 (63.2)	6 (15.8)	4 (10.5)	4 (10.5)	<0.001[b]	0.085
Since surgery, n = 24	15 (62.5)	4 (16.7)	3 (12.5)	2 (8.3)		
≥1 y before follow-up, n = 14	9 (64.3)	2 (14.3)	1 (7.1)	2 (14.3)		
Seizures, n = 23	2 (8.7)	11 (47.8)	6 (26.1)	4 (17.4)		
20-y follow-up, n = 22						
Seizure-free, total n = 14	9 (64.3)	4 (28.6)	1 (7.1)	0	0.031[b]	0.039[b]
Since surgery, n = 8	6 (75.0)	1 (12.5)	1 (12.5)	0		
≥1 y before follow-up, n = 6	3 (50.0)	3 (50.0)	0	0		
Seizures, n = 8	1 (12.5)	3 (37.5)	1 (12.5)	3 (37.5)		
IQ <70						
5-y follow-up, n = 11						
Seizure-free, total n = 4	1 (25.0)	1 (25.0)	1 (25.0)	1 (25.0)		
Since surgery, n = 1	0	0	1 (100)	0		
≥1 y before follow-up, n = 3	1 (33.3)	1 (33.3)	0	1 (33.3)		
Seizures, n = 7	2 (28.6)	2 (28.6)	0	3 (42.9)		
10-y follow-up, n = 37						
Seizure-free, total n = 5	1 (20.0)	1 (20.0)	1 (20.0)	2 (40.0)		
Since surgery, n = 3	0	1 (33.3)	1 (33.3)	1 (33.3)		
≥1 y before follow-up, n = 2	1 (50.0)	0	0	1 (50.0)		
Seizures, n = 32	3 (9.4)	2 (6.3)	10 (31.3)	17 (53.1)		
15-y follow-up, n = 44						
Seizure-free, total n = 8	3 (37.5)	2 (25.0)	2 (25.0)	1 (12.5)		
Since surgery, n = 5	3 (60.0)	0	2 (40.0)	0		
≥1 y before follow-up, n = 3	0	2 (66.7)	0	1 (33.3)		
Seizures, n = 36	3 (8.3)	3 (8.3)	6 (16.7)	24 (66.7)		

Continued

Table 3 Employment outcome in relation to seizure outcome *(continued)*

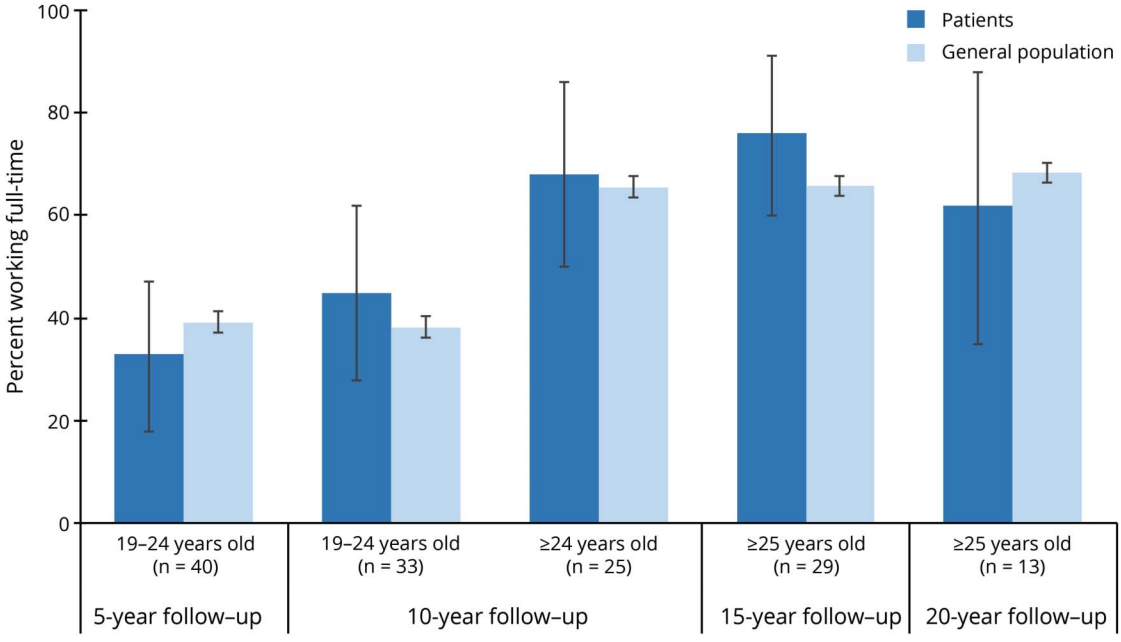
Seizure outcome	Employment outcome, n (%)				*p* Value (full-time work)[a]	*p* Value (full-time or part-time work)[a]
	Full-time work	Part-time work	Student	On benefits		
20-y follow-up, n = 20						
Seizure-free, total n = 3	0	1 (33.3)	0	2 (66.7)		
Since surgery, n = 2	0	1 (50.0)	0	1 (50.0)		
≥1 y before follow-up, n = 1	0	0	0	1 (100)		
Seizures, n = 17	0	1 (5.9)	0	16 (94.1)		

