Supplementary appendix

Supplementary Table 1. Overview of D,L-3-hydroxybutyrate treatment in 34 patients with inborn errors of metabolism; results from the systematic literature review. Legend: Phenotype MIM number: http://www.omim.org/. The presence (+) or absence (-) of clinical improvement regarding [a]liver symptoms including hepatic/hyperammonemic encephalopathy (+), hypoglycemia (+) and poor metabolic control (+); [b]muscle symptoms including myopathy (+) and hypotonia (+). [c]Personal knowledge or communication; [d]unclear which patient(s). Abbreviations (in alphabetical order): CACT, carnitine-acylcarnitine translocase; GSD, glycogen storage disease; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; multiple acyl-CoA dehydrogenase deficiency; NR, not reported; PA, propionic acidemia; PHHI, persistent hyperinsulinemic hypoglycemia of infancy; RFVT, riboflavin transport; VLCAD, very long-chain acyl-CoA dehydrogenase.

Reference	Inborn error of metabolism (#MIM)	n (M/F)	Age onset	Age start D,L-3-HB	D,L-3-HB dose range (mg/kg/d)	D,L-3-HB indication: X Clinical improvement: (+/-/NR)					Side effect(s)
						Cardiomyopathy	Leukodystrophy	Liver[a]	Muscle[b]	Respiratory failure	
Francois, 1981	HMG-CoA lyase deficiency (246450)	1 (1/0)	1 d	8 m	760			X (+)			NR
Bougneres, 1983	PHHI (256450)	4 (4/0)	1 - 10 d	3 - 32 m	115 - 150			X (+)			No
Bonham, 1999; Olpin, 2004	MADD (231680)	1 (0/1)	NS	14 m	1 - 10 g/d			X (+)	X (+)		No
Van Hove, 2001, 2003; Grunewald, 2008	MADD (231680)	3 (2/1)	6 d - 5 m	2 - 28 m	80 - 900	X (+)	X (+)	X (+)	X (+)		No
Plecko, 2002	PHHI (256450)	2 (1/1)	0 - 1 d	6 m	880 - 4000			X (NR)			No
Van Spronsen, 2005	RFVT3 deficiency[c] (211530)	1 (1/0)	5 m	5 m[c]	700				X (+)[c]	X (+)	Constipation, diarrhea[c]
Al-Hertani, 2008	MADD (231680)	1 (0/1)	6 m	NR	NR		X (+)[c]				No[c]
Marquardt, 2009	MADD (231680)	2 (NR)	NR	NR	NR			X (NR)			Metabolic alkalosis, nephrocalcinosis
Bhattacharya, 2010	HMG-CoA lyase deficiency (246450)	1 (1/0)	1 d	1.5 m	300		X (+)				No
Dalkeith, 2010, 2013	MADD (231680)	4 (NR)	<1 m - 5 m	7 d - 5 m	300 - 900	X (+)[c]		X (+)	X (+)	X (+)[c]	NR
	HMG-CoA lyase deficiency (24645)	2 (NR)	NR	3 m - 16 y	300 - 900	Youngest patient was treated empirically (NR); the oldest for liver symptoms (NR).					NR
	CACT deficiency (212138)	1 (NR)	NR	<1 m	300 - 900	X (+)		X (+)			
Van, 2010	GSD type III (232400)	2 (NR)	NR	1 - 9 y	600 - 900	X (+)[d]			X (+)[d]		No
	Mitochondrial complex IV deficiency (220110)	2 (NR)	NR	1 - 9 y	600 - 900						
	VLCAD deficiency (201475)	1 (NR)	NR	1 - 9 y	600 - 900						
	PA (606054)	1 (NR)	NR	1 - 9 y	600 - 900						

