

# Health-Related Quality of Life Compared With Cardiopulmonary Exercise Testing at the Midterm Follow-up Visit After Tetralogy of Fallot Repair: A Study of the German Competence Network for Congenital Heart Defects

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**Abstract** This nationwide study aimed to evaluate health-related quality of life (QoL) experienced by children after tetralogy of Fallot repair and to compare self-reported physical ability with objective exercise performance. This prospective nonrandomized, government-funded multi-center study enrolled 168 patients (70 girls; ages 8–16 years) after tetralogy of Fallot repair at eight German

heart centers. Health-related QoL was analyzed by the self-reported KINDL-R quality-of-life questionnaire. The patients' actual exercise capacity was evaluated by a cardiopulmonary exercise test. Health-related QoL and cardiopulmonary exercise capacity were compared with those of an age-matched German standard population. Correlation of health-related QoL with self-estimated physical rating and cardiopulmonary exercise capacity were analyzed. Health-related QoL in children and adolescents after tetralogy of Fallot repair is without limitation. Compared with the standard population, all the items evaluated by the KINDL-R questionnaire showed better or similar values, whereas objective exercise capacity compared with that of the standard population was impaired. Peak oxygen uptake correlated significantly with the physical well-being ( $p = 0.002$ ) and the total score ( $p = 0.01$ ) of the KINDL-R questionnaire. Health-related QoL experienced by children and adolescents after tetralogy of Fallot repair is comparable with that of the healthy standard population. However, closer inspection shows that self-estimated physical functioning is significantly overestimated compared with actual exercise capacity. Quality-of-life instruments and exercise tests, therefore, should be used in a complementary manner with children to avoid eventually fatal misinterpretation of patient-estimated physical ability.

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Approximately 2.5 % of all infants born with congenital heart disease have a diagnosis of tetralogy of Fallot (TOF) [23]. Before the beginning of surgical repair in the 1950s of the last century, almost half of the patients with TOF died within their first year of life [3, 9].

After significant perioperative mortality at the beginning of surgical repair, mortality rates have decreased steadily over the past 50 years [13–15].

Currently, almost all infants born with TOF can expect survival of surgical repair. The main outcome criteria for these patients has changed from mortality to morbidity. Functional parameters such as residual stenosis, pulmonary regurgitation, right ventricular failure, ventricular arrhythmias, and exercise tolerance have been brought into focus. Changes in TOF management in the 21st century have been guided by these functional parameters after surgical repair adopted in the second half of the 20th century [1].

The term “quality of life” (QoL) was first mentioned in 1920 in economic journals. Initially accepted in social science, the term later was adopted in medicine. Disease-specific QoL measurement was introduced in the 1980s and 1990s [11].

Currently, health-related QoL is an important part of medical research and has become a more important parameter for treatment recommendation [19]. Therefore, different QoL instruments such as the KINDL-R questionnaire have been developed. Little is known about health-related QoL life experienced specifically by children after TOF repair or the relation of self-reported QoL assessments and objective functional parameters measured by cardiopulmonary exercise tests (CPET).

This nationwide prospective study aimed to analyze health-related QoL in a large group of children after TOF repair and to evaluate whether physical functioning self-assessed by the KINDL-R QoL predicts objective physical functioning evaluated by CPET.

## Methods and Patients

### Patient Cohort

From December 2005 to March 2008 the German Competence Network for Congenital Heart Defects conducted a nationwide prospective study of patients after repaired TOF to determine the prevalence and extension of post-operative restrictions. In this observational cross-sectional study, 200 pediatric patients with surgically corrected TOF (including pulmonary atresia with ventricular septal defect) were identified from eight German centers.

This study analyzed patients’ health-related QoL. Self-estimated physical functioning was analyzed by a self-reported QoL questionnaire and compared with patients’ actual objective exercise capacity evaluated by core lab-reviewed CPET. Influences that different types of corrective surgery (transannular patch vs. valve-sparing surgery) had on health-related QoL and cardiopulmonary exercise capacity were compared.

The study was registered, designed, performed, and controlled according to the current guidelines of good clinical practice (title: Follow-up of Post-Repair Tetralogy of Fallot, ClinicalTrials.gov–NCT00266188) and approved by all the ethics committees of the participating centers. Informed written consent was obtained from all the patients or their caretakers.