[a] *p* Values represent results from Fisher exact test comparing full-time employment and any employment (full-time or part-time) between seizure-free patients (since surgery or during the year before follow-up) and patients with persisting seizures.
[b] $p < 0.05$.

early adulthood. In line with studies of patients operated in childhood, employment outcomes after surgery in adults are disparate. A US multicenter study on resective procedures showed that 55% of patients were employed after 2 years,[18] whereas 2 cross-sectional long-term studies with mean follow-up periods of about 10 years revealed that 70% were employed following TLR[19] and 34% following all types of resective surgery.[20] Furthermore, a previous longitudinal study on vocational outcomes after surgery in adults by our group showed a declining trend in employment figures.[15] Although no firm conclusions should be drawn due to differences in baseline characteristics between adult and pediatric series and markedly higher age at follow-up in studies on adults, it is worth noting that patients with IQ ≥70 in the present study had higher long-term employment rates compared to most previous studies on surgery in adults.

In the current study, rates of full-time employment in the IQ ≥70 group were significantly higher among seizure-free patients at all time points except the 5-year follow-up. In contrast, when full-time and part-time employment were analyzed together, no significant differences with respect to seizure outcome were found except at the 20-year follow-up. An interpretation of this finding could be that active epilepsy in many cases led to a reduction in working hours rather than unemployment. In most previous pediatric studies, small

Figure 3 Full-time employment in seizure-free patients with IQ ≥70 compared to general population reference data



Proportions of seizure-free patients with preoperative IQ ≥70 in full-time employment at each follow-up compared to age- and sex-matched general population mean values (2005–2017). Error bars represent 95% confidence intervals. Numbers in the x-axis labels represent the total number of seizure-free patients with preoperative IQ ≥70 in each age group.

Table 4 Univariate logistic regression analyses of predictors for employment (full-time or part-time) in patients with preoperative IQ >70

