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Bone mineral density and fractures in institutionalised children with epilepsy and intellectual disability

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Abstract

Background Long-term use of antiseizure drugs is associated with a low bone mineral density (BMD) and an increased fracture risk. The literature regarding institutionalised children on chronic antiseizure drugs is limited. Therefore, the aim of this cross-sectional study is to evaluate the prevalence of low BMD and the history of fractures in institutionalised children with epilepsy and intellectual disability (ID).
Methods A dual-energy X-ray absorptiometry of lumbar spine (L1–L4) and hip was performed in 24 children, residing in a long-stay care facility in the Netherlands. Additionally, serum concentrations of albumin, calcium and 25-hydroxyvitamin D were

determined. Data on fractures were retrospectively extracted from the medical files.
Results Ages of the children (14 male and 10 female) ranged from 5 to 17 years with a mean age of 13.0 (±3.2). The criteria of the International Society for Clinical Densitometry (ISCD) were used for classification of bone mineral disorders. Eight (33.3%) children had a normal BMD (Z-score > -2.0). Of the 16 children with a low BMD (Z-score ≤ -2.0), three were diagnosed as osteoporotic, based on their fracture history. Ten children (41.7%) were reported to have at least one fracture in their medical history. Serum concentrations of albumin-corrected calcium (2.28–2.50 mmol/L) and (supplemented) vitamin D (16–137 nmol/L) were within the normal range.
Conclusions This study demonstrated that 67% of institutionalised children with epilepsy and ID had low BMD and 42% had a history of at least one

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fracture, despite supplementation of calcium and vitamin D in accordance with the Dutch guidelines.

Keywords Antiepileptic drugs (AEDs), Bone mineral density (BMD), Children, Dual-energy X-ray absorptiometry (DXA), Epilepsy, Intellectual Disability (ID), Osteoporosis

Background

Epilepsy is one of the most common neurological disorders, affecting people of all ages. Worldwide, approximately 50 million people are diagnosed with epilepsy (WHO 2019). Treatment often consists of life-long therapy with antiseizure drugs. However, antiseizure drugs are shown to be associated with a decreased bone mineral density (BMD) and an increased fracture risk (Vestergaard 2005; Lee *et al.* 2010; Shen *et al.* 2014), especially when used in polytherapy (El-Hajj Fuleihan *et al.* 2008; Fong *et al.* 2018). As the peak bone mass of humans is reached between the age of 20 and 30 years, childhood is a critical period for bone mass development. Exposure to antiseizure drugs during this period may lead to a lower peak bone mass and as a result, an increased fracture risk later in life (Sheth 2004). Children with epilepsy who are institutionalised may be more prone to several other risk factors which could affect BMD, such as feeding difficulties and malnutrition (Henderson *et al.* 2002; Sharawat and Sitaraman 2016), severe neurological impairments (Henderson *et al.* 2002), immobility (Jaffe *et al.* 2005; Tosun *et al.* 2017) and less sunlight exposure (Ko *et al.* 2020). Additionally, BMD is found to be significantly lower among persons with intellectual disability (ID) (Coppola *et al.* 2012; Tosun *et al.* 2017). The literature regarding BMD and fractures in institutionalised children on chronic antiseizure drugs is limited.

Therefore, the aim of this study is to evaluate the prevalence of low BMD and the history of fractures in institutionalised children with epilepsy and ID.

Methods

Participants

This cross-sectional study included children (<18 years) from a long-stay care facility for people with epilepsy and ID in the Netherlands. All children have epilepsy, caused by a variety of factors (i.e. genetic, structural, metabolic, immunologic, infectious or unknown) and some degree of ID, ranging from mild to profound. All children were of the same ethnicity (White).

The study was approved by the local medical ethical committee (METC 16.04), and informed consent was obtained from the legal representatives (in most cases parents) of the children. During measurements, all children were informed verbally and guided by a familiar nurse and/or family member. Procedures were stopped when a child refused to cooperate or showed significant signs of resistance.

Data collection

In November 2016, all 33 children were invited to undergo a dual-energy X-ray absorptiometry-scan (DXA) of hip and lumbar spine (L1–L4) and blood samples were taken. Of these, 26 children (78.8%) participated. The legal representative(s) of two children had refused because of the presence of anxiety/agitation. In the other five children the reasons for refusal were not reported.

