Physical activity in people with epilepsy: A systematic review

Emma Johnson[1,2]

J Helen Cross[1,2,3]

Colin Reilly[1,3]

Affiliations

[1]Research Department, Young Epilepsy, Lingfield, Surrey, RH7 6PW, UK.

[2]Great Ormond Street Hospital for Children NHS Trust, Great Ormond Street, London WC1N 3JH, UK.

[3]UCL Great Ormond Street Institute of Child Health (ICH), 30 Guilford Street London WC1N 1EH UK.

Correspondence to: Emma Johnson, Research Department, Young Epilepsy, Lingfield, Surrey, RH7 6PW, UK. ejohnson1@youngepilepsy.org.uk 01342 832243

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Summary

This study aimed to systematically review studies focussing on levels of physical activity (PA) in people with epilepsy (PWE) compared with non-epilepsy controls, and identify factors associated with PA in PWE. Intervention studies were also reviewed to consider the effects of psychological interventions on levels of PA, and the effects of PA-based interventions on seizure activity, psychiatric comorbidity and health related quality of life (HRQoL). PRISMA guidelines were followed. Searches were conducted using PubMed, Cochrane Controlled Register of Trials, PsychINFO and EMBASE. Forty-six studies met inclusion criteria including case-control, cross-sectional and intervention studies. Assessment measures included questionnaires, activity trackers and measures of physiological fitness. Twelve of 22 (54.5%) case-control studies utilising self-report questionnaire measures reported that PWE were performing lower levels of PA, less likely to be engaging in PA or less likely to meet PA guidelines than controls. The remaining studies did not find a difference between PWE and controls. Eight of 12 (67%) case-control studies utilising exercise/fitness tests reported that PWE performed significantly poorer than controls, whilst in two studies PWE performed better than controls. One of three studies investigating the relationship between PA and seizure frequency found that increased self-reported PA was associated with having fewer seizures, whilst two did not find a significant relationship. All seven cross-sectional studies which included measures of HRQoL and depression/anxiety found a positive relationship between levels of PA and HRQoL/reduced levels of depression and anxiety. All four studies that used PA-based interventions demonstrated improvements in levels of PA and increased HRQoL. Study quality was almost universally low. In conclusion, there is some evidence that PWE engage in less PA than peers, and that interventions can improve PA levels and HRQoL.

However, there is a need for more robust study designs to better understand PA in individuals with epilepsy.

Introduction

Physical inactivity significantly contributes towards poor physical and mental health as well as quality of life and is considered a leading risk factor for mortality[1,2]. In addition to the documented detrimental effects of a lack of physical activity (PA), there is corresponding evidence that suggests that regular PA (or levels of PA that meet established guidelines) has beneficial effects on physical and mental health, cognitive function and HRQoL for both adults[3,4] and children[5,6]. These benefits may be particularly pertinent for people with epilepsy (PWE) as the condition, in both children and adults, is often associated with an increased risk for mental health difficulties[7,8], cognitive impairments[9,10] and impaired HRQoL[11,12].

Individuals with epilepsy face barriers with respect to accessing opportunities for PA due to the perceived increased risk of seizure activity, fear of seizure-related injury and the provision of inappropriate advice from medical professionals[13,14,15]. These concerns, although persistent and pervasive, have been addressed by the International League Against Epilepsy (ILAE) Task Force Report on Sport and Epilepsy[16] which concluded that few sports should be considered off-limits for PWE, provided that appropriate, individualised risk assessment has been undertaken. The report also suggested that contrary to historical belief PA may beneficially affect seizure frequency and severity, and that PA is unlikely to provoke seizure activity even when intensity of physical effort is increased to a point of exhaustion. Despite this, many PWE report experiencing stigma associated with their engagement in PA[17]. In addition to the benefits of PA on physical health, there may be also benefits with respect to HRQoL and mental health for PWE[18].

