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Review article

Cognitive functioning and mental health in mitochondrial disease: A systematic scoping review

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ABSTRACT

Mitochondrial diseases (MDs) are rare, heterogeneous, hereditary and progressive in nature. In addition to the serious somatic symptoms, patients with MD also experience problems regarding their cognitive functioning and mental health. We provide an overview of all published studies reporting on any aspect of cognitive functioning and/or mental health in patients with MD and their relatives.

A total of 58 research articles and 45 case studies were included and critically reviewed. Cognitive impairments in multiple domains were reported. Mental disorders were frequently reported, especially depression and anxiety. Furthermore, most studies showed impairments in self-reported psychological functioning and high prevalence of mental health problems in (matrilineal) relatives. The included studies showed heterogeneity regarding patient samples, measurement instruments and reference groups, making comparisons cautious.

Results highlight a high prevalence of cognitive impairments and mental disorders in patients with MD. Recommendations for further research as well as tailored patientcare with standardized follow-up are provided. Key gaps in the literature are identified, of which studies on natural history are of highest importance.

1. Background

Mitochondrial diseases (MDs) are heterogeneous, hereditary and progressive diseases with an estimated prevalence of 1 in 4,300 adults (Gorman et al., 2015b). Here MDs are defined as genetic defects affecting the normal function of the mitochondrial oxidative phosphorylation system (Mancuso et al., 2017). Affected mitochondria may cause symptoms in any organ or tissue, and patients often present with multi-system involvement. Organs with the highest energy requirement, such as the brain and muscles, are most likely to be affected (Smeitink et al., 2006). Brain involvement (encephalopathies) are common in MD, and neuronal cell loss can be caused by acute events or more global prolonged loss of cells (Alston et al., 2017). Symptoms of MD may present at any age and their presentation is characterized by a large heterogeneity (Rahman, 2020). To date, the prognosis and trajectory of the disease cannot be predicted using for example, lactate levels in blood/CFS or genetics (Rahman, 2020). In addition to the severe somatic symptoms, many patients with MD also experience problems regarding cognitive functioning (Finsterer, 2008, 2009, 2012; Moore et al., 2020), and mental health (Anglin et al., 2012b; Fattal et al., 2006; Marin and

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Saneto, 2016; Parikh et al., 2017). The nature of the relation between MD and both cognitive functioning and mental health is complex, because they may be a consequence of having a chronic illness such as MD (e.g., related to coping with impairments) or inherent to the disease itself. To date, reseach on cognitive functioning and mental health in patients with MD is limited.

In the terminology of MD it is important to distinguish between primary MDs, caused by either variant(s) in mitochondrial DNA (mDNA) or nuclear DNA (nDNA), and secondary mitochondrial dysfunctions, caused by other factors such as environmental factors or by defective genes without a role in mitochondrial function or assembly (Niyazov et al., 2016). In the latter group, a growing body of evidence suggests an important role for mitochondrial dysfunction in cognitive or mental disorders (Allen et al., 2018; Bansal and Kuhad, 2016; Irwin et al., 2016; Kacho et al., 2019; Morris and Berk, 2015; Petschner et al., 2018; Shao et al., 2008; Streck et al., 2014). In primary MD, less is known about this relation, while cognitive functioning and mental health greatly impact on daily life (Koene et al., 2013).