	Dependent variable							
	Employment at 5-y follow-up		Employment at 10-y follow-up		Employment at 15-y follow-up		Employment at 20-y follow-up	
Independent variable	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value
Seizure freedom	2.00 (0.67–6.00)	0.216	1.96 (0.78–4.91)	0.150	2.89 (0.93–8.97)	0.067	13.00 (1.11–152.35)	0.041[a]
Preoperative neurologic impairment	0.35 (0.08–1.439)	0.145	0.89 (0.24–3.24)	0.858	0.42 (0.11–1.62)	0.208	0.09 (0.01–1.39)	0.086
Age at surgery	1.03 (0.85–1.26)	0.753	1.29 (1.09–1.53)[a]	0.003[a]	1.24 (1.07–1.44)[a]	0.005[a]	1.11 (0.91–1.35)	0.297
Relative epilepsy duration	0.87 (0.12–5.44)	0.835	0.30 (0.06–1.43)	0.129	0.28 (0.05–1.76)	0.175	0.05 (0.01–2.30)	0.123
>30 Seizures/mo at baseline	1.20 (0.42–3.42)	0.729	0.41 (0.16–1.03)	0.058	0.25 (0.07–0.79)	0.018[a]	0.75 (0.10–5.69)	0.781
Sex (ref female)	2.00 (0.67–6.00)	0.216	1.39 (0.57–3.39)	0.477	1.19 (0.40–3.60)	0.754	1.60 (0.20–12.69)	0.656

Abbreviations: CI = confidence interval; OR = odds ratio.
Relative epilepsy duration: epilepsy duration (from onset to surgery) divided by age at surgery.
[a] $p < 0.05$.

cohort sizes, young age at follow-up, and the use of outcome variables combining work and studies have precluded analyses of the association between seizure outcome and employment.[9–11,21] A significant association between seizure freedom and higher employment rates has been shown in 2 previous studies of epilepsy surgery in childhood[7,12] as well as in several studies of surgery on adults.[15,17,22]

Comparisons of employment outcomes across countries and time periods are complicated by several factors including economic fluctuations and differences in national social welfare and labor market policies. A means of overcoming these difficulties is to compare results with general population reference data. Seizure-free patients with preoperative IQ ≥70 in our series had rates of full-time employment similar to the general population during the same time period. Although sample sizes were small, this is an encouraging finding. To our knowledge, there is only one previous report on pediatric epilepsy surgery that has included comparisons with general population reference figures; the authors concluded that although there was no difference with respect to a composite measure of employment and school attendance, wages earned were significantly lower.[11]

We found few predictors of employment in this study. Higher age at surgery was associated with greater chances of employment at the 10- and 15-year follow-ups, possibly reflecting the effect of older age at follow-up. Further, seizure freedom was a positive predictor for employment at the 20-year follow-up, while >30 seizures/mo at baseline was a negative predictor of employment at the 15-year follow-up. To our knowledge, predictors of employment after pediatric epilepsy surgery have not been previously investigated apart from seizure outcome. Studies on surgery in adults have shown preoperative employment status to be a strong predictor of postoperative employment.[15,17] Although potential effects of the tested clinical variables may have gone unnoticed in the analyses due to small sample sizes, it is probable that factors not available in the register (e.g., school grades and parents' level of education) would have a greater influence on employment outcomes.

Information in the literature about the educational level of adults who had epilepsy surgery in childhood or adolescence is scarce and comparisons between countries are complicated by differences in educational systems. Previous studies have included individuals followed up in early adulthood and show figures of postsecondary education ranging from 23% to 57%.[7,10,11] Only one study from Canada has compared results to general population data and found no significant difference.[11] In agreement with that study, the proportions of seizure-free patients in our study with a postsecondary education were similar to those of the general population. As discussed above in relation to employment outcomes, the sample sizes were small, and the results should thus be interpreted with caution. In Sweden, all education is tuition-free and low-interest government student loans are available to everyone regardless of parental income. It thus can be argued that these results are difficult to generalize as access to higher education is probably more universal in Sweden than in many other countries.