A previous review[19] focused on the pooled mean time PWE spent physically active, and the pooled percentage of PWE complying with the general population health recommendation of at least 150 minutes of moderate intensity PA per week. This review noted that adults with epilepsy were less likely to comply with PA recommendations than controls and were more inactive, whilst data about PA levels in children were inconsistent. The current review examines PA in individuals with epilepsy in a more comprehensive way by including multiple measures of PA and by considering the effects of study quality on study findings. The primary aims of this review are to compare levels of PA between PWE and people without epilepsy - including general population controls - and identify factors associated with PA in PWE. A further aim is to investigate the effects of psychological interventions on levels of PA and the effects of PA-based interventions on seizure activity, psychiatric comorbidities, and HRQoL by reporting on intervention studies exclusively recruiting PWE. A final aim is to consider the impact of study quality on findings.

Method

The review process was carried out according to PRISMA (Preferred Reporting Items for Systematic Review) guidelines[20]. Literature searches were conducted on 10th May 2019 using the electronic databases PubMed, Cochrane Controlled Register of Trials (CENTRAL), PsychINFO and EMBASE. Combinations of the following keywords were used as search terms: ‘epilepsy’, ‘children’, ‘exercise’, ‘physical exercise’ and ‘physical activity’. The search strategy, including specific combinations of terms searched, is in Supplement 1. Studies were excluded from review if they met any of the predetermined criteria listed in Supplement 2,

which were applied hierarchically. In addition to self-report or activity tracker measures of PA, measures of physiological fitness were also considered representative of PA.

A data extraction form was developed (see Supplement 3) to assist in the identification of main study characteristics and results. The review was registered at https://www.crd.york.ac.uk/prospero/.

Details of all studies included in the review are shown in Table 1 (case-control studies), Table 2 (cross-sectional studies) and Table 3 (intervention studies). For the purposes of this review, case-control studies are defined as studies that feature two discrete groups of participants, with the key characteristic differentiating the groups being the presence or lack of epilepsy diagnosis. The groups must have been compared in terms of levels of PA and/or likelihood of reporting specific barriers to PA. Cross-sectional studies are defined as studies in which all participants have epilepsy, but are categorised based on differences on another variable (e.g. AED taken). The discrete groups are then compared in terms of levels of PA and/or likelihood of reporting specific barriers to PA. Intervention studies are defined as studies in which participants were required to engage with a specific activity over a set period of time, with pre- and post-intervention measures compared to identify changes that occurred over the intervention period. PA may be either the intervention activity, or the dependent variable the intervention is expected to affect. All significant differences, associations or changes reported were significant at the $p<0.05$ level.

Study quality was assessed by two raters (ECJ and CR). Disagreements were resolved by consensus. The quality of case-control studies was assessed using the Newcastle-Ottawa Quality Assessment Scale[21] and cross-sectional studies were assessed using the National

Institute of Health's Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools accessed 18th October 2019). Intervention studies were assessed using the Effective Public Health Practice Project quality rating tool[22]. In some cases, quality assessment criteria needed to be adapted and any adaptions are described in Supplement 4. Overall study quality was rated as good/strong, fair/moderate or poor/weak on the three measures.

Results

The search process is shown in Figure 1. The literature search initially identified 1965 records. After removal of duplicates, 893 records were assessed for eligibility based on title and/or abstract. The remaining 362 articles were subjected to full-paper screening against exclusion criteria (Supplement 2), with 46 articles remaining for review inclusion. During data extraction it was found that two studies[23,24] reported on the same participants engaged in the same intervention, but with data gathered at different times post-intervention. It was decided that both studies should remain in the review as they allow for comparison of intervention outcomes at different follow-up times.

Studies were undertaken in 15 different countries, with the most common being Brazil (10 studies), followed by the USA (nine) and Canada (seven). The total number of participants included in all 46 studies was 715,275, with 7725 having epilepsy. Participants ranged in age from 3 to 82+ years old. Thirteen studies exclusively recruited child participants (aged 17 or younger)[23-35], 22 studies exclusively recruited adult participants (aged 18 or older)[37-57] and 11 studies recruited both child and adult participants[18,58-67]. Across the 41 studies that specified male:female ratio of participants, the proportion of males was 47.93% (range 0-66.7%). One study recruited exclusively female participants[53].

Physical activity in PWE compared to controls

Table 1 shows the 27 case-control studies that compared levels of PA in PWE to a control group (more detailed information on study findings is available in Supplement 5). In 23 studies[27,30,32,34-44,49,60-67] these were general population controls and one study[26] used general population controls and controls with non-neurological conditions. A further study[33] used controls with long-term illnesses or disabilities other than epilepsy and another study used controls with intellectual disability without epilepsy[57]. One study used sibling controls[28]. Matched controls were used in 11 studies[27,30,34,35,40,41,43,61,62,66].