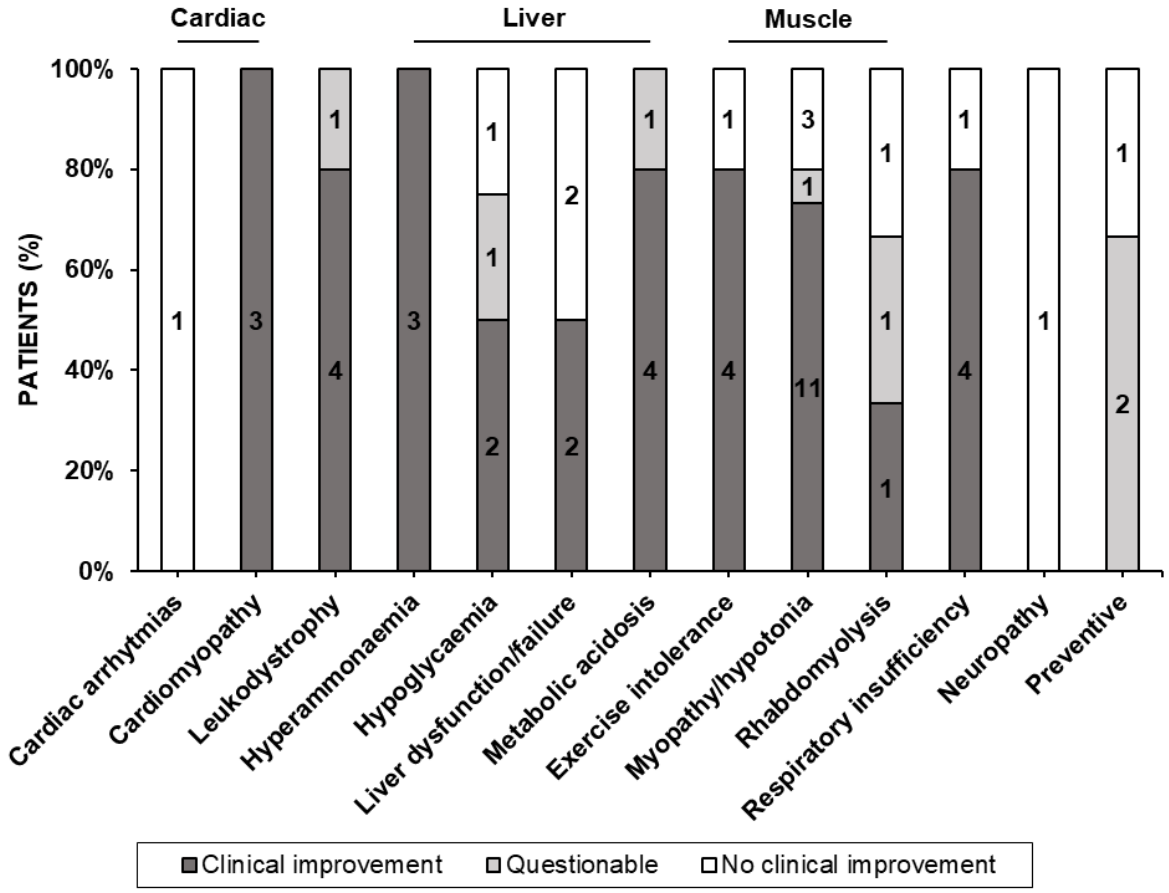
Bosch, 2011	RFVT3 deficiency (211530)	1 (0/1)	6 m[c]	7 m[c]	480 - 860[c]				X (-)[c]	X (-)[c]	NR
Hale, 2011	Presumptive MADD (231680)	1 (0/1)	1 d	7 m	300 - 1200	X (-)				X (-)	NR
Valayannopoulos, 2011	GSD type III (232400)	1 (1/0)	NR	2 m	400 - 800	X (+)		X (+)			No
Van Rijt, 2014	MADD (231680)	1 (0/1)	0 d	7 m	450 - 2600	X (+)	X (+)[c]		X (+)[c]	X (+)[c]	*Mild* dehydration, diarrhea, vomiting[c]
Gautschi, 2015	MADD (231680)	1 (1/0)	2.5 y	4 y	300 - 900		X (+)		X (+)		Indigestion, dehydration

Supplementary Table 2. Individual D,L-3-hydroxybutyrate treatment characteristics and outcome; results from the retrospective cohort study. Legend: The presence (+) or absence (-) of clinical improvement regarding [a]liver symptoms including hyperammonemia (+), hypoglycemia (+), liver dysfunction/failure (+) and metabolic acidosis (+); [b]muscle symptoms including exercise intolerance (+), hypotonia (+), myopathy (+) and rhabdomyolysis (+). [c]Patient has been published before in relation to D,L-3-HB treatment, see corresponding reference in manuscript; [d]consanguinity; [e]deceased; [f]diagnosed prenatally due to family history; [g]prescribed as food supplement (Ketoforce). Abbreviation: NR, not reported.