To date, research focusing on cognitive functioning and mental health in the field of primary MD is fragmented. Due to the rarity and clinical as well as genetic heterogeneity of primary MDs, most studies comprise single-case descriptions or specific genetic types of MD. There is a clear lack of generic research studying the broader spectrum of cognitive functioning and mental health in patients with different types of primary MD. To understand the impact of the disease on cognitive functioning and the patients' mental health, we need to map different domains: 1) the level and profile of cognitive (dys)function, 2) the presence and prevalence of mental disorders and 3) psychological and social functioning. Furthermore, mental health in the patients' relatives may also provide valuable information about the (mental) impact of the disease on care givers. In addition, genetic vulnerabilities in carrier relatives may also affect their cognitive functioning and mental health, as mitochondria may not function optimally. An overview of the extent and nature of the existing studies on this spectrum is needed to guide future research and yield more focused hypotheses regarding working mechanisms in the relationship between cognitive functioning and mental health with mitochondrial disease, and unravel the causes and consequences. Knowledge about cognitive functioning and mental health is, furthermore, needed to provide guidelines for diagnostics and to define targets for potential (non-)pharmacological treatment of these sequelae and to understand outcomes closely related to patient-reported impact of the disease on daily life (Koene et al., 2013). To date, no cure is available and treatments for MD are only supportive, tackle complications and improve coping with the disease and its consequences (Garone and Viscomi, 2018; El-Hattab et al., 2017). In practice, patients often receive a combination of interventions: dietary supplements, pharmacological treatment, symptomatic treatments and medical aids, physical / occupational therapy and psychological interventions. Studies focusing on interventions targeting aspects of cognitive functioning or mental health seem scarce. This scoping review will explore existing studies on these topics.

This scoping review aims to map the literature and provide an overview of published studies reporting cognitive functioning and mental health in patients with MD, their relatives, as well as intervention studies focusing on these aspects. Our findings have the potential to improve the understanding of cognitive functioning and mental health in patients with primary MD, improve patient care with recommendations based on literature findings, reveal gaps in the literature, and identify directions for future research.

2. Methods

We used the scoping review framework outlined by Arksey and O'Malley (2005) with additional recommendations by Levac et al. (2010) and the JBI guidelines (Peters et al., 2020). This combined methodology is used to examine broader research questions to map key concepts and identify gaps in the existing literature. To ensure transparency and complete reporting, we followed the PRISMA-extension for scoping reviews (Tricco et al., 2018).

2.1. Defining the research questions

Our scoping review addresses the following research questions, which were developed and refined through an iterative process:

- What has been reported about the cognitive functioning and mental health of patients with MDs and their relatives?
- What recommendations for patient care and future research can be made based on the existing literature?

An exploratory search in PROSPERO and the Cochrane library revealed no comprehensive reviews addressing both cognitive functioning and mental health in patients with MD.

2.2. Identifying relevant studies

We conducted a thorough search of the literature in the following databases: EMBASE, PubMed, Web of Science, PsychInfo and Medline using a search strategy based on the research questions and definitions of key concepts and keywords. The main keywords were "mitochondrial disease" and its synonyms and the confirmed mitochondrial syndromes, combined with search terms on cognitive functioning and mental health. No time constraints were given; all years of publication were included. The search was conducted on July 20, 2018, with an additional search on February 18, 2020. An example of the search query for PubMed is presented in Supplementary Table 1. EndNote was used to manage the output.

2.3. Study selection

The study selection comprised two separate rounds. Predefined inclusion and exclusion criteria were set and iteratively developed for the inclusion of studies for each round (Table 1).

First, two independent researchers screened titles and abstracts to map the existing literature. Two reviewers (JC and IK) screened the titles and abstracts independently. JC an IK met after approximately 10 % of titles had been screened to ensure that the inclusion and exclusion criteria were clear. Intercoder agreement of these two reviewers on the

Table 1
Inclusion and exclusion criteria of the study selection.

Study characteristics	Inclusion criteria	Exclusion criteria
Design	Randomized controlled trial, non-randomized test, descriptive report (correlational, prevalence, diagnostic, prognostic, comparison studies)	Study protocol
Publication	(peer-reviewed) journal Full-text available in English, German or Dutch Case studies Article in press	Conference paper Letters (Guest) Editorial Review articles
Participants	Patients of all ages with primary mitochondrial disorder	No mitochondrial disorder No focus on cognitive functioning or mental health Animal research Neurological disorders, incl. dementia Post-mortem research
Outcome Measure	Primary or secondary cognitive functioning or mental health outcomes	

eligibility of articles based on the title was 97 %, resulting in a weighted kappa score of 0.72. Two other reviewers (KL and CV) were consulted if questions arose about the eligibility of an article for inclusion in the scoping review.