Fourteen studies[26,28,33-35,37-39,42,56,57,60,64,65] exclusively used questionnaires, five studies[30,32,36,49,66] exclusively used exercise/fitness tests and seven studies[40,41,43,44,61,62,67] used both methods of data collection. One study[27] used questionnaires, an exercise/fitness test and a pedometer.

Studies using questionnaire measures

Five studies[35,40,41,57,67] used bespoke questionnaires (created specifically for the study or used for the first time in that study), 16 studies[26-28,33,34,37-39,42-44,60-62,64,65] used standardized questionnaires, and one study[63] used a nationwide lifestyle questionnaire.

Twelve studies reported that PWE were performing lower levels of PA[27,28,33,34,38,61,63], were less likely to be engaging in PA[37,42,57,67], or less likely to meet PA guidelines than controls[26,27,37,39]. In one study[27] this difference was demonstrated through self-report questionnaires but not by pedometer data. In another study[28] this difference was only significant for participants aged 13-17, and only demonstrated by parent-report, not self-report,

whilst in a further study[33] this difference was only significant for PWE not participating in organised sport. Ten studies[26,35,39-41,43,44,60,62,64] did not demonstrate differences in levels of PA between PWE and controls. One longitudinal study[65] reported that the odds of PWE participating in PA decreased over time relative to controls.

Studies using exercise/fitness tests

Seven studies[27,30,36,40,41,66,67] employed standardised protocols. One study[49] asked participants to rest for 20 minutes then exercise at a constant level of 20 minutes whereas the remaining studies[32,43,44,61,62] used non-specified graded incremental exercise tests.

Eight studies reported that PWE demonstrated poorer performance than controls on exercise/fitness tests, quantified as maximal oxygen uptake (VO_{2max})[43,44,61], anaerobic threshold (AT)[61], heart rate recovery (HRR)[66], agility, movement skills and muscular endurance[27], performance on a walking test, muscle strength endurance and flexibility[67], metabolic equivalent of task (MET), chronotropic incompetence, distance walked, Bruce protocol stage and Duke score[40], and performance in tests of muscle power[41]. In two studies PWE performed better than controls on measures of peak systolic Blood Pressure (BP)[66] and peak Heart Rate (HR)[40]. Nine studies[27,30,32,36,40,49,61,62,66] found no differences in exercise performance quantified using varying physiological measures.

Studies identifying factors associated with levels of PA for PWE

Questionnaire measures

Studies reporting factors associated with levels of PA based on questionnaires are summarised in Table 4.

Seizure frequency

One study[47] found that increased PA was associated with having fewer seizures, while one study[27] found no relationship.

Epilepsy type or seizure type

One study[50] found a diagnosis of temporal lobe epilepsy with hippocampal sclerosis to be a predictor of stopping PA due to fear of seizures. Epilepsy type or etiology[27,28] or seizure type[27,28] were not found to be associated with levels of PA in other studies.

AED burden and side effects

Two studies reported that treatment with two or more[48] or three or more[28] AEDs was associated with lower levels of PA but four studies[25,27,41,44] found no association. One study[18] reported that increased AED side-effects were associated with lower levels of PA.

HRQoL, psychological well-being and sleep

Higher levels of PA were associated with better HRQoL in the four studies[18,34,44,50] where it was considered. Higher levels of perceived stigma were associated with lower levels of PA[50]. Participation in school sport was negatively associated with self-esteem[30]. All studies investigating the relationship between PA and depression[18,46,50,64] or anxiety[18,48,64] reported that lower levels of PA were associated with more symptoms of depression or anxiety. One study[18] reported that increased sleep quality was associated with higher levels of PA.

Age and time

One study[27] reported a negative relationship between level of PA and age. However, another study[50] found this relationship to be non-significant. One study[65] reported PA decreasing over time for PWE and odds of participating in PA for PWE decreasing over time compared to controls.