Patient	Age start D,L-3-HB	D,L-3-HB indication: X Clinical improvement reported: (+/-)						Range of D,L-3-HB dose (mg/kg/d)	Administration method(s)	Safety	D,L-3-HB discontinued
		Cardio-myopathy	Leuko-dystrophy	Liver[a]	Muscle[b]	Respiratory failure	Neuropathy				
1[c(#7)d]	7 m	X (+)	X (+)		X (+)	(+)		450 - 2600	Gastrostomy/ nasogastric tube, oral	*Prolonged* hospitalization, *mild* dehydration, diarrhea, vomiting	No
2	10 + 1/12 y				X (+)			250 - 500	Oral	*Infrequent* abdominal pain	No
3[e]	9 d	Preventive treatment aspect (-), deceased after 1 d.						900 - 1800	Nasogastric tube	Death	Yes, death
4[c(#17,18)de]	19 d			X (+)	X (+)	X (+)		300 - 600	Oral	Death	Yes, death
5	9 m			X (+)	X (+)			130 - 1000	Nasogastric tube	*Mild* vomiting	No
6[c(#17,18)]	6 m	X (+)		X (+)	X (+)			200 - 650	Gastrostomy tube, oral	-	No
7	6 m	Questionable due to preventive treatment aspect.						200 - 2000	Gastrostomy/ nasogastric tube	*Chronic* nausea and vomiting	Yes, side effects
8[de]	2 m	Liver, muscle and preventive treatment; questionable due to very early start and preventive treatment aspect, patient seemed more stable.						355 - 395	Nasogastric tube	Death	Yes, death
9	2 m	Low C2 carnitine (-).						100 - 950	Oral	-	No
10	2 + 5/12 y				X (+)	X (+)		650 - 1200	Oral	-	No
11[e]	28 + 6/12 y			X (+)	X (+)			450	Oral	-	Yes, costs
12[c(#17,18)]	5 m				X (+)			200 - 300	Oral	-	Yes, no treatment compliance
13[c(#15)]	4 + 3/12 y		X (+)					500	Oral	-	No
14	4 + 6/12 y	Leukodystrophy and muscle treatment; questionable due to short treatment duration of only three months at time of data collection.						150	Oral	-	No
15	24 + 9/12 y		X (+)		(+)			560 - 600	Oral	*Mild* dehydration, abdominal pain, constipation	No
16[df]	5 + 1/12 y				X (+)			300 - 1000	Oral	*Mild* diarrhea	No
17[c(#8)d]	3 + 11/12 y		X (+)		X (+)			480 - 900	Gastrostomy tube	*Mild* dehydration	No
18	25 + 11/12 y			X (+)	X (+)			900	Nasogastric tube	-	Yes, clinical improvement

19	25 y			X (-)		X (-)	500 - 750[g]	Oral	-	Yes, ineffectiveness and costs
20[c(#17,18)e]	3 m		X (+)	X (+)			300 - 600	Oral	Death	Yes, death
21[e]	3 m	X (+)					NR	Oral	Death	Yes, death
22[c(#10)]	5 m			X (+)	X (+)		330 - 730	Nasogastric tube, oral	Constipation, diarrhea	Yes, clinical improvement
23[c(#11)]	7 m			X (-)	X (-)		480 - 860	Nasogastric tube	-	Yes, ineffectiveness

Supplementary Figure 1. Symptom based indication and efficacy of D,L-3-hydroxybutyrate treatment.



