

SUPPLEMENTAL FIGURE 1 Study details of the ketogenic diet and quality of life¹

Study detail	Study design	Study objectives	Participants	Results	Study limitations
1. Bergqvist et al. (2) Children’s Hospital of Philadelphia	Descriptive, longitudinal (15 mo)	KD, vitamin D status [25(OH)D and 1,25(OH)D concentrations]	<ul style="list-style-type: none"> • <i>n</i> = 45 children with IE • Age at enrollment: (5.1/ 2.7)^ay • 12 girls • 33 boys • Low 25(OH)D due to AEDs 	<ul style="list-style-type: none"> • KD for 3 mo increased 25(OH)D by 8 ng/mL, <i>P</i> < 0.001 • KD for 3–15 mo: 25(OH)D declined by ~0.5 ng/mL (<i>P</i> = 0.003) • Baseline: parathyroid hormone concentrations positively associated with age and number of AEDs; no significance for 1,25(OH)D • Vitamin D supplementation improves vitamin D status over first 3 mo • Suboptimal growth and sedentary or low active life correlated with energy requirement 	<ul style="list-style-type: none"> • Diet adherence not mentioned, dropout rate and reasons not discussed • QoL associated with low growth, low activity, and overall EER not discussed
2. Bergqvist et al. (26) Children’s Hospital of Philadelphia, PA	Comparison study (15 mo)	KD and bone health in children with IE, compared with healthy children	<ul style="list-style-type: none"> • <i>n</i> = 48 started at enrollment, subsample <i>n</i> = 25 used for results • <i>n</i> = 847 control group • Age at enrollment: (7.3/1.9)^a y • 16 girls • 9 boys 	<ul style="list-style-type: none"> • BMC significantly reduced in the whole body and spine and after correction for both age and height, <i>P</i> < 0.001, and with prescribed vitamin D and Ca supplements • Serum vitamin D suboptimal in patients on KD • BMC negatively correlated with younger age at start of KD and with low BMI, nonambulatory 	<ul style="list-style-type: none"> • Diet adherence not mentioned • We calculated 48% dropout rate • Reasons for dropout not discussed • Weight bearing and physical activity not controlled for but positively associated with BC
3. Carabello et al. (20) Garrahan Hospital and Italian Hospital in Buenos Aires, and Centro de Neurociencias del Litoral in Santa Fe, Argentina	Retrospective study with multicenter collaboration	Efficacy and tolerability of KD for different epilepsy syndromes	<ul style="list-style-type: none"> • <i>n</i> = 216 with IE despite 2–3 AEDs • Age at KD implementation: (1–18)^b y • Excluded: liver, kidney, heart, gastrointestinal, psychiatric diseases, and progressive encephalopathy with/without metabolic markers, except those metabolic diseases in which KD is used as a treatment 	<ul style="list-style-type: none"> • 140 (65%) remained on the KD through the full the study • 29 (20.5%) became seizure-free, and 50 (36%) had 75–99% decrease in seizures. 56% had seizure control of >75% • Of the 29 seizure-free patients, 20 discontinued the KD, but seizures recurred • KD should be considered early in myoclonic astatic seizures, Dravet syndrome, cryptogenic Lennox–Gastaut, and West syndrome • KD discontinued due to: <ul style="list-style-type: none"> • seizure freedom for >2 y (14%) • seizure reduction of >50% for >2 y (28%) • severe toxicities (5%) • inability to adhere to diet (10%) • lack of efficacy (8%) • patient or family request (8%) • 5 patients died from pneumonia (2), sepsis, status epilepticus, unknown 	<ul style="list-style-type: none"> • Comorbidities not controlled for • Death of 5 patients indicates variable health status at entry • No QoL measures or factors • Families requested exit and inability to adhere to diet indicates burden • Retrospective design • Length of time required to be classified as seizure-free not defined

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SUPPLEMENTAL FIGURE 1 (Continued)