Sport/PA-related factors

One study[33] reported that higher levels of participation in organised sport were associated with higher levels of moderate-to-vigorous PA per day. Another study found performing less PA to be associated with reporting more activity-limited days[37]. Uncertainty about how to begin or proceed with a PA programme, having no one to exercise with, fear of looking stupid or unattractive whilst exercising, and soreness and tiredness after exercising were all associated with increased probability of being classed as 'inactive'[46,48]. Fear that exercise will cause seizures, fear of being embarrassed by a seizure whilst exercising, and being advised by a physician to avoid PA were also associated with increased probability of being classed as 'inactive'[46]. Previous experiences of seizures during PA was associated with inactivity in two studies[46,48], however, one study[45] found this relationship to be non-significant.

Factors not associated with level of PA

Age of epilepsy onset[50] was not found to be associated with levels of PA. No studies found a significant association between epilepsy duration/time elapsed since onset and level of PA[28,41,48,50]. Level of education was not found to be associated with level of PA[50]. One study[41] reported no association between habitual PA and self-reported health.

Exercise/fitness tests

Studies reporting factors associated with performance on exercise/fitness tests are summarised in Table 5. Higher seizure frequency[44], older age of epilepsy onset and AED polytherapy[40] were associated with poorer performance, quantified as METs[40] and VO_{2max}[44] but one study[27] however, did not find seizure frequency or AED burden to be associated with performance. Epilepsy type[27,30], epilepsy duration[27], seizure type[27] and Vagus Nerve Stimulator (VNS) implant side effects[49] were not considered to be associated with performance. Increased age[27], lower BMI[27] and being female[40] were associated with improved performance, as measured by physical competence[27] and METs[40]. One study[31] found that participants with focal epilepsy showed reductions in epi-index scores during exercise (compared to baseline and post-exercise) but no difference was found for those with generalised epilepsy.

Interventions

Effects of interventions promoting physical activity in people with epilepsy

Eight studies[23,29,51-54,56,58] reported the effects of interventions on subsequent levels of PA (see table 3). Two of these studies[29,58] were randomised controlled trials (RCTs) with the control groups consisting of PWE not engaging in the PA-based intervention activity. None of the other six studies[23,51-54,56] used a control group. The interventions used in four studies[23,51,56,58] required participants to engage in regular PA over the intervention period. All of these studies demonstrated improvements in PA across the intervention period[23,51,56,58]. One study utilised a behavioural counselling intervention[29], one study[52] used an educational intervention and required participants to set individual exercise goals, and epilepsy surgery was considered the intervention in the remaining study[54]. None of these forms of intervention affected subsequent levels of PA.

Effects of physical activity interventions on psychological well-being, cognition, behaviour and health-related quality of life

One study[52] reported improvements in scores on depression measures but three studies[23,27,53] did not demonstrate this effect. No changes to scores on anxiety measures were observed in studies where it was considered[23,53]. Improvements in mood state for participants engaged in a PA intervention were demonstrated by one study[58]. This improvement was not demonstrated by the control group. Two studies[23,24], conducted using the same child participants with differing follow-up times, reported improvements in attention and executive function. No changes to prevalence of behavioural problems were observed immediately following the intervention[23] but after a further 30 weeks following a home-based exercise programme there was a reduction in internalising behavioural problems[24]. Four studies[23,24,55,58] reported HRQoL scores improving across the intervention period. Two studies[29,52] showed no differences in HRQoL scores.

Effects of physical activity interventions on clinical aspects of epilepsy

A decrease in seizure frequency with increased PA was demonstrated in three studies[53,55,59], but two studies[31,52] demonstrated no change.

Effects of physical activity interventions on physiological variables

One study[53] reported a decrease in cholesterol and cholesterol:HDL cholesterol ratio across the intervention period, and another study[59] reported a decrease in the number of participants meeting criteria for autonomic dysfunction. No differences were observed in BP or HR[53].

Studies identifying factors associated with intervention outcomes

Increased compliance with PA intervention was associated with decreases in cholesterol, cholesterol:HDL cholesterol ratio and seizure frequency[53].

Study quality

Study quality ratings are shown in Supplement 4. All case-control and cross-sectional studies were awarded overall quality ratings of 'poor/weak' except for six[18,25,27,41,43,48] which were all awarded ratings of 'fair'. All intervention studies were awarded overall quality ratings of 'poor/weak' except for one[29] which was awarded a rating of 'moderate'.