Demographic and epilepsy characteristics

Demographic and epilepsy characteristics were collected through the medical records. Demographic characteristics included age (years), sex (male/ female), ID (mild/moderate/severe/profound), Tanner stage (pre-pubertal/pubertal/post-pubertal), weight (kg), height (m), nutritional status (regular food/tube-fed), mobility (not able to walk/walk with aid/walk without aid), current use of calcium, vitamin D and bisphosphonates and Barthel index (0–20).

The Barthel index is a ten-item scale which assesses a person's daily functioning in activities of daily living (ADL). A score of 0 means total dependency on others, and the maximum score of 20 implies complete independency in ADL. As for Tanner stages, the most recent (<6 months) assessments of the paediatrician were used for classification; stage 1 (G1/M1) was classified as pre-pubertal, stages 2 to 4 as pubertal and 5 (G5/M5) as post-pubertal (Marshall and Tanner 1969; Marshall and Tanner 1970). In girls, onset of breast development (M2) before the age of eight was considered as early puberty and after the age of 12 as late puberty. In boys, onset of testicular

enlargement (G2) before the age of nine was considered as early puberty and after the age of fourteen as late puberty (van den Akker 2016). Furthermore, body mass index was calculated by dividing weight by the square of height and was classified using the WHO child growth references 5–19 years. A cut-off score for thinness was a body mass index less than −2*SD*. Overweight and obesity were classified using cut-off scores of > + 1*SD* and > + 2*SD*, respectively (WHO 2007).

All epilepsy characteristics in the medical records had been established by neurologists. All children had been diagnosed with epilepsy in the past, based on the presentation of seizures and/or diagnostic tests. Collected data for this study included cause of epilepsy (genetic, structural, metabolic, immunologic, infectious or unknown), age of onset, duration and current antiseizure drug use.

Bone mineral density

All measurements were made with the same densitometer (Hologic, Discovery A [S/N 80847]). BMD was expressed as the amount of mineral (g) divided by the area scanned (cm²) and as *Z*-scores. *Z*-scores compare data of the children with age-matched, race-matched and sex-matched normative data provided by the manufacturer.

The criteria of the International Society for Clinical Densitometry (ISCD) were used to classify bone mineral disorders (Gordon *et al.* 2014). A *Z*-score equal to or below −2.0 was considered as low BMD.

The diagnosis of osteoporosis was made based on the following criteria (Gordon *et al.* 2014):

- Low BMD (*Z*-score ≤ − 2.0) AND a clinically significant fracture history:
1 Two or more long bone fractures under the age of 10 years; and
2 Three or more long bone fractures under the age of 19 years.

Serum concentrations

Blood samples were taken (simultaneously with periodical laboratory testing in January/February) and serum concentrations of calcium (mmol/L), albumin (g/L) and 25-hydroxyvitamin D (nmol/L) were defined. Serum concentrations of calcium were corrected for albumin if the level of albumin was below 35 g/L.

Fractures

Information on clinical fractures was retrospectively extracted from radiology reports in the medical records. All clinical fractures were classified according to the ICD-10. Fractures of hip/femur (S72.0–S72.2), spine (S12, S22.0–S22.1, S32.0–S32.2, S32.7–S32.8), forearm/wrist (S52) and upper arm/humerus (S42.2–S42.4) were considered as major osteoporotic fractures. No vertebral fracture assessments were performed.

Statistical analysis

Data are presented as means (±*SD*) or as frequencies (percentages). Differences in serum concentrations of albumin-corrected calcium and 25-hydroxyvitamin D between groups (fractures yes/no and low/normal BMD) were compared using the Student *t* test (parametric) or Mann–Whitney *U* test (nonparametric), after checking for normality (histogram, Q–Q plots and boxplot).

All statistical tests were two-tailed with a level of significance of.05. Statistical analyses were conducted using SPSS version 26 (IBM Corporation, UK).

Results

Demographic and epilepsy characteristics

From a total of 26 children, two were excluded due to unreliable scans of hip and lumbar spine (movement during the scans). Therefore, 24 children (14 male and 10 female) were successfully measured by DXA at the hip and/or lumbar spine. In one child, hip measurements were missing due to movement, and in five children, lumbar spine was not measured, due to osteosynthesis material (*n* = 1) or movement during the scan (*n* = 4).