About 1 in 3 patients in our cohort had a preoperative IQ of <70, a high figure compared to other pediatric series.[23,24] In part, the inclusion of nonresective procedures, which are performed more often in patients with intellectual disabilities, explains this difference. As employment prospects for intellectually disabled patients are markedly decreased,[25] we chose to report outcomes for this group separately. The cutoff at IQ 70 was chosen to align with current criteria for the diagnosis of intellectual disability, which in turn is a prerequisite for admittance to special education in Sweden.[26] Indeed, a large majority of the patients with IQ <70 were shown to have attended special education at follow-up, although a few had completed regular compulsory school or high school and in one case even postsecondary education. With respect to employment outcomes, most relied on social benefits, while a smaller proportion were either students or employed. These outcomes should be interpreted with caution. First, as IQ measurements were made preoperatively and as there is no information about adaptive functioning in the register, it is possible that a few patients in the low IQ group did not meet the diagnostic criteria for intellectual disability at follow-up. Second, special education in Sweden is provided until 20 years of age, after which some individuals take part in further basic vocational training aimed at people with special needs. In part, this explains the finding that a significant proportion of the patients with low IQ were students as adults. Finally, people with permanently reduced working capacity can be entitled to wage subsidies, and it is reasonable to believe that this was the case for some patients in the IQ <70 group, although we have no information about this in the register.

The strengths of this study include the prospective, population-based design, which allows us to report results representative for the whole Swedish epilepsy surgery population. As follow-ups took place during a period of more than 10 years, our study is less sensitive to economic fluctuations compared to cross-sectional studies. Moreover, the relatively large cohort size and the long follow-up time made it possible to stratify employment outcomes according to age. This is a major strength of our study since employment outcomes are age-dependent and results from cross-sectional cohorts of patients in the young adult age span might be difficult to interpret. Finally, this is one of few studies of employment outcomes after epilepsy surgery that include comparisons to general population reference data. The design of this study also carries some limitations. First, the register data did not permit analyses of wages, occupational complexity, or the extent of part-time work, and the study also lacks postoperative cognitive assessments. Sample sizes of some subgroups (seizure-free patients with IQ <70 and 20-year follow-up data in both IQ groups) were small, and therefore, the results should be interpreted with caution. Furthermore, we did not have follow-up data on all patients at each time point. Finally, the absence of a nonsurgical reference group with intractable epilepsy is a weakness.

A majority of patients with preoperative IQ in the normal range were either employed or studying at long term after pediatric epilepsy surgery. Overall employment rates were higher compared to most previous studies on surgery in adults. Seizure-free patients were significantly more likely to work full-time and showed rates of full-time employment and attainment of postsecondary education similar to the general population. These are encouraging findings that will be of importance in the presurgical counseling process of patients and families. Further research is warranted to evaluate whether outcomes persist into middle age and to analyze occupational distribution and wages.

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Ingrid Olsson, MD, PhD	Gothenburg University, Sweden	Author	Study concept and design, analysis and interpretation of data, critical revision of the manuscript for intellectual content, study supervision
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Long-term employment outcomes after epilepsy surgery in childhood
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Disputes & Debates: Editors' Choice

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Editors' Note: In Vivo Distribution of α-Synuclein in Multiple Tissues and Biofluids in Parkinson Disease