Discussion

The findings of this systematic review indicate that there is some evidence that PWE engage in less physical activity (PA) than their peers, and that interventions can improve PA levels and HRQoL. Many of the studies reviewed indicate that PWE are undertaking less PA than controls without epilepsy, and demonstrate poorer or similar levels of physiological fitness - as evidenced through questionnaire and pedometer measures and exercise/fitness tests. However, a number of studies reported no differences between PWE and controls in terms of levels of PA or physiological fitness. Increased levels of PA in PWE were consistently associated with better mental health and HRQoL. Additionally, increased levels of reported PA for PWE are not associated with increased seizure activity. Interventions that include PA, as opposed to psychological or psychoeducational interventions, increased subsequent levels of PA.

The finding that reduced levels of PA in PWE compared to controls was noted in some, but not all, questionnaire-based studies likely reflects in part the wide range of methods used to measure PA. Despite this variety of methods used, no studies found increased levels of PA in PWE compared to controls, suggesting that physical inactivity may be a significant problem in

PWE. The reduction in levels of PA noted in questionnaire-based studies may be a contributory factor to the lower levels of physical fitness among PWE reported in some studies. Differences in results between studies which have focussed on levels of physical fitness in PWE and controls is again likely to reflect, in part, the heterogeneity of measures used but also how PWE and controls are selected/recruited. In the two studies where PWE were noted to have better levels of PA the measure of PA (systolic BP and peak HR) could be considered proxy measures of PA/fitness and therefore could potentially reflect factors such as use of AEDs as opposed to actual fitness or PA. Given the potential detrimental effects of physical inactivity on physical and psychological wellbeing[68], the lower level of PA reported in the majority of studies is concerning and likely to have significant negative consequences for PWE. Reasons for lowered rates of PA in the epilepsy population are likely to be multifaceted and may reflect to some degree the historical misconception that people with epilepsy need to be cautious regarding engaging in sport and exercise[69].There is limited data on what negative effects inactivity may have in the epilepsy population but there is evidence of an increased bone fracture rate in PWE, and it is known that bone health can be improved with weight bearing PA. PWE report barriers to engaging in PA including fear of injury, lack of social support, stigma and exercise–induced seizures (e.g. through overheating and/or high exercise intensity level)[13]. Importantly, PWE also report that educating others about epilepsy can reduce stigma and potentially lead to increased participation in team and group sports[17].

The positive relationship between reported levels of PA and reduced symptoms of both depression and anxiety is particularly encouraging given the high level of mental health problems in both children and adults with epilepsy[71,72]. This supports findings from studies reporting that abnormalities in certain neurotransmitter systems (including serotonin, noradrenaline and dopamine) are evident in both mood disorders and epilepsy, and that these

neurotransmitter systems can be positively modulated by PA[73]. The positive relationship between levels of HRQoL and levels of PA adds to the evidence that PA is likely to have wide-ranging positive effects in this group. In one study the relationship between PA and activity-limited days was stronger for PWE than controls[37], and in another study[34] the relationship between PA and HRQoL was only significant for PWE, suggesting these positive effects of PA are particularly pertinent for PWE. The lack of significant a negative relationship between seizure frequency and reported levels of PA suggests that PA may not increase seizure activity and may even have a positive effect. Animal models have demonstrated that - due to PA altering neurotransmitter systems responsible for mediating and balancing excitatory/inhibitory activity - habitual PA can delay seizure onset and improve seizure frequency and severity[73]. The lack of a consistent pattern with respect to other epilepsy factors suggests that there may be a 'general epilepsy effect' that contributes to reduced PA in PWE as opposed to a specific clinical aspect. This general epilepsy effect may include fear or stigma in PWE, their families and medical professionals who manage their care.

All interventions that successfully increased levels of PA in PWE required participants to engage in regular PA throughout the invention period, suggesting that structured PA may be a key component of effective intervention. The two interventions based on psychoeducation or counselling were less successful, highlighting the need to include actual physical activities in any programmes. The majority of intervention studies showed an improvement in HRQOL highlighting the beneficial effects of PA in the everyday lives of PWE. Despite the positive association between PA and good psychological well-being noted in case-control and cross-sectional studies, a reduction in these symptoms was not noted in the majority of intervention studies. This may be due to heterogeneity in how these constructs were measured, insufficient follow-up time or participant characteristics (e.g. level of baseline mental health symptoms).