Study detail	Study design	Study objectives	Participants	Results	Study limitations
4. Christodoulides et al. (22) London, UK	Two-group RCT and pairwise comparisons with baseline	Assess risk of micronutrient deficiency in children treated with classical or MCT KD by measuring plasma vitamin A and E, Zn, Se, and Mg concentrations at baseline, 3, 6, and 12 mo	<ul style="list-style-type: none"> • $n = 145$ enrolled into RCT with results from $n = 91$ [classical: $n = 46$ (21 female; 25 male); MCT: $n = 45$ (21 female; 24 male)] • Orally fed (classical: $n = 37$; MCT: $n = 41$) • Gastrostomy fed (classical: $n = 5$; MCT: $n = 3$) • Oral and gastrostomy fed (classical: $n = 4$; MCT: $n = 1$) • Age at enrollment: (2–16)^b y 	<ul style="list-style-type: none"> • Classical KD group (baseline to 12 mo)—vitamin A: 1.41 to 1.13 $\mu\text{mol/L}$, $P < 0.001$; vitamin E: 22.7 to 33.2 $\mu\text{mol/L}$, $P < 0.001$ • MCT (baseline to 12 mo) vitamin A: 1.52 to 1.81 $\mu\text{mol/L}$, $P < 0.001$; vitamin E: 22.3 to 23.3 $\mu\text{mol/L}$, $P < 0.05$ • Both (baseline to 12 mo) Se: 0.95 to 0.88 $\mu\text{mol/L}$, $P < 0.05$; Mg: 0.87 to 0.83 $\mu\text{mol/L}$, $P < 0.001$ • Zn: no change 	<ul style="list-style-type: none"> • We calculated 37% dropout rate • Reasons for dropout not discussed • Micronutrient interaction not measured • Selenium not measured
5. Coppola et al. (27) Epilepsy Unit of the Clinic of Child Neuropsychiatry, Second University of Naples, Naples, Italy	Comparison observational study	KD and endothelial function, arterial morphology, and cardiac diastolic function in children with IE	<ul style="list-style-type: none"> • $n = 23$, control $n = 20$ • Age at enrollment: (11/8)^ay • 12 girls • 11 boys • 3 excluded because they did not attend all examinations 	<ul style="list-style-type: none"> • Patients had significantly higher Alx, β-index, and blood cholesterol concentrations vs. controls, $P < 0.001$ • No increased carotid intima thickness vs. controls (NS) • Age, gender, AEDs, BMI, plasma glucose, and serum creatinine did not affect arterial stiffness • β-Stiffness and total blood cholesterol correlated ($P < 0.05$) • Alx values and serum triglycerides, $P < 0.001$ 	<ul style="list-style-type: none"> • Side effects of KD and patient/family tolerance not discussed • Dropout rate not documented • Neither QoL nor factors measured
6. Dressler et al. (21) Austria	Qualitative, retrospective case series	Evaluating long-term efficacy/tolerability of KD in IE	<ul style="list-style-type: none"> • $n = 52$ • Age at enrollment: (4.5/3.55)^ay • 28 girls • 22 boys 	<ul style="list-style-type: none"> • $n = 52$; 2 dropped out after 6 d of KD by refusing meals, • 50% of patients responded to KD: EEG background activity improved ($P = 0.014$) and there was a lower rate of epileptic discharges ($P = 0.009$) • 28% had side effects • KD effective if initiated early • Effective with multiple seizure types, and generalized tonic clonic seizures • Favorable treatment outcome associated with shorter disease duration ($P = 0.025$) and GTC seizures ($P = 0.059$) 	<ul style="list-style-type: none"> • Patients left study refusing meals, which shows the difficulty of KD prescribed diet • Retrospective design • Length of time to be considered seizure-free not defined

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SUPPLEMENTAL FIGURE 1 (Continued)