### QoL

Patients’ QoL was assessed by a self-reported QoL questionnaire for healthy and ill children (KINDL-R). The KINDL-R instrument is a short, self-reporting, easily completed instrument specifically developed to assess age-related QoL in children of different age classes [17]. It is a discriminant, predictive, and evaluative instrument for the measurement of health-related QoL. The test has high acceptance and can be completed by healthy children and those who are chronically or acutely ill.

Since its introduction, the KINDL-R instrument has been used in several epidemiologic and longitudinal studies of children in different age classes [2, 21, 22]. The kid-KINDL-R questionnaire was used for children 8–11 years old and the kiddo-KINDL-R questionnaire for adolescents 12–16 years old.

The KINDL-R questionnaire contains a subjective scoring system using 24 scaled items with scores of 1 (never) to 5 (all the time) among six domains: physical well-being, emotional well-being, self-esteem, family, friends, and everyday functioning during the prior week. Raw scores are converted to a scale of 0 to 100, with higher scores denoting higher health-related QoL. Reference data on the KINDL-R questionnaire was obtained by an assessment of 1,700 German children and adolescents ages 11–17 years reported by Ravens-Sieberer et al. [18].

### Cardiopulmonary Exercise Test

All the patients underwent a symptom-limited CPET on an upright bicycle ergometer or a treadmill ergometer. The CPET adhered to the following protocol. Oxygen uptake was measured breath by breath. Peak oxygen uptake was defined as the highest mean uptake of any 30-s interval during exercise. The end of the CPET was marked by a leveling off in oxygen uptake for 30s as an indication of maximal cardiopulmonary exertion.

Further criteria for terminating the CPET were an increase in heart rate greater than 200 minus age in years, a limitation of breathing reserve, arrhythmia/ischemia, a rise in the respiratory exchange ratio exceeding 1.15, and exhaustion of the patient.

### Cycle Ergometer

The patients underwent a symptom-limited CPET on an upright bicycle ergometer. After a starting load of 0.5 W/kg, the load was increased 0.5 W/kg stepwise every 2 min. The exercise was followed by a recovery period with a load of 0.5 W/kg.

### Treadmill Ergometer

After a 90-s warm-up period with a speed of 2 km/h and a 0 % increase in the horizontal angle of the treadmill, the workload was increased by 2.5-km/h stepwise increases in the walking speed and 3 % increases in the angle every 90s. The limitation of the angle was 21 % without limitation of speed. The exercise was followed by a 90-s recovery period with a speed of 2 km/h and an angle of 0 %.

The bicycle and treadmill data were compared with the reference data of Dubowy et al. [4]. All the exercise reports were reviewed by one expert pediatric cardiologist.

### Statistical Analysis

Data were processed using a standard statistical package (SPSS 15.0, SPSS Inc, Chicago, IL, USA) for Windows software. All data are reported as mean  $\pm$  standard deviation or mean and range. For construction of normalized centiles, the least mean square method was used. For comparison of KINDL-R questionnaire scores and reference values, the two-sided unpaired *t* test was used. For correlation of the peak oxygen uptake with the KINDL-R questionnaire scores, Pearson's correlation coefficients were calculated.

For the primary outcome of the total score for the KINDL-R questionnaire, statistical analysis was performed at a significance level defined as lower than 5 % ( $p < 0.05$ ). For the secondary outcome of the KINDL-R questionnaire subscales (physical, emotional, self-esteem, family, friends, school), Bonferroni's correction for multiple testing was used. For subscales, statistical analyses were performed at a significance level defined as lower than 0.7 % ( $p < 0.007$ ).

## Results

Of 200 pediatric patients with surgically corrected TOF, 29 were excluded because the QoL questionnaire data were not fully completed. Another three patients had to be excluded because their CPET were insufficient. Thus, the study enrolled 168 patients (70 girls and 98 boys) after

TOF repair with a mean age of  $12.6 \pm 2.25$  years (range, 8–16 years).

Chromosome 22q11 deletion syndrome was detected in five patients (limited genetic diagnostics must be considered, especially in older TOF patients). The mean time after surgical repair was  $11.2 \pm 2.36$  years (range, 1.0–16.0 years).