Full-text articles were reviewed focusing on cognitive functioning and mental health in patients with mitochondrial disease and their relatives. We included full-text reports written in English, German or Dutch, which provided specific information on patients with MD, and information on cognitive functioning and/or mental health. Cognitive functioning is described based on studies using neuropsychological assessments (in contrast to self-reported cognitive complaints). Studies focusing solely on neuroimaging of the brain were not included. Mental health included mental disorders, psychological functioning, and social functioning. Mental disorders were included only if the patients had been diagnosed based on a clinical interview following the DSM or ICD criteria. Psychological functioning was based on self-reports or screening questionnaires on mental health. Psychological functioning also included quality of life, distress and other subjective emotional, mental and social experiences related to living with their disease. The cognitive functioning and mental health were mapped out and synthesized to clarify the current status of research in this field, and to observe possible gaps in the literature related to psychological functioning in patients with MD. Studies focusing on cognitive functioning and mental health in relatives were additionally included and described separately.

2.4. Data extraction

Data of full-text articles were extracted by two reviewers (IK and KL), including article details (authors, year of publication, title, study design, country), sample characteristics (recruitment, in- and exclusion criteria, sample size, group characteristics, age, sex, ethnicity, diagnosis, if applicable: age first symptoms, age diagnosis, psychological symptoms before/after diagnosis MD) and study outcomes (cognitive functioning, mental health outcomes, measurement instruments and main results). Articles were divided into research articles and case studies / series. Research articles were defined as studies analyzing multiple patients on group level. Articles were defined as case studies or case series when one or more patients were described in detail and on an individual level.

Articles were then divided into the following categories: 1) cognitive functioning, including 1.1) global cognitive functioning, indicating more general cognitive functioning as assessed by a global cognitive screener of composite scores of multiple tests; 1.2) intellectual functioning, as measured by intelligence tests; 1.3) specific cognitive domains, including visuospatial and visuoconstructive skills, executive functioning, memory, attention and concentration, and verbal skills/language performance; 1.4) cognitive functioning across repeated assessments; 2) mental health, including; 2.1) mental disorders, including mood, anxiety and psychotic disorders; 2.2) psychological functioning, including psychological symptoms and fatigue 2.3) social functioning, including experiences related to social interactions and social support and 2.4) quality of life, describing the overall experienced impact of the disease on several domains including mental disorders, distress, and burden of the disease and 3) interventions focused on cognitive function or mental health outcomes in patients with MD and 4) family-focused studies including 4.1) cognitive functioning 4.2) mental health. Finally, case studies / series were also divided into these major categories (cognitive functioning, mental health, interventions and family-focused studies).

2.5. Data analysis and presentation

Data were reported in a narrative format. The number of studies were defined as "*k*" and the number of participants with "*n*". The included research articles were summarized and synthesized in the results, including the study characteristics and main results. Following the guidelines of Arksey and O'Malley (2005) all relevant literature was included and described, regardless of methodological quality. Following discussions in Pham et al. (2014), a quality assessment is recommended to identify gaps in the methodological evidence (Pham et al., 2014). However, given the wide range of study designs and diagnostic criteria for MDs, no quality assessment was performed using a validated tool. Instead, two authors (IK and KL) described several criteria which may influence the quality of studies: diagnostic heterogeneity, recruitment/representativeness, measurement instruments, and comparison group. By doing so, more information is provided regarding these criteria instead of solely assessing and rating the quality.

In addition, a short overview of the relevant outcomes described in the case studies were reported for each category in the results.

3. Results

3.1. Literature search and selection

The initial search resulted in 9,963 articles; after removing duplicates 6,591 articles remained. All articles were screened on title, 373 articles were screened on abstract and 102 articles were included in the synthesis (Fig. 1), one article was included both as a research article and as a case study / series (Schreiber, 2012). Table 2 provides an overview of the included research articles and a more detailed description of the main outcomes of both research articles and case studies is presented in Supplementary Tables 2−6.

The following study characteristics have been described for the included 58 research articles: study population and measurement instruments; the main characteristics of case studies have been shown as well. An overview of the study characteristics of the research articles