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7. Hallböök et al. (33). Sweden	Quantitative observational study, longitudinal (12 mo)	Sleep patterns in correlation to KD, seizure severity and frequency, QoL, attention, and behavior; in children, IE, QoL was measured with a visual analog scale, parent's feedback of child behavior and attention assessed with child behavior checklist	<ul style="list-style-type: none"> • $n = 18$ • Age at KD implementation: (7.5/2-15)^c y • 9 girls • 9 boys 	<ul style="list-style-type: none"> • 18 participants examined at 1 and 3 mo • 11 participants (61%) left at 12 mo • KD induced a decrease in total sleep ($P = 0.05$) and total night sleep ($P = 0.006$); REM sleep increased ($P = 0.01$) • Seizure frequency reduction at 3 mo ($P = 0.001$) and 12 mo ($P = 0.003$) • QoL improved after 3 and 12 mo ($P < 0.001$, $P = 0.005$), and increased REM sleep was correlated with improved QoL (Spearman $r = 0.6$, $P = 0.01$) 	<ul style="list-style-type: none"> • Sleep is variably affected by epilepsy and seizures; wide variations before KD • Confounder sleep is protective and triggers seizure • Lack of generalizability • Parental reports may have subjective bias
8. Hawkes et al. (23) Children's Hospital of Philadelphia, PA	Case series, retrospective chart review	Describe 3 children who developed hypercalcemia while on KD	<ul style="list-style-type: none"> • $n = 3$ • Age at enrollment: (2.5–5.5)^b y • Patients on KD for 6–12 mo 	<ul style="list-style-type: none"> • Suggests an association between KD and hypercalcemia • KD may impair osteoblast activity, prevent reuptake of Ca • Each patient had elevated Ca concentrations, normal phosphate, moderately elevated urinary Ca excretion, and low alkaline phosphatase, parathyroid hormone, and 1,25(OH)D 	<ul style="list-style-type: none"> • Diet adherence not mentioned, dropout rate and reasons not discussed • Only 3 subjects on variable time period • Limited generalizability • Retrospective chart review may have missing data
9. Kim et al. (30) Yonsei Medical Center in Seoul, Korea	Retrospective chart review comparing z scores for height, weight, and BMI at baseline, 2 y of KD, and 1 y after KD	Assess growth delay in children; verify catch-up growth 1y after KD; define association between growth and patient characteristics, i.e., ambulatory status, seizure outcome, and age of KD start	<ul style="list-style-type: none"> • $n = 40$ • Age at KD implementation: (0.58–15.52)^b y • 20 girls • 20 boys 	<ul style="list-style-type: none"> • Compared with baseline: height significantly reduced ($P = 0.000$) with 2 y of KD; no difference 1 y after weaning ($P = 0.569$); significant weight drop at 2 y of KD ($P = 0.004$); no difference 1 y after weaning ($P = 0.060$) • Significant catch-up growth 1 y after KD • Catch-up growth positively associated w/ambulation; negatively associated w/early age of KD start and IE 	<ul style="list-style-type: none"> • Retrospective design; missing data • Diet adherence not mentioned • Dropout rate and reasons not discussed

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10. Kossoff et al. (11) The Johns Hopkins Hospital, MD	Single case report	Patient with tuberous sclerosis complex and epilepsy on KD for 21 y	<ul style="list-style-type: none"> • $n = 1$ (male) • Followed from 6y_{oa}–26y_{oa} • Subject began 3:1 KD at 6 y of age, switching to 4:1 KD after 1 mo 	<ul style="list-style-type: none"> • Current meals now range from 2:1 to 4.6:1 with consistent annual urine ketones at 160 mg/dL • Longest known duration of individual continuous adherence to KD at time of publication • Seizures have been reduced to once annually • Minimal adverse effects: no reported kidney stones, constipation, acidosis, fatigue, or bone fractures • Adverse effects: shorter height, mild hypocholesteremia, hypocarnitinemia (asymptomatic) 	<ul style="list-style-type: none"> • Limited generalizability • No cause-effect relation • Danger of overinterpretation • Publication bias • Retrospective design • Longest duration of KD not attributed to anything; lack of understanding why adherence for so long
11. Lambrechts et al. (32) Netherlands	Comparison study (6 mo), quantitative through use of parent report questionnaires and cognitive- oriented psychological tests	Effects of KD on cognition, mood, and social behavior in children with IE	<ul style="list-style-type: none"> • $n = 15$ • Age at KD implementation: (12/3.6)^ay 	<ul style="list-style-type: none"> • No results on a statistically significant level • Dropout rate 27% ($n = 4$) due to low treatment efficacy for seizure control ($n = 3$) and increased seizure frequency with behavior issues ($n = 1$) • 33% ($n = 5$) had >50% seizure reduction • 40% ($n = 6$) remained on the KD with <50% seizure reduction but had improved alertness and seizure control • Cognition levels showed a small trend of improvement, with a slight decrease in psychosocial adjustment and an increase in mood problems 	<ul style="list-style-type: none"> • Parental reports of seizures may have subjective bias, may miss absent seizures • Small sample size • No control group, pre-/posttest used