Before corrective surgery, surgical palliation was performed for 28 patients. The mean age at corrective surgery was 0.92 years (range, 0–9 years). Corrective surgery by transannular patch was performed for 79 patients and valve-sparing surgery for 70 patients. For 20 patients, the type of corrective surgery was not clearly documented. Further cardiac operations after corrective surgery were performed for 44 patients, 22 of whom received pulmonary valve replacement. The incidence of reoperation did not differ significantly between the patients corrected by transannular patch and the patients corrected by valve-sparing surgery.

### Subjective QoL

Health-related QoL was fairly good in the whole patient group compared with the healthy standard population, as published by Ravens-Sieberer et al. [18] (Table 1). To compare the results of the KINDL-R questionnaire, the study population was separated into three age groups. Table 1 shows the KINDL-R scores of the 11- to 13-year-olds and 14- to 16-year-olds and their relation to the age-related reference values. The reference values according to the self-reported KINDL-R questionnaire for the 8- to 10-year-olds were not available until currently.

The patients of all age- and gender-related subgroups reported good health-related QoL results. Further on, the group of 11- to 13-year-olds showed significantly higher self-esteem results after TOF repair than the reference group. After TOF repair, the 14- to 16-year-olds exhibited significantly higher physical well-being and everyday function (school) results.

Sex-related differences were identified for only one item. After TOF repair, the boys presented significantly higher scores in the physical well-being dimension. Further items showed similar results between the boys and the girls (Table 2). Neither the total score nor the subscales of the KINDL-R questionnaire showed any significant difference in the health-related QoL between the TOF patients corrected by transannular patch and those corrected by a valve-sparing operation.

### Cardiopulmonary Exercise Test

Of the 168 CPET, 56 were done by cycle ergometer and 112 by treadmill ergometer. All the CPET were performed

**Table 1** Results of the KINDL-R quality-of-life questionnaire in 11- to 13-year old and 14- to 16-year-old tetralogy of Fallot (TOF) patients in relation to their age-related reference values [18]

KINDL-R	11- to 13-year-olds		<i>p</i> value	14- to 16-year-olds		<i>p</i> value
	TOF ( <i>n</i> = 65)	Reference		TOF ( <i>n</i> = 65)	Reference	
Physical	75.4 ± 16.2	74 ± 16	0.51	75.9 ± 18.5	68.5 ± 16.9	<0.01*
Emotional	80.5 ± 14.1	83.2 ± 10.7	0.056	79.5 ± 16.1	80.5 ± 13.7	0.57
Self-esteem	65.5 ± 17.3	56.3 ± 18.5	0.001*	63.8 ± 17.9	59.9 ± 18.1	0.09
Family	82.6 ± 16.7	84.6 ± 13.4	0.26	81.6 ± 17.3	81.1 ± 16.4	0.80
Friends	79.5 ± 16.3	80.9 ± 13.4	0.43	74.6 ± 21.8	75.2 ± 15.0	0.76
School	71.4 ± 16.0	71.8 ± 16.6	0.87	68.8 ± 15.7	64.2 ± 16.4	0.03*
Total	75.8 ± 10.5	75.1 ± 9.3	0.56	74.1 ± 10.9	71.5 ± 10.6	0.06

All items are presented as mean ± SD

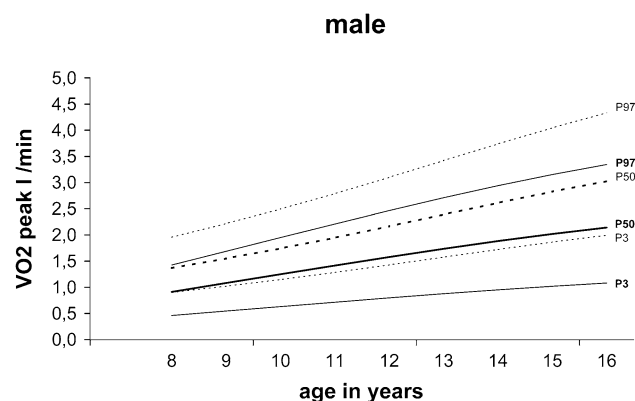
\* *p* < 0.05 was accepted as significant

**Table 2** Results of the KINDL-R quality-of-life questionnaire for 168 patients after tetralogy of Fallot repair related to the patients' gender