Demographic characteristics are summarised in Table 1. Age ranged from 5 to 17 years (mean 13.0 ± 3.2) and residence duration from 3 months to 12 years (mean 5.1 ± 3.5 years). Four children (16.7%) were wheelchair dependent. The rest were able to walk, with (*n* = 5) or without aid (*n* = 15). None of the children were completely independent in ADL (Barthel index ranged from 0 to 17 with a

Table 1 Demographic characteristics of 24 children with epilepsy and intellectual disability

	n (%)	Mean (SD)
Sex		
Male	14 (58.3)	
Female	10 (41.7)	
Age (in years)		13.0 (3.2)
Duration of residency (in years)		5.1 (3.5)
Intellectual disability		
Mild (IQ 55–70)	2 (8.3)	
Moderate (IQ 40–55)	8 (33.3)	
Severe (IQ 25–40)	8 (33.3)	
Profound (IQ < 25)	6 (25.0)	
Tanner stage		
Unknown	3 (12.5)	
Pre-pubertal	9 (37.5)	
Pubertal	6 (25.0)	
Post-pubertal	6 (25.0)	
BMI category†		
Thinness (< −2SD)	1 (4.2)	
Normal weight	19 (79.2)	
Overweight (> +1SD)	4 (16.7)	
Nutritional status		
Regular food	18 (75.0)	
Regular food (plus tube-fed)	4 (16.7)	
Tube-fed (plus regular food)	2 (8.3)	
Mobility		
Not able to walk	4 (16.7)	
Walk with aid	5 (20.8)	
Walk without aid	15 (62.5)	

†Classification according to the WHO child growth references 5–19 years.

Table 2 Aetiology of epilepsy and the use of antiseizure drugs in 24 children with epilepsy and intellectual disability

		N (%)
Aetiology of epilepsy		
Genetic		12 (50.0)
Structural		3 (12.5)
Infectious		2 (8.3)
Unknown		7 (29.2)
Number of antiseizure drugs		
One		4 (16.7)
Two		7 (29.2)
Three		7 (29.2)
Four		6 (25.0)
Enzyme inducing†		
Strong	Carbamazepine	1 (4.2)
Phenobarbital	1 (4.2)	
Weak	Oxcarbazepine	2 (8.3)
Topiramate	7 (29.2)	
Non-enzyme inducing†		
	Acetazolamide	1 (4.2)
	Clobazam	11 (45.8)
	Clonazepam	1 (4.2)
	Ethosuximide	1 (4.2)
	Lamotrigine	4 (16.7)
	Levetiracetam	7 (29.2)
	Perampanel	3 (12.5)
	Stiripentol	2 (8.3)
	Valproic acid	19 (79.2)
	Zonisamide	4 (16.7)

†Antiseizure drugs are used in various combinations: due to polytherapy and/or the use of both enzyme and non-enzyme inducers, total numbers add up to more than 100%.

median of 8.5). In all six children (25.0%) with a feeding tube, tube feeding was used in combination with regular food. One child was diagnosed with early puberty. As for bone status, none of the children were previously diagnosed with osteoporosis or treated with bisphosphonates.

Age of onset of epilepsy ranged from birth to 4 years and 4 months (mean 1.3 ± 1.3 years). Duration of epilepsy, at the time of the study, ranged from 4 years to 17 years and 4 months. All children were on antiseizure drugs (Table 2; mean number of drugs 2.6 ± 1.1). Four children (16.7%) were on monotherapy [valproic acid (2×), topiramate and oxcarbazepine]. Eleven children (45.8%) were prescribed one enzyme-inducing antiseizure drug and 22 (91.7%) were prescribed one or more non-enzyme-inducing drugs.

Bone mineral density

Based on the Z-scores (Table 3), eight children (33.3%) had a normal BMD, and 16 children (66.7%) a low BMD (Z-score ≤ − 2.0). In view of the fracture history, three of the latter group (12.5%) were considered as osteoporotic according to the criteria of the ISCD (Gordon *et al.* 2014). They were 8, 10 and 17 years old at the time of BMD measurements.