Legend: Proportion of MADD(-like)-patients with symptom based indication and efficacy of D,L-3-HB treatment, with the numbers presented in the columns.

Supplementary Data 1. Detailed description of the systematic literature review methods.

Presentation of the original search strategy. Original search strategy implemented in PubMed database retrieved 310 hits on September 27th, 2016.

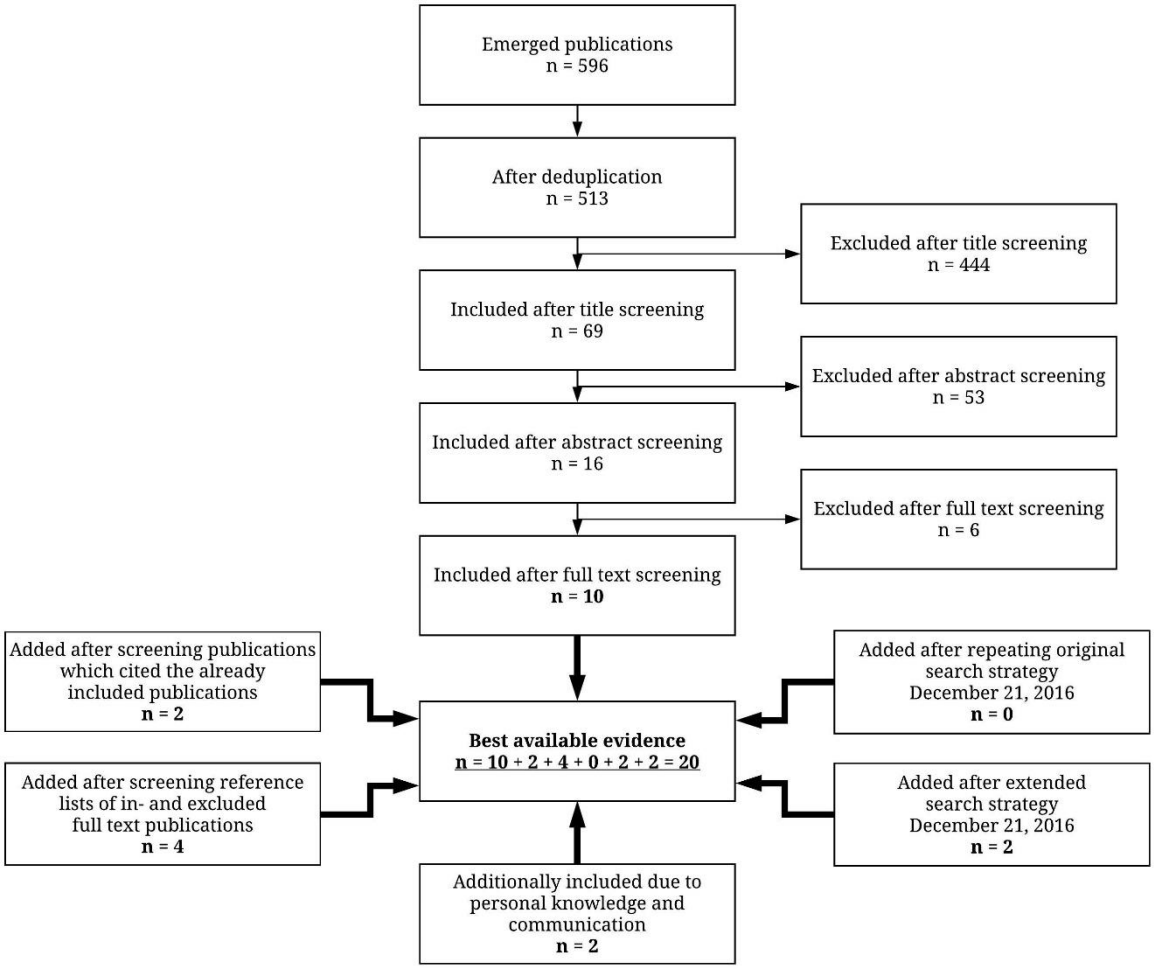
("Hydroxybutyrates"[Mesh] OR "3-Hydroxybutyric Acid"[Mesh] OR "Ketone Bodies"[Mesh] OR 3-Hydroxybutyr*[tiab] OR beta-Hydroxybutyr*[tiab] OR 3hydroxybutyr*[tiab] OR b-hydroxybutyr*[tiab]) AND ("Metabolism, Inborn Errors"[Mesh] OR "Multiple Acyl Coenzyme A Dehydrogenase Deficiency"[Mesh] OR MADD[tiab] OR Multiple Acyl-CoA Dehydrogenase Deficien*[tiab] OR "Glutaric Aciduria"[tiab] OR ETFDH Deficien*[tiab] OR ETFA Deficien*[tiab] OR ETFB Deficien*[tiab]) NOT (("Animals"[Mesh] NOT "Humans"[Mesh]) OR animal[ti] OR mouse[ti] OR mice[ti] OR rodent*[ti] OR rat[ti] OR rats[ti])