KINDL-R	Boys 8–16 years old ( <i>n</i> = 98)	Girls 8–16 years old ( <i>n</i> = 70)	<i>p</i> value
Physical	79.4 ± 14.1	73.7 ± 20.2	0.03*
Emotional	80.4 ± 14.8	82.7 ± 13.7	0.31
Self-esteem	67.2 ± 18.7	63.7 ± 17.7	0.21
Family	81.7 ± 16.0	83.2 ± 15.9	0.54
Friends	77.6 ± 20.4	77.9 ± 15.8	0.91
School	70.8 ± 17.1	71.2 ± 16.1	0.88
Total	76.2 ± 10.6	75.4 ± 11.5	0.64

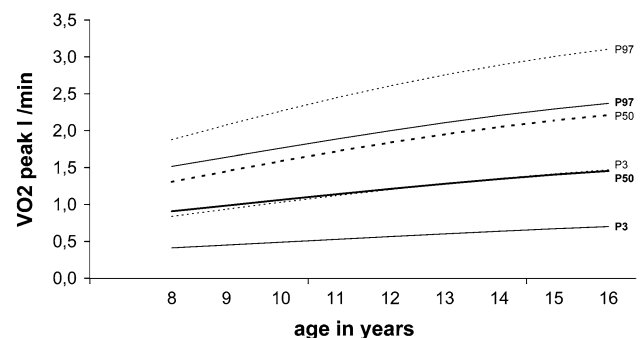
All items are presented as mean ± SD

\* *p* < 0.05, two-sided unpaired *t* test

**Fig. 1** Centiles of male tetralogy of Fallot patients for peak uptake of oxygen (l/min) compared with those of the healthy male standard population. *Solid line*: male TOF patients; *dotted line*: healthy male standard population

without complications. Although some patients showed excellent results, the male and female study population overall had lower centiles (Figs. 1, 2) than the age- and sex-related reference values [4]. The cardiopulmonary

### female

**Fig. 2** Centiles of female tetralogy of Fallot patients for peak uptake of oxygen (l/min) compared with those of the healthy female standard population. *Solid line*: female TOF patients; *dotted line*: healthy female standard population

exercise capacity did not differ significantly between the patients corrected by transannular patch and those corrected by a valve-sparing operation [peak oxygen consumption (peak VO<sub>2</sub>), 35.8 ± 7.7 vs. 34.1 ± 7.4 ml/kg/min; *p* = 0.79].

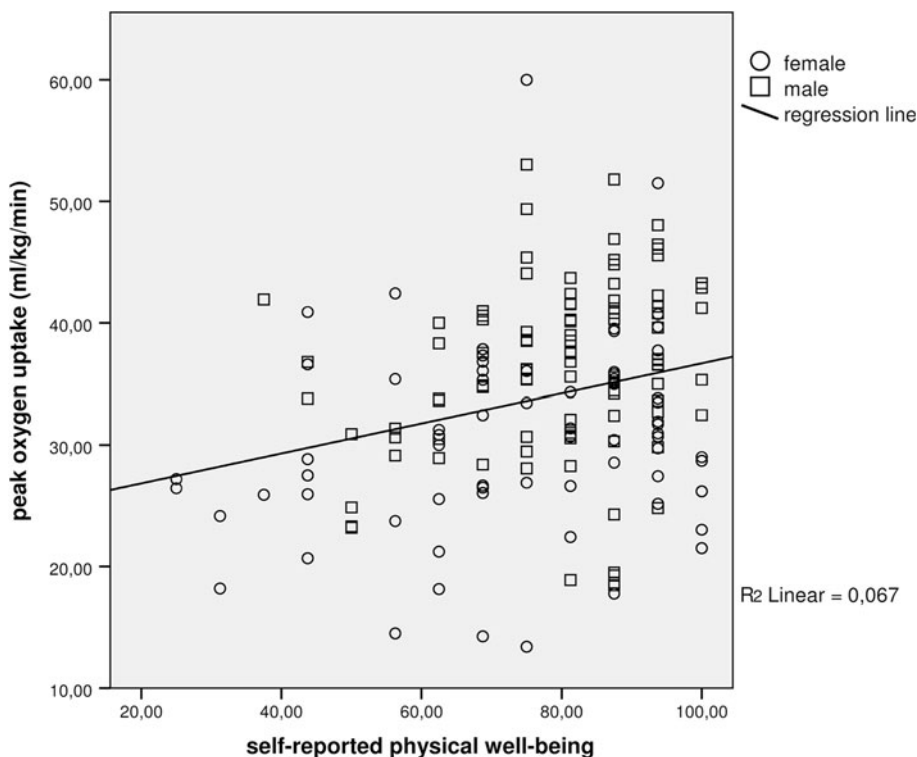
### Correlation of QoL Scores with Cardiopulmonary Exercise Test Results