Clinical implications and Future research

Professionals working with PWE can be optimistic in advising that PWE engage in regular PA given the likely benefits to both physical health and HRQoL, and possible reductions in symptoms of mental health conditions. The lack of positive relationship between reported levels of PA and seizure frequency can be used to reassure patients, although there will be a need for careful clinical assessment of the individual risk–benefit ratio. Given the possibility of overprotection, fear and stigma, clinicians should not only ask PWE about their attitudes towards PA but also their views on the opinions of family members and their wider community. Understanding attitudes towards PA may allow clinicians to address fears and reassure both PWE and their families and friends.

With respect to study quality, none of the studies reviewed were rated as 'strong'/'good', prohibiting the reporting of firm conclusions and highlighting the need for more robust designs in future research in this area. The validity of self-report measures should be considered in future studies as the high rates of cognitive impairments observed in epilepsy may affect recall and subsequent self-reporting, and the accuracy of using such measures in this population is yet to be determined. It is possible that differences exist between children and adults with epilepsy with regards to both levels of PA and factors associated with levels of PA. Future studies should look at PA across the age spectrum in order to understand possible differences and develop age-appropriate guidelines. The heterogeneous nature of epilepsy likely contributed to the mixed findings reported in this review, and future research into the relationship between PA and specific epilepsy diagnoses/characteristics is advisable, to investigate if there is a 'general epilepsy effect' or if individual clinical characteristics are influential. Design of future studies needs to include the appropriate selection of representative samples of PWE and - in intervention studies - control participants without epilepsy, in order

to clarify if any outcomes are exclusive or absent in PWE compared to peers without epilepsy. Future research efforts are likely to benefit from utilising agreed protocols and measures regarding the assessment of PA. Given that the relationship between self-reported PA and state of physiological fitness is of low to moderate strength in the general population[74,75], further understanding of this relationship in the context of PWE is needed in order to identify which physiological measures are valid and appropriate in this population. Studies should include measures of the wide range of potential factors associated with PA in epilepsy including epilepsy factors, measures of psychological well-being, cognition, socioeconomic factors and attitudes towards epilepsy among PWE and family members. Regarding future intervention studies, it would be useful to screen potential participants to identify PWE who are currently not engaging in sufficient PA, and thus include participants who actually need to increase their levels of PA. There is also a need for studies to follow participants over longer periods of time to see if gains are maintained and if the effects extend beyond PA levels into psychosocial domains. There is a need for intervention studies to focus on reducing potential stigma around PA in epilepsy. This is likely to mean include educational intervention components aimed at those working in sport facilities and clubs. There is a particular need for more studies in the pediatric population given the few studies that have exclusively focused on children. Finally, there is a need for studies to better understand if PA can significantly impact on epileptic activity and the mechanisms underlying this relationship.

Conclusion

There is some evidence that PWE engage in less PA than controls, and perform less well on measures of physical fitness. Lack of agreement across studies likely reflects the use of a wide range of assessment methods. Increased levels of PA in the epilepsy population would appear to be associated with better HRQoL and psychological well-being. Intervention studies to

improve levels of PA need to include forms of PA. Although no studies reviewed reported increases in seizure frequency relating to PA, it will be important to consider the potential risks of any PA-based intervention activities and ensure that participants' safety is prioritised. There is need for future studies to include both questionnaire measures of PA and activity trackers in representative samples of PWE with appropriate controls. Intervention studies need to include PWE who have low levels of PA and consider a wide range of possible contributors to changes in levels of PA over longer periods in order to better understand how PA can positively impact the lives of PWE.

Key points:

- PWE engaged in less PA than controls in the majority of questionnaire-based studies
- PWE performed less well than controls on measures of physical fitness in the majority of studies where there was a difference
- There was a positive association between level of PA and HRQoL/reduced symptoms of depression and anxiety
- There was no evidence of increased seizure frequency with increased levels of self - reported PA
- PA-based interventions improved PA levels and HRQoL

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Disclosure of Conflict of Interest

None of the authors has any conflict of interest to disclose.

Ethical Publication Statement

We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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