In the Systemic Synuclein Sampling Study (S4)—a cross-sectional observational study of 59 participants with early, moderate, or advanced Parkinson disease (PD) and 21 healthy controls (HCs)—Dr. Chahine et al. found lower total α-synuclein levels in the CSF of patients with PD compared with HCs with a reasonable sensitivity of 87%, but this finding had low specificity. On the other hand, α-synuclein immunoreactivity in skin and submandibular gland was specific for PD but not sensitive. In response, Dr. Gibbons et al. cite previous studies that reported much higher sensitivities (80%–95% vs 24.1%) for the detection of α-synuclein in the skin in patients with PD. They argue that this discrepancy cannot be explained by inclusion of late-stage PD in such studies, citing high-detection rates of phosphorylated α-synuclein in patients with early-stage PD and REM sleep behavioral disorder (RBD), and low-false positivity. They propose that the discrepant results in the S4 study may be explained by the study's methodology of formalin fixation of the skin biopsies, which they claim has not gained acceptance in the study of peripheral nerve tissue because of the diminished integrity of peripheral antigen retrieval; paraffin embedding of the tissue, which they argue provides only a fraction of the volume obtained with larger frozen tissue sections; and automated immunohistochemical staining. They suggest that future studies in this area should use more accepted standardized methods for processing skin biopsy tissue for phosphorylated α-synuclein. Responding to these comments, the authors suggest that previous conflicting results have primarily been due to relatively low levels of study rigor in assessing the accuracy of the various immunohistochemistry methods, which, in the S4 study group, included multiple independent slide-reading judges, third-party blinding of such judges, and validation against gold standard neuropathologic diagnosis. They agree that reports of high sensitivity of peripheral α-synuclein detection in patients with idiopathic RBD are encouraging for the early detection of α-synucleinopathies but argue that not all patients with PD have preceding RBD and that those who do tend to have more widespread and severe brain synucleinopathy. They counter that technical differences in paraformaldehyde and formalin fixation are minimal and cite previous methods from S4 authors supporting the use of formalin-fixed, paraffin-embedded (FFPE) tissue. They also argue that the multiple S4 tissue sections that they assessed for each tissue site and subject resulted in sufficient tissue volumes to overcome any limitations of individual paraffin-embedded samples. They note that thick sections and immunofluorescent signal development methods require rare technical expertise, whereas FFPE methods and autostainers are more widely available, with autostaining methods also providing greater replicability and potentially better long-term storage than free-floating immunohistochemical methods. This exchange highlights enduring methodological uncertainties, tradeoffs, and debates regarding the detection of antigens such as synuclein in tissue samples, which need to be more definitively resolved before such detection is adopted into clinical practice.

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Reader Response: In Vivo Distribution of α-Synuclein in Multiple Tissues and Biofluids in Parkinson Disease

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We read with interest the publication entitled "In vivo distribution of α-synuclein in multiple tissues and biofluids in Parkinson disease."[1] In the article, Chahine et al.[1] discuss the results of the Systemic Synuclein Sampling Study (S4 study). This was an important step toward the in vivo diagnosis of synucleinopathy. Unfortunately, although the detection of phosphorylated alpha-synuclein was highly specific, sensitivity was quite poor, particularly for skin (with a sensitivity of 24.1%). The authors note that there were several explanations for such findings, including the earlier diagnosis of PD in the S4 study compared with the relatively small studies performed at other centers.

At present, there are many studies that include the use of skin for the detection of alpha-synuclein, many with numbers of similar or even larger size than the results of the present study with sensitivities of testing in the 80%–95%+ range.[2-4] Chahine et al. suggest that the high-positive rates in the previous publications are because of the inclusion of late-stage disease PD. This notion has largely been disproven by the high-detection rates of phosphorylated alpha-synuclein in patients with REM sleep behavioral disorder and in studies only including Hoehn and Yahr stages 1 and 2, which confirm that early detection is not only possible but can be performed with sensitivities much higher than reported in the S4 study.[1,5-7] The notion of higher rates of false-positive cases in previous studies—as also suggested by Chahine et al.—is opposed to the 100% specificity that has been reported before.[8,9]

To understand the major discrepancies between the S4 study and the synuclein literature published by several different groups, one must closely compare the methods between the groups. Based on our long experience in skin biopsy processing, the lack of sensitivity in the S4 study can be explained by the following: the methodology used in the S4 study included formalin fixation of the skin biopsies, paraffin embedding of the tissue, and automated immunohistochemical staining.[10]

The use of formalin-fixed paraffin-embedded tissue has never gained acceptance in the study of peripheral nerve tissue, where decades of peripheral nerve research have resulted in well-defined, standardized methods for standard skin biopsy processing using only thick, freshly fixed frozen tissue sections.[11,12] These international standards have been established because formalin fixation reduces the integrity of peripheral antigen retrieval, and therefore, only paraformaldehyde-based fixatives are used.[3,11,13,14] In addition, there is a need to obtain thicker tissue sections for adequate cutaneous nerve fiber and tissue sampling. As the authors of the S4 study note, the deposition of alpha-synuclein is "patchy." A standard 4-mm-thick paraffin-embedded tissue section provides only a fraction of the tissue volume obtained with a 20–50-mm frozen tissue section.[3,13,15] Thus, a significant sampling error is introduced by using paraffin-embedded sections unless much greater numbers of samples are processed. In addition, thin tissue sections disrupt a nerve fiber structure and reduce the ability to visualize intraneural synuclein deposition.