The findings showed significant correlation of peak oxygen uptake with the scale of physical well-being (Fig. 3) and the total score (Fig. 4) for the KINDL-R questionnaire. No further correlations of the remaining KINDL-R questionnaire scales with the objective CPET were found (Table 3).

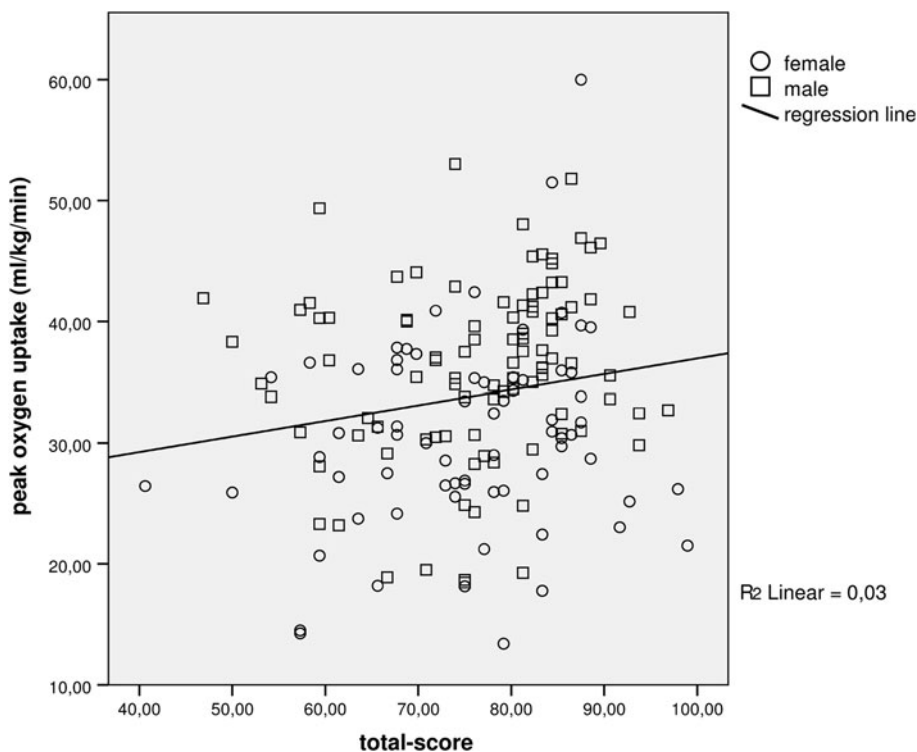
### Discussion

This study shows excellent overall results of QoL for children after TOF repair compared with the reference data

**Fig. 3** Comparison of the self-reported physical well-being score from the KINDL-R quality-of-life questionnaire with peak oxygen uptake from a cardiopulmonary exercise test in 168 patients after tetralogy of Fallot repair ( $p < 0.001$ )



**Fig. 4** Comparison of the total score on the KINDL-R quality-of-life questionnaire with peak oxygen uptake in 168 patients after tetralogy of Fallot repair ( $p < 0.024$ )



obtained by an assessment of German children. For all the diagnostic items of the KINDL-R questionnaire, the study population was similar to the reference population, as published by Ravens-Sieberer et al. [18], or significantly better.