Protocol of the screening process and data extraction.
The screening process was performed independently by two reviewers (WvR & EJ). Articles were included based upon the presence of detailed patient data concerning D,L-3-HB or ketone body treatment as well as a confirmed diagnosis by biochemical (acylcarnitine or organic acid profile), DNA, or enzymatic analysis. The following exclusion criteria were maintained: a) no detailed patient data described, b) lack of accessibility of the abstracts or articles, c) no availability in English or Dutch language.
Nine articles were included as search outcome after completion of the screening process and one was added due to personal knowledge of the literature.[1] To prevent missing any publications, we extended our search with two approaches: 2) screening publications, identified via Web of Science, which cited the already included publications, and 3) screening the reference lists of already previously retrieved (included and excluded) full text publications. This resulted in the addition of two and four publications to our search outcome, respectively (n = 16 in total). To minimize the risk of missing data, we expanded our original search strategy with terms used in abstracts or articles which were only found through the 2nd and 3rd search approach. This lead to the inclusion of two more publications (n = 18 in total). Finally, two more publications were added due to personal knowledge and communication (n = 20 in total).[2,3]
General study characteristics and data on clinical presentation and D,L-3-HB treatment per inborn error of metabolism were collected independently by two reviewers (WvR & EJ).
Consensus on eligibility during the screening process and data extraction was reached through regular meetings. If necessary, a third, independent reviewer (TD) was consulted to make the final call on eligibility.

Presentation of the extended search strategy. Extended search strategy implemented in PubMed database retrieved 333 hits on December 21st, 2016.

("Hydroxybutyrates"[Mesh] OR "3-Hydroxybutyric Acid"[Mesh] OR "Ketone Bodies"[Mesh] OR 3-Hydroxybutyr*[tiab] OR beta-Hydroxybutyr*[tiab] OR 3hydroxybutyr*[tiab] OR b-hydroxybutyr*[tiab] OR D,L-3-hydroxybutyr*[tiab] OR OH-B[tiab] OR 3-HB[tiab] OR B-OHB[tiab] OR BOHB[tiab]) AND ("Metabolism, Inborn Errors"[Mesh] OR "Multiple Acyl Coenzyme A Dehydrogenase Deficiency"[Mesh] OR MADD[tiab] OR Multiple Acyl-CoA Dehydrogenase Deficien*[tiab] OR Multiple Acyl CoA Dehydrogenase Deficien*[tiab] OR "Glutaric Aciduria"[tiab] OR ETFDH Deficien*[tiab] OR ETFA Deficien*[tiab] OR ETFB Deficien*[tiab] OR "3-Hydroxy-3-Methylglutaryl-CoA Lyase Deficiency"[Mesh] OR "HMG-CoA lyase"[tiab] OR "HMG Co-A lyase"[tiab] OR 3-hydroxy-3-methylglutaryl-coenzyme A lyase deficien*[tiab] OR "Congenital Hyperinsulinism"[Mesh] OR "persistent hyperinsulinemic hypoglycemia"[tiab] OR PHHI[tiab] OR "persistent hypoglycemia and hyperinsulinism"[tiab] OR "Glycogen Storage Disease Type III" [MESH] OR "Glycogenosis type III"[tiab] OR "Glycogen storage disease type 3" [tiab] OR "Cytochrome-c Oxidase Deficiency"[MESH] OR "Deficiency in complex IV of respiratory chain"[tiab] OR "Mitochondrial complex IV deficiency" [tiab] OR "VLCAD deficiency"[MESH] OR "Deficiency on very long chain acyl-CoA dehydrogenase"[tiab] OR "Very long-chain acyl-coa dehydrogenase deficiency"[tiab] OR "Propionic academia"[MESH] OR "Ketotic hyperglycinemia"[tiab]) NOT (("Animals"[Mesh] NOT "Humans"[Mesh]) OR animal[ti] OR mouse[ti] OR mice[ti] OR rodent*[ti] OR rat[ti] OR rats[ti])