The association between the use of thicker cryosections and the higher sensitivity of phospho-alpha-synuclein detection is reflected in the literature: phosphorylated alpha-synuclein was first reported in premortem skin biopsies of patients with Parkinson disease with low sensitivity by using formalin-fixed paraffin-embedded tissue.[16] In 2013, 3 independent research groups—all

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from the field of peripheral nerve research with long experience in the study of cutaneous autonomic and somatosensory small fibers—simultaneously reported the detection of phospho-alpha-synuclein or an increase of total alpha-synuclein in dermal nerve fibers in patients with the Parkinson disease with a much higher sensitivity.[8,9,17] In the meantime, several studies have been published confirming these data.[18-20]

The results of the current study simply confirm that formalin-fixed paraffin-embedded tissue sections should not be used in the study of the skin biopsy analysis of peripheral nerve and do not inform about the utility of skin biopsy in the detection of phosphorylated alpha-synuclein. Future studies of this nature should be performed using the accepted standardized methods for processing of skin biopsy tissue for phosphorylated alpha-synuclein.

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Author Response: In Vivo Distribution of α-Synuclein in Multiple Tissues and Biofluids in Parkinson Disease

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We appreciate the opportunity to reply to the letter by Gibbons et al. on our article.[1] Over recent years, there have been many, often widely conflicting reports on the diagnostic accuracy for the Parkinson disease (PD) of immunohistochemical (IHC) staining of pathologic α-synuclein (aSyn) in peripheral tissue biopsies.[2] We suggest that these conflicts have primarily

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been because of the relatively low levels of study rigor in assessing the accuracy of the various IHC methods. Unlike for the S4 study, other published diagnostic IHC methods for aSyn in skin or any other peripheral tissues subjected to rigorous assessments are rare—such as those performed in a series of studies conducted under the sponsorship of the Michael J. Fox Foundation—including the S4 study,[1] which is the subject of the current communications. These rigorous studies have included multiple independent slide-reading judges, third-party blinding of such judges, and validation against gold standard neuropathologic diagnosis.[3-5] We answer specific points mentioned by Gibbons et al. below:

1. Regarding the sensitivity of IHC aSyn methods in participants with idiopathic REM sleep behavioral disorder (RBD), we agree that these are encouraging for the early detection of α-synucleinopathies but point out that not all participants with PD or dementia with Lew bodies (DLB) have RBD and those who do tend to have more widespread and severe aSyn brain histopathology as compared with those without RBD.[6] This may also be true for prodromal participants with and without RBD.
2. Regarding the difference between paraformaldehyde and formalin fixation, we believe that this is minimal or nonexistent provided the concentration, in solution, of formaldehyde is equivalent. Most laboratories use commercially obtained 10% formalin in aqueous buffer, which has a formaldehyde concentration of approximately 4%. Many other laboratories, as indicated by Gibbons et al., prepare fixative solutions from solid paraformaldehyde, but this converts on dissolution into formaldehyde, and most laboratories aim for a final formaldehyde concentration of 4%. Because of this, formalin-fixed and paraformaldehyde-fixed tissues cause equivalent antigen (epitope) masking as long as they have equivalent formaldehyde concentrations. Much published work is available that indicates that excellent sensitivity may be obtained in formalin-fixed, paraffin-embedded (FFPE) tissue when optimal antigen exposure methods are used, including published work by some of the S4 authors on aSyn IHC methods.[7]
3. Greater section thicknesses such as those obtained with sliding-freezing microtomes or vibratomes do give additional tissue volume as compared to thinner paraffin sections, and this may give increased sensitivity, but, as Drs. Gibbons, Freeman and co-workers pointed out themselves in their very recent publication,[8] this is easily made equivalent by staining more paraffin sections to give equivalent tissue volumes. We believe that the multiple S4 tissue sections that we assessed for each tissue site and participant will have given the study sufficient tissue volumes so as to exclude this as a limiting factor for achieving optimal sensitivity. The S4 group has, in fact, conducted follow-up studies that confirmed that additional stained sections did not further improve sensitivity.
4. Although thick sections and immunofluorescent signal development—such as those used by Gibbons et al.—have been used by some (but not all) laboratories for the investigation of peripheral nerve pathology, these methods have distinct and limiting drawbacks. They require technical expertise that a very few laboratories possess, whereas FFPE methods and autostainers are used by virtually every diagnostic hospital pathology unit in the developed world. The use of autostainers and associated standardized reagents provides replicable interlaboratory slide staining that is difficult to obtain with free-floating section methods that are idiosyncratic to each laboratory. The fluorescent slides obtained with the free-floating section methods are not well preserved in long-term storage and would be difficult to exchange between centers.