In the psychological domain, the 11- to 13-year-old patients showed significantly higher self-esteem results than the reference group. The 14- to 16-year-old patients showed significantly higher everyday functioning (school)

**Table 3** Pearson's correlation coefficients for subjective quality of life and objective cardiopulmonary exercise capacity (peak oxygen uptake) for 168 patients after tetralogy of Fallot repair

	<i>r</i> value	<i>p</i> value
Total	0.17	0.02*
Physical	0.26	<0.01*
Emotional	0.05	0.55
Self esteem	0.18	0.02
Family	0.15	0.05
Friends	0.02	0.76
School	0.02	0.83

For the primary outcome of the total score

\*  $p < 0.05$  was accepted as significant. For the secondary outcome of subscales (physical, emotional, self-esteem, family, friends, school),

\*  $p < 0.007$  was accepted as significant

than the healthy children. Further psychological QoL dimensions were similar between the patients and the reference data. Published health-related QoL results from the last decade shows similar observations in children, adolescents, and adults after TOF repair tested by the KINDL-R, Child Health Questionnaire–Parent Form 50 (CHQ PF 50) or the Medical Outcomes Survey–Short Form 36 (SF-36) questionnaire [5, 6, 8, 10, 16].

Our data confirm that psychological items in health-related QoL questionnaires are not reduced in pediatric patients with repaired TOF. Health-related QoL did not differ between patients corrected by transannular patch and those who had valve sparing surgery. The long-time adaptation to their cardiopulmonary situation during a medium period of 11.2 years after surgical repair in our study population and the absence of pain or apparent handicaps in patients after TOF repair might explain these findings.

In contrast to these results, Utens et al. [20] published behavioral and emotional problems after surgical correction for congenital heart disease tested by the Child Behaviour Checklist and the Youth Self-Report in 1993. Perhaps improvements in surgical procedures and intensive care medicine or changes in the QoL testing are responsible for this development.

The special interest of this study was focused on the physical item of the KINDL-R questionnaire. Are children after TOF repair able to estimate their physical functioning using the questions asked by the KINDL-R questionnaire?

In our study population, the score for the physical domain of the KINDL-R questionnaire by the 11- to 13-year-olds ( $n = 65$ ) was virtually identical to that by the healthy children. For the 14- to 16-year-olds after TOF repair ( $n = 65$ ), the score for the physical domain of the KINDL-R was even significantly higher than for the reference group. Pilla et al. [16] interviewed a considerably

younger population (medium age, 6.1 years) using the Child Health questionnaire and in a parent-reported questionnaire found a trend of worse physical results for patients after TOF repair compared with the reference data. Published data of adults showed reduced or similar physical items assessed by different health-related questionnaires [5, 6, 10, 12].

We aimed to determine whether children and adolescents completing the KINDL-R questionnaire overestimate their physical fitness and whether they are in better physical condition than adults after TOF repair. To assess the cardiopulmonary fitness of our study population, the peak oxygen uptake, considered to be the best parameter for cardiopulmonary fitness, was analyzed by cardiopulmonary exercise testing [7]. The tests showed markedly lower centiles for peak oxygen uptake in all age groups than in the healthy standard population [4].

Influences of corrective surgery types on cardiopulmonary exercise capacity were not found. This implies an overestimation of physical functioning by the KINDL-R questionnaire for patients after TOF repair.

For adult patients with congenital heart disease, Gratz et al. [5, 6] also described an overestimation in self-reported physical functioning compared with measured aerobic capacity, but objective exercise capacity correlates with some physical aspects of QoL. Complementary use of exercise tests and QoL instruments has been advised for appropriate evaluation of health status in adults with congenital heart disease [7].

Little is known about the relation between self-estimated physical functioning and actual exercise capacity in children with congenital heart disease. In our pediatric study population, a significant positive correlation was found between the physical domain of the KINDL-R questionnaire and peak oxygen uptake [7]. The children with lower exercise ability reported lower QoL scores. Further on, the total score of the KINDL-R questionnaire and peak oxygen uptake also showed a significant positive correlation. Correlations of other items, especially psychological items, with peak oxygen uptake were poor.

According to our understanding, these results underscore the fact that children and adolescents after TOF repair generally are able to estimate their physical functioning, whereas the results of the KINDL-R questionnaire overestimate their physical functioning and do not sufficiently reflect the impaired exercise capacity of the study population in relation to the healthy reference population.

## Conclusion

The health-related QoL in children and adolescents after TOF repair is comparable with that of the standard

population. However self-estimated physical functioning is markedly overestimated compared with actual exercise capacity. Complementary use of QoL instruments and exercise tests with children is therefore recommended to avoid eventually fatal misinterpretation of patient-estimated physical ability.

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**Conflict of interest** None declared.

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