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SUPPLEMENTAL FIGURE 1 (Continued)

Study detail	Study design	Study objectives	Participants	Results	Study limitations
12. McNamara et al. (29) Michigan	Qualitative questionnaires based on chart review within past 10 y	<ul style="list-style-type: none"> To assess medical and psychosocial factors of “successful” KD treatment Successful treatment = discontinuation of KD once seizure-free or clinically indicated 	<ul style="list-style-type: none"> n = 82 parent questionnaires sent Age at epilepsy diagnosis: (0–4.7)^by 	<ul style="list-style-type: none"> (30%) 25 returned questionnaires with 2 incomplete 14 of 23 patients considered successful treated with KD Lower seizure frequency before KD initiation ($P = 0.02$) and post-diet seizure improvement ($P = 0.01$) associated with increased odds of success Family reported challenges: time to prepare food ($n = 11$), diet too restrictive ($n = 9$), no support network ($n = 7$); having someone to call such as a family with KD experience would be helpful Information parents wished they knew before starting KD: how much the KD affected family ($n = 9$), side effects ($n = 8$), supplies needed for KD ($n = 6$), time to prepare meals ($n = 6$) 52% ($n = 12$) became seizure-free or had frequency reduction $\geq 95\%$ with the KD, 26% ($n = 6$) observed no change to seizure control, 22% ($n = 5$) saw seizure reduction $\leq 50\%$ Reasons for KD discontinuation: seizure freedom ($n = 4$), no improvement with treatment ($n = 5$), adverse effects ($n = 3$) 	<p>Low response rate unexplained:</p> <ul style="list-style-type: none"> Parent response to questionnaires may have subjective bias, may miss some seizures Length of time to seizure freedom not defined Most participants were Caucasian and on Medicaid Surveys returned primarily by mothers, fathers may have had different perspective
13. Raju et al. (25) India	Quantitative, randomized comparison (3 mo)	Compare efficiency and feasibility of a 2.5 g:1 g (fat:carbohydrate/protein) vs classic 4:1 KD	<ul style="list-style-type: none"> n = 38 with ≥ 2 seizures/mo despite adherence to > 2 AEDs Age at enrollment: (0.5–5)^by Randomly enrolled in 2 groups ($n = 19$/group): 4:1 diet (female = 3, male = 16) and 2.5:1 diet (female = 4, male = 15) 	<ul style="list-style-type: none"> 16% ($n = 6$ or 3 from each group) discontinued the KD before conclusion of study due to: unsatisfactory seizure control, nonacceptance by family, and child’s refusal to eat n=2 from 4:1 group and n=1 from 2.5:1 group were hospitalized for respiratory tract infections and KD was discontinued At 3 mo, 58% ($n = 11$) of the 4:1 group and 63% ($n = 12$) of the 2.5:1 group had $> 50\%$ seizure reduction ($P = 0.78$); 26% ($n = 5$) of the 4:1 group and 21% ($n = 4$) in the 2.5:1 group were seizure-free 2.5:1 group displayed a trend ($P = 0.06$) toward higher cholesterol and HDL at 3 mo 	<ul style="list-style-type: none"> Seizure frequency monitored with parent records of seizure-free, $> 50\%$ seizure reduction and $< 50\%$ seizure reduction Length of time to reach seizure freedom not defined and subject to parental interpretation Small sample size and parent records risk of subjective error and missing myoclonic and absent seizures