Serum concentrations

Except for one child, all (95.8%) were on vitamin D supplementation at the time of the study with a mean duration of 4.7 years (±3.1). Ten children used a combination of vitamin D and calcium. In one child (4.2%), albumin was below 35 g/L. Mean serum concentration of albumin-corrected calcium and

Table 3 Bone mineral density (BMD) and Z-scores (*n* = 24)

	n	**BMD (in g/cm^2)** Mean (*SD*)	**Z-score** Mean (*SD*)	**Low BMD (Z-score ≤ −2.0)** *n* (%)
Lumbar spine (L1–L4)	19	0.725 (0.151)	−1.0 (1.3)	4 (21.1)
Femoral neck	23	0.594 (0.116)	−2.5 (1.2)	15 (65.2)
Total hip	23	0.667 (0.142)	−2.3 (1.2)	15 (65.2)
				16 (66.7)
Total				

25-hydroxyvitamin D were 2.41 (±0.06) mmol/L and 87.2 (±33.3) nmol/L, respectively. Three children had a 25-hydroxyvitamin D concentration below 50 nmol/L (16, 41 and 48 nmol/L). One of them (41 nmol/L) was not on vitamin D supplementation at the time of the study. The child with the lowest serum concentration had a normal BMD and no historic fractures.

Serum concentrations of albumin-corrected calcium and 25-hydroxyvitamin D did not differ between children with a low or a normal BMD, and no differences in serum concentrations were found between children with and without fractures.

Fractures

Ten children (41.7%) were reported to have had at least one fracture in their medical history. According to the medical files, seven children had suffered one fracture [humerus, forearm (3×), femur, lower leg and toe], one child had suffered two fractures (finger and toe) and one child nine fractures [forearm, thumb, fingers (3×), lower leg, talus, foot and great toe]. One child had sustained multiple fractures, caused by a trauma incident, but they were not further specified. Of the eight children diagnosed with a normal BMD, one child (12.5%) had a history of fracture vs. nine of the sixteen children with a low BMD (56.3%).

Three fractures had been caused by an accidental trauma (16.7%); one finger had been fractured during a ballgame, one finger had been caught between the door and one foot had been fractured by bumping it to a doorframe. Seven fractures (38.9%) had been caused by a fall (humerus, forearm (3x), thumb, femur, lower leg), of which at least three (forearm, thumb, lower leg) were the result of a seizure. Circumstances of the eight remaining fractures (forearm, finger (2x), lower leg, talus, great toe, toe (2x)) were not reported (44.4%).

Five fractures (27.8%) are considered as major osteoporotic fractures, based on their locations (humerus, forearm (4x)). Four of these five (the cause of one fractured forearm was unknown), had been caused by a low-level fall from standing height or less.

Discussion

In this study, we found a high prevalence of low BMD (67%) and historic fractures (42%) in institutionalised children with epilepsy and ID.

The total number of fractures during lifetime, though, might be slightly underestimated as all children lived at home before they moved to the care facility. Age at admittance in the care facility ranged from 1.0 to 13.8 years. Fractures (especially minor ones) that occurred before institutionalisation may not have been documented in the medical files. Nevertheless, at least 41.7% of the children had suffered from one or more fractures during their lives. This is higher than what Simm *et al.* (2017) found (34.8%) in children with at least 1 year of antiseizure drug exposure, but they excluded children who suffered from neurodevelopmental disorders or immobility. Overall, in the Netherlands, the incidence of fractures in children between 6 and 16 years of age is estimated at 40% for males and 28% for females (Federatie van Medisch Specialisten 2019). In our study, those percentages were 50% and 30%, respectively. However, three-quarter of our study participants has not yet reached the age of 16. In addition, the peak of fractures for males lies around the age of 15 and for females around the age of 12 (Verhaar and van Mourik 2008). Half of our study participants (eight males younger than 15 and four females younger than 12) have not yet reached the age of peak

fracture incidence. This implies that it may be expected that the proportion of children with a fracture until the age of 16 in our cohort will further increase.

In our study, circumstances of eight fractures were not reported. In those cases, we are not able to differentiate between low and high impact fractures. Overall, based on the locations, five fractures (27.8%) were considered major osteoporotic fractures. The other had been minor fractures, involving mainly fingers and toes. In children that already suffer from multiple physical disabilities, even minor fractures may have a major impact on daily living and cause pain, discomfort, stiffness and further limitations.

