Inborn errors of metabolism causing Sudden Infant Death: a systematic review with implications for population neonatal screening programs

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Supplemental Data 1. Detailed presentation and assessment of the search strategy.

CINAHL, Cochrane, Pubmed and Embase were searched using both MeSH terms and free text. The key search strategy for PubMed: ("Metabolism, Inborn Errors"[Mesh] OR "inborn errors of metabolism" OR "mitochondrial fatty acid oxidation") AND ("Sudden Infant Death"[Mesh] OR "sudden infant of death" OR "sudden infant death syndrome" OR "unexpected death" OR "sudden unexpected death of infant" OR "Reye Syndrome"[Mesh]) AND (Humans[Mesh]) AND ("Infant, Newborn, Child, Adolescent"[Mesh] OR newborn OR infant OR child). Search strategy was conducted on February, 15th 2013. Due to the elapsed time between the execution of the search strategy and the completion of the manuscript, the search strategy was repeated on August, 28th 2015, to screen for possible extra IEMs. Only articles with newly associated IEMs were included and added to the best available evidence, since the evidence of additionally found articles for already enrolled IEMs was no longer necessary for argumentation. Subsequently, this lead to the inclusion of only one additional IEM associated with either SID and/or RS: dihydrolipoamide dehydrogenase deficiency (DLD deficiency; MIM #246900).

All reports published since 1990 were included, corresponding with the first publications about the availability of TMS and general progressions made in the field of molecular and enzymatic confirmatory testing in the field of IEMs. References published before 1990 were only included when available upon request. The inclusion of a diagnosis as a cause of SID and/or RS was based on the presence of detailed patient data and a confirmed diagnosis in the full text articles. Specific exclusion criteria were (1) no detailed patient data reported; (2) lack of accessibility of the articles; (3) confirmatory metabolite, molecular or enzymatic studies were inconclusive; (4) when there had been a (possible) additionally

contributing cause of death; (5) patients suffering from SID and/or RS aged above 18 years and/or (6) abstract and/or article not available in English or Dutch language.

As IEMs are very rare disorders, the best available evidence of our systematic review consisted only of observational studies, case series and expert opinions. Therefore, not all items on the attached PRISMA-P 2015 checklist are applicable.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page(s)
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	-
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	-
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Presented in below mentioned Contributors' Statement
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	-
Support:			
Sources	5a	Indicate sources of financial or other support for the review	2
Sponsor	5b	Provide name for the review funder and/or sponsor	2
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	2
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4

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	5, 6 and supplemental 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	5, 6 and supplemental 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	Flowchart and supplemental data 1
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	5, 6
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)	5, 6
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	5, 6
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	5, 6
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5, 6, 7, 8
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	5, 6, 9, 10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	-
	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)	-
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	-

	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Table 1
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9, 10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	-

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Contributors' Statement:

Ms Van Rijt performed the full text articles screening of all selected references, collected and analyzed the data, drafted the flowchart, composed a clear representation of the results in table form, compiled the references list, drafted the first version of the manuscript, performed the PRISMA-assessment, critically revised the manuscript and wrote the final manuscript as submitted;

Ms Koolhaas carried out the search strategy, performed the title and abstract screenings, performed the full text articles screening of all selected references, collected and analyzed the data, drafted the flowchart, composed a clear representation of the results in table form, drafted the first version of the manuscript, critically reviewed and revised the manuscript and approved the final manuscript as submitted;

Dr Bekhof critically reviewed and revised the manuscript with important intellectual content and approved the final manuscript as submitted;

Dr De Koning critically reviewed and revised the manuscript with important intellectual content and approved the final manuscript as submitted;

Dr Visser critically reviewed and revised the manuscript with important intellectual content and approved the final manuscript as submitted;

Dr Schielen critically reviewed and revised the manuscript with important intellectual content and approved the final manuscript as submitted;

Prof Dr van Spronsen critically reviewed and revised the manuscript with important intellectual content and approved the final manuscript as submitted;

Dr Derks performed the title and abstract screenings, performed the full text articles screening of all selected references, collected and analyzed the data, initiated and drafted the first version of the manuscript, performed the PRISMA-assessment, critically reviewed and revised the manuscript and wrote the final manuscript as submitted.