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14. Selter et al. (12) The Johns Hopkins Hospital, MD	Retrospective chart review (5 y, 8 mo)	Dietary and medication adjustments for improved seizure control on KD therapy	<ul style="list-style-type: none"> • $n = 200$ beginning 3:1 KD for seizure control October 2007 to June 2013 • Mean age at KD implementation: $(4.3)^d$ y • 99 girls • 101 boys • Consuming the KD for 0.1–4.5 y (mean 1.1 y) 	<ul style="list-style-type: none"> • No difference across dietary changes in seizure control ($P = 0.58$) • Patients with $>1\%$ further seizure reduction with dietary changes started KD younger (3.6 vs. 5.1 y, $P = 0.2$) and had earlier age of seizure onset (1.2 vs. 2 y, $P = 0.049$) • 27% ($n = 12$) no interventions, immediately became seizure-free with KD • 78% ($n = 156$) had ≥ 1 intervention during KD • 24% of medication changes led to $>50\%$ further seizure reduction vs. 15% of diet changes ($P = 0.08$) • 62% ($n = 124$) had $\geq 50\%$ improvement in seizure control on the KD, 29% ($n = 58$) saw periods of prolonged seizure freedom • Individualizing KD therapy can improve its therapeutic effects; 1/5 patients experienced added benefit from interventions • Fewer medication changes than dietary changes occurred • Provide counseling to parents, reassure that medication added with KD does not mean KD is ineffective 	<ul style="list-style-type: none"> • Diet adherence not mentioned, dropout rate and reasons not discussed • No definition of seizure freedom, length of time to be considered seizure-free not discussed • Seizure calendars completed by parent reports have risk of subjective bias and may miss some seizures • Retrospective study, no control group with no interventions • Multiple interventions occurring simultaneously with diet and medication changes, difficult to determine which adjustment responsible change in seizure frequency • Interventions were primarily modifications of diet to address adverse effects of diet, e.g., calorie intake increase or adding a supplement • Implication parents were confused by KD

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Study detail	Study design	Study objectives	Participants	Results	Study limitations
15. Sharma et al. (28) India	Qualitative prospective, open label, uncontrolled study	Evaluate tolerability and efficacy of KD in young Indian children with IE and assess change in biochemical and lipid profile	<ul style="list-style-type: none"> • $n = 41$ eligible having $1 \geq$ seizure/d or 7 seizures/wk despite ≥ 3 AEDs • Age at enrollment: (2.5/0.75-5)^c y • Excluded: systemic illness, surgically remedial causes, and metabolic related illnesses 	<ul style="list-style-type: none"> • 88% on KD at 3 mo; 55% on KD at 6 mo; 37% on KD at 1 y • 48% had >50% reduction in seizures; 18.5% seizure-free • 34% ($n = 14$) families eligible but refused their child to receive the KD: restricting diet, financial reasons, apprehension, transportation issues, time-consuming to maintain KD • During the 12 mo study, 41% ($n = 17$) discontinued the KD: 2 subjects refused to eat, 3 developed serious infections, 11 unsatisfactory seizure control, 1 from parental fatigue • No significant biochemical change, except decreased serum albumin ($P = 0.0453$) and increased urine calcium-creatinine ratio ($P = 0.035$) 	<ul style="list-style-type: none"> • Seizure freedom limitations not defined. Length of time to be considered seizure-free not discussed • Seizure reports by parents, may have subjective bias and miss absent seizures • Generalizability limited to Indian children
16. Sirikonda et al. (24) Morgantown, WV	Single case report	KD patient developing acute cardiovascular issues secondary to Se deficiency post-elective surgery	<ul style="list-style-type: none"> • $n = 1$ (male) • Mean age at study: 5 y • Subject with IE on KD for 2.5 mo • Subject's additional comorbidities: developmental delay, psychomotor retardation, tracheostomy with night-time ventilator dependence, gastrostomy tube, scoliosis 	<ul style="list-style-type: none"> • Patient became tachycardic and hypotensive postspinal surgery (Day 1) • KD ceased for 10 d with Se supplemented to treat Se deficiency-induced cardiomyopathy • Empiric supplementation started; patients' serum Se was $<25 \mu\text{g/L}$ (baseline serum Se before KD, $104 \mu\text{g/L}$) • Cardiac function normalized but unable to return to prior neurologic function, compassionate withdrawal of support chosen by parents • ECG, echocardiogram, and selenium levels should be determined preoperatively for those on KD 	<ul style="list-style-type: none"> • Parental reports of seizures may have subjective bias, may miss absent seizures • Limited generalizability • No control group, pre-/posttest used