Flowchart of the screening process. Implementation of the original search strategy in PubMed and EMBASE databases on September 27th, 2016 resulted in 310 and 286 hits, respectively.



PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist. Adapted from Moher et al, 2015.[4]

Section and topic	Item No	Checklist item	Reported in section
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Introduction, Methods
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	N/A
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Title page
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Suppl. Data 1
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Methods
Sponsor	5b	Provide name for the review funder and/or sponsor	Methods
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Methods
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Introduction
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Introduction, Methods
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Methods, Suppl. Data 1
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Methods, Suppl. Data 1
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Suppl. Data 1
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Suppl. Data 1
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Suppl. Data 1
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Suppl. Data 1
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Methods, Suppl. Data 1

Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Methods, Suppl. Data 1
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Discussion, Suppl. Data 1
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Suppl. Data 1, Suppl. Table 1
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	N/A
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	N/A
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Suppl. Data 1, Suppl. Table 1
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Discussion, Suppl. Data 1
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Retrospective cohort study, Discussion

References to Supplementary Data 1

1. Bosch AM, Abeling NG, Ijlst L, et al. Brown-vialetto-van laere and fazio londe syndrome is associated with a riboflavin transporter defect mimicking mild MADD: A new inborn error of metabolism with potential treatment. *J Inherit Metab Dis*. 2011;34(1):159-164.

2. van Spronsen FJ, de Weerd W, Goorhuis J, et al. Respiratory insufficiency as first presentation of multiple acyl-CoA dehydrogenase deficiency (MADD). *J Inherit Metab Dis*. 2005;28(Suppl 1):115.

3. Al-Hertani W, Mineyko A, Humphreys P, Chakraborty P, Geraghty MT. Glutaric aciduria type II presenting with lipid myopathy, progressive leukodystrophy; intrafamilial variation in two siblings. .

4. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*. 2015;4(1):1.

Supplementary Data 2. STROBE Statement - Checklist of items that should be included in reports of *cohort studies*.

	Item No	Recommendation	Reported in section
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Abstract, Introduction, Methods
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction
Objectives	3	State specific objectives, including any pre-specified hypotheses	Introduction, Methods
Methods			
Study design	4	Present key elements of study design early in the paper	Methods
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Methods
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods
Bias	9	Describe any efforts to address potential sources of bias	Methods
Study size	10	Explain how the study size was arrived at	Methods
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Methods
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Methods
		(*b*) Describe any methods used to examine subgroups and interactions	Methods
		(*c*) Explain how missing data were addressed	Methods
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study - eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Results
		(b) Give reasons for non-participation at each stage	Results
		(c) Consider use of a flow diagram	N/A

Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Results
		(b) Indicate number of participants with missing data for each variable of interest	Results
		(c) Summarise follow-up time (eg, average and total amount)	Results
Outcome data	15*	Report numbers of outcome events or summary measures over time	Results
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Results
		(*b*) Report category boundaries when continuous variables were categorized	Results
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done - eg analyses of subgroups and interactions, and sensitivity analyses	Results
Discussion			
Key results	18	Summarise key results with reference to study objectives	Discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Discussion
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussion
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Methods