We therefore disagree with Gibbons et al. in their conclusion that FFPE sections should not be used for skin biopsy analysis, whether for the study of aSyn or other features. We look forward to more rigorous assessments of the free-floating aSyn IHC methods used by the authors, including the usage of third-party blinding, multiple independent judges, and gold standard autopsy diagnosed cases. Such a rigor is especially critical before aSyn detection methods are offered in the clinical setting.

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Editors' Note: Longitudinal Changes of Brain Microstructure and Function in Nonconcussed Female Rugby Players

Dr. Manning et al. found cross-sectional and longitudinal changes in the white matter diffusion measures and resting-state functional MRI network connectivity in 73 concussion-free female rugby players compared with 31 age-matched female swimmers and rowers. They concluded that longitudinal changes occur in the microstructure and function of the brain in otherwise healthy, asymptomatic athletes participating in contact sport and that further research is needed to understand the long-term brain health and biological implications of these changes. In response, Drs. Shahim and Diaz-Arrastia note that repetitive head impacts over decades have been associated with late-life dementia in previous studies of professional contact-sport athletes, but that it is less clear whether participation in such sports at the amateur level poses similar risks. They note that the finding of white matter microstructural disruption seen in the study by Dr. Manning et al. is also seen as a consequence of more severe traumatic brain injuries. While commending the longitudinal data provided by the study, they caution that imaging techniques such as diffusion tensor imaging and rsfMRI may detect small degrees of disruption that are not functionally limiting and also have limited availability and cumbersome processing needs that preclude their use for routine assessment of athletes. They call for further studies of more inexpensive blood-based biomarkers and their correlation with imaging markers of axonal disruption after concussive and subconcussive head impacts. Responding to these comments, the authors agree that cognitive reserve in the individuals studies may be sufficiently high that they are functionally unaffected by the identified MRI markers of tissue and network disruption but argue that they may eventually affect the brain's response to other insults later in life. They agree that these MRI approaches are presently intended for research purposes. Noting that they have undertaken further work on blood-based markers on this cohort, they comment that metabolomic signatures may be more relevant than classical markers of injury while acknowledging the need for better correlation with imaging results and cognitive testing. This exchange underscores our evolving, but incomplete, understanding of the clinical significance of imaging and blood-based markers of axonal injury in otherwise healthy athletes engaged in contact sports.