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SUPPLEMENTAL FIGURE 1 (Continued)

Study detail	Study design	Study objectives	Participants	Results	Study limitations
17. Tagliabue et al. (31) Department of Child Neuropsychiatry IRCCS Casimiro Mondino Foundation, Pavia, Italy	Prospective, single-arm observational study (6 mo)	Nutritional status, REE, and substrate oxidation rates pre- and post-6 mo of KD	<ul style="list-style-type: none"> $n = 18$ with IE Age at enrollment: (12.4/5.6)^ay 10 girls 8 boys 	<ul style="list-style-type: none"> All subjects completed the 6 mo study Seizures decreased from median of 5/d at baseline to 2/d with KD, $P < 0.001$ No significant differences in terms of height, weight, BMI z scores, and REE pre- and post-KD Respiratory quotient decreased 0.80 ± 0.06 to 0.72 ± 0.05, $P < 0.001$ Fat oxidation increased 50.9 ± 25.2 to 97.5 ± 25.7 mg/min, $P < 0.001$ Carbohydrate oxidation decreased 72.5 ± 54.1 to 21.5 ± 48.2 mg/min, $P < 0.001$ Increase in fat oxidation main independent predictor in seizure reduction ($\beta = -0.97$, $t = -6.3$, $P < 0.05$) 	<ul style="list-style-type: none"> 6-mo period may not be adequate to assess impact of KD on height and weight Only Italian children used in this study
18. Taub et al. (7) Children's Hospital of Philadelphia, PA	Retrospective cohort study, quantitative using caregiver-reported seizure diary as unchanged, improved, or worse compared with baseline	Risk of seizure recurrence in children who achieved ≥ 1 mo of seizure freedom on KD	<ul style="list-style-type: none"> $n = 276$, records from 1991–2009 Age at enrollment: (5/3.2)^ay $n = 65$ achieved seizure freedom for ≤ 1 mo within 2 y of initiating the KD Daily seizures ($n = 45$, 69%), seizures > 1 time/wk at baseline ($n = 55$, 85%), unsuccessful treatment on ≥ 4 AEDs ($n = 50$, 77%) 	<ul style="list-style-type: none"> No statistically significant results Seizures recurred in 53 (82%) patients in follow-up All but 6 patients had seizure frequency decreased from baseline 19 patients (29%) had complete seizure remission lasting ≥ 1 y while consuming the KD; 9 of these 19 patients remained seizure-free for a median of 2.5 y after KD completion Provide counseling to families of children who become seizure-free, as breakthrough seizures are likely to occur but does not mean decline to baseline 	<ul style="list-style-type: none"> 1 of the patients with myoclonic astatic epilepsy was seizure-free for 2 y post-KD but had breakthrough seizures Retrospective study Missing data Could not verify details of seizure frequenc

¹ Values are ^aMean/Standard Deviation; ^bRange; ^cMedian/Range; ^dMean. AED, antiepileptic drug; AIX, augmentation index; BMC, bone mineral content; ECG, electrocardiography; EEG, electroencephalogram; EER, energy efficiency ratio; GTC, generalized tonic-clonic; IE, intractable epilepsy; KD, ketogenic diet; MCT, medium-chain triglyceride; QoL, quality of life; RCT, randomized control trial; REE, resting energy expenditure; REM, rapid-eye movement; 1,25(OH)D, 1,25-hydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D