In the study of Shiek Ahmad *et al.* (2012), half of the falls (49%) had been caused by a seizure and about one-third of the fractures (31%) in persons on antiseizure drugs had been seizure-related. In our study, seven fractures were reported to be caused by a fall (38.9%). At least three of these falls had been the result of a seizure. Presumably, many seizures go unwitnessed and it is difficult to determine whether a fall is seizure-related or not. For this reason, it is hard to determine whether a fracture is a result of a seizure or of the fall itself. Grzonka *et al.* (2019) performed a systematic review of the literature regarding fractures as a direct consequence of convulsive seizures in adults and identified 39 studies. Most frequently reported in these studies were bilateral posterior fracture-dislocations of the shoulders, thoracic and lumbar vertebral compression fractures, skull and jaw fractures and bilateral femoral neck fractures. In our study, none of these fractures were reported, suggesting that the fractures might be more likely to be a consequence of the fall, rather than the seizure itself although seizure-related fractures may occur at other locations in adults than in children.

Gniatkowska-Nowakowska (2010) observed a group of 126 children with epilepsy. During 5 years, 17% of the children on monotherapy had suffered a fracture, vs. 49% of the children on add-on therapy. In our study, percentages of children with fractures for mono- and polytherapy were 25.0 and 45.0% respectively, but this should be interpreted with caution due to the small number of children on monotherapy in our study ($n = 4$).

The combination of bone mineral disorders (osteopenia/osteoporosis) and the use of antiseizure drugs has first been described around 1970 (Dent *et al.* 1970; Linde *et al.* 1971; Hahn 1976) and

included cytochrome P450-inducing antiseizure drugs, such as carbamazepine, phenobarbital, phenytoin and primidone. But also newer antiseizure drugs with minimal or no enzyme-inducing effects seem to have an effect on bone metabolism, even though not all results are consistent (Fan *et al.* 2016; Diemar *et al.* 2019; Mitta *et al.* 2019). In our study, no conclusions can be drawn regarding the effects of enzyme-inducing vs. non-enzyme-inducing drugs, as only one child used carbamazepine and one child phenobarbital. The rest of the children were on antiseizure drugs with minimal (topiramate/oxcarbazepine) to no enzyme-inducing effects.

A low BMD was found in 67% of the children. In the same care facility, the prevalence of low BMD in adults was 80%, and one-third was diagnosed with osteoporosis (Beerhorst *et al.* 2013). As childhood is a critical period for bone mass development, the proportion of children with low bone mass (67%) or osteoporosis (12.5%) is alarming. Similar percentages of children on antiseizure drugs with osteoporosis were found by Gniatkowska-Nowakowska (2010) (7.1%) and Coppola *et al.* (2009) (14.6%), although both studies applied different classification methods and did not include fracture history in the diagnosis.

A complicating factor in diagnostics is the accuracy of the DXA scans. Mergler *et al.* (2012) studied a group of children with severe neurological impairment and ID and found a mean number of 5.3 distorting factors and artefacts per child. The most frequently occurring factors they identified were movement during measurement, scoliosis, contractures, gastrostomy catheters, aberrant body composition and a height below the fifth centile for age. In our study, two children were excluded due to movement during the scans, 10 children had a form of scoliosis, six children had a gastrostomy catheter and five children had a height below the fifth centile. The presence of contractures and aberrant body composition were not reported or assessed in our study. However, one child was diagnosed with early puberty which could have affected the results of the DXA. As distorting factors and artefacts can lead to both overestimation and underestimation of BMD, it is uncertain how this influenced the outcomes in our study. Most of the factors that were identified will be more likely to affect BMD of the spine than BMD of the hip.

In a meta-analysis including nine studies, a significant association was found between antiseizure

drug treatment and a decreased 25-hydroxyvitamin D, in persons without vitamin D supplementation (Zhang *et al.* 2015). In our study, 25-hydroxyvitamin D levels had been measured in the middle of the winter, when they are at the lowest, and we identified only three children with a level below 50 nmol/L. The rest of the children had a sufficient level of serum vitamin D (56–137 nmol/L), but it has to be noted that except for one child, all (95.8%) were on vitamin D supplementation at the time of the study. The higher tendency for vitamin D supplementation may be explained by a previous study undertaken in the care facility. Between 2012 and 2014, Snoeijen-Schouwenaars *et al.* (2015) studied the effects of vitamin D supplementation. Some of the children participated in that study, as well as in the current study. Presumably, the previous study led to an increased awareness among general practitioners regarding supplementation. Vitamin D supplements were prescribed, as part of standard care, in doses which were at least equal to the amount recommended by the Dutch guidelines. Eight fractures (44.4%), in four children, occurred after the prescription of vitamin D (ranging from 8 months to 9 years and 4 months).

Serum concentrations of albumin-corrected calcium (2.28–2.50 mmol/L) of the children were within the normal range, similar with the findings in other studies (Gniatkowska-Nowakowska 2010; Rauchenzauner *et al.* 2010; Serin *et al.* 2015). However, those studies excluded institutionalised children or children with physical and/or intellectual disabilities.

Limitations

Despite our best efforts to contribute to the literature regarding BMD and fractures in institutionalised children on chronic antiseizure drugs, we acknowledge several limitations of our study.

First of all, it was a cross-sectional study at a single institute. The number of participants was small and they represent a complex, heterogeneous population with differences regarding sex, age, nutritional status, mobility, type and number of antiseizure drugs, and so forth. As all children have a different background and medical history, we cannot rule out additional factors that may have affected BMD and/or the number of fractures, such as the influence of genetic syndromes and comorbidity, or the possibility of physical abuse before institutionalisation. Due to these uncertainties in background and medical history and the heterogenicity of our study group, our findings may not be completely generalisable to other institutionalised children with epilepsy and ID.

Although the main focus of our report was on the chronic use of antiseizure drugs, we emphasise the multifactorial nature of the causes of osteoporosis and recognise several other risk factors in our study group, for instance, physical activity. Nine children (37.5%) were not able to walk independently, and the median score on the Barthel index was 8.5. Even though these parameters do not necessarily reflect a child's activity level, they may imply a lower physical activity.

Despite limitations regarding heterogenicity of the study group and generalisability, our results should be taken seriously. Screening of BMD in children with epilepsy is not part of routine care in the Netherlands. Although a DXA could be helpful to identify children who are at risk for fractures, it should only be performed when the results impact further treatment. However, there is a lack of evidence regarding treatment of low BMD in children. In adults, the first-choice treatment for low BMD (T score $\leq - 2.5$), is the use of bisphosphonates (CBO 2011). For children, caution is advised with regard to prescribing bisphosphonates, due to the limited data on the (late) effects and the duration of treatment (Saraff and Hogler 2015; Simm *et al.* 2018). Consequently, prophylactic bisphosphonate therapy (treating low BMD in the absence of fractures) is not recommended (Simm *et al.* 2018).

Regardless of DXA results, it is advised to take safety measures to prevent falls and to educate caregivers. These interventions, as well as a careful (re-)evaluation of prescribed antiseizure drugs and the feasibility of lifestyle changes, should be part of the care plan. In order to optimise bone health in children who are at risk of fractures, physical activity, especially weight-bearing exercises (Gunter *et al.* 2012) and an adequate calcium and vitamin D intake remain important (Ko *et al.* 2020). But above all, more research is needed towards optimal treatment options. We undertook this study to contribute to the literature and to raise awareness about the risk of bone mineral disorders in children on chronic antiseizure drugs.

Conclusion

The prevalence of a low BMD in institutionalised children with epilepsy and ID is found to be high (67%). Osteoporosis might already be present at a very young age (the youngest in our study was 8 years), despite vitamin D supplementation in accordance with the Dutch guidelines. This study emphasises the need for more understanding of this complex population, in order to adequately manage bone mineral problems. Further research in a larger population, with more accurate fracture data and a focus on treatment is needed, to gain more insight and establish optimal treatment options in children who are at risk of bone mineral disorders.

Conflict of interest

J. v. d. B. has received research funding from UCB, Eli Lilly and Amgen not related to the work presented in this paper. The other authors have no conflicts of interest to disclose. 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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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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