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Reader Response: Longitudinal Changes of Brain Microstructure and Function in Nonconcussed Female Rugby Players

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We read the article by Manning et al.[1] with interest. Studies of professional contact-sports athletes have made clear that exposures to repetitive head impacts over decades are associated with late-life neurodegenerative dementia.[2,3] It is less clear whether participation in contact sports at the amateur level results in comparable risks. The study by Manning et al. found white matter (WM) microstructural disruption—especially in the corpus callosum and impaired functional connectivity in the default mode network over time in concussion-free and asymptomatic female rugby players—using diffusion tensor (DTI) and resting-state connectivity MRI (rsMRI), respectively.[1] These WM tracts are known to be disrupted as a consequence of more severe traumatic brain injuries.[4] In contrast to the existing studies,[5] Manning et al. assessed WM and functional changes in female athletes and noncontact sport athletes longitudinally, which is a novel and strong study design. Although the results of the Manning et al. study are compelling, they should be interpreted with caution. Although DTI and rsMRI are sensitive for identifying WM disruption, it is likely that there is substantial cognitive reserve built into brain and that these elegant imaging techniques may detect small degrees of disruption that are unlikely to result in functional limitations. Future studies with larger sample sizes and longer follow-up will be required to answer this important question. Finally, the DTI and rsMRI methods have several limitations, including limited availability and cumbersome image processing, which limits their usefulness for routine assessment of athletes. Future studies should include blood-based biomarkers, such as neurofilament light and glial fibrillary acidic protein, which are inexpensive and straightforward to interpret, as markers of axonal disruption. How well blood biomarkers correlate with the imaging biomarkers of axonal injury after concussive and subconcussive head impacts is a critical issue which remains to be resolved.

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Author Response: Longitudinal Changes of Brain Microstructure and Function in Nonconcussed Female Rugby Players

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We are in agreement with the caveats put forward by Drs. Shahim and Diaz-Arrastia regarding our article.[1] It is entirely possible that the MRI methods put forward in this paper are so sensitive that they detect changes that are of no functional consequence now. It is also possible that cognitive reserve in these individuals is sufficiently high that these changes have no consequence in the future. However, one could imagine that every life event that chips away at the brain's capacity for recovery and plasticity can ultimately affect the brain's response to a later-in-life insult, such as stroke or plaque formation. It is simply unknown whether this is a linear process or one in which a threshold needs to be surmounted, and hence, whether these

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are important or trivial changes. We would not advocate that these MRI approaches be used in a diagnostic manner. As noted in the comment, these are sophisticated and expensive approaches and are designed to study populations and inform directions for further research (and perhaps policy). One such direction is the use of blood biomarkers. We do have additional publications with data on this cohort in preparation but can note in passing that GFAP showed no changes at the sensitivity threshold of our techniques. In mild TBI or asymptomatic participants, metabolomic signatures may be more relevant than the classical markers such as GFAP or NFL, as we have previously noted.[2] These would be more appropriate as accessible screening tools once we understand their relationship to the imaging results and perhaps more incisive cognitive testing.

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CORRECTIONS

Long-term Employment Outcomes After Epilepsy Surgery in Childhood

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In the article "Long-term Employment Outcomes After Epilepsy Surgery in Childhood" by Reinholdson et al.,[1] there is an error in figure 1. The blue box (sixth from the bottom) directly below the green and yellow boxes titled "15-year" should read: "Included: 105 Lost: 16." The authors regret the error.

Reference

1. Reinholdson J, Olsson I, Tranberg AE, Malmgren K. Long-term employment outcomes after epilepsy surgery in childhood. *Neurology* 2020;94:e205–e216.

Quality Improvement in Neurology

Headache Quality Measurement Set

Neurology® 2020;96:969. doi:10.1212/WNL.0000000000011419

In the AAN Special Article "Quality Improvement in Neurology: Headache Quality Measurement Set" by Robbins et al.,[1] author Nathaniel M. Schuster was listed incorrectly in the author list. The publisher regrets the error.

Reference

1. Robbins MS, Victorio MC, Bailey M, et al. Quality improvement in neurology: Headache Quality Measurement Set. *Neurology* 2020;95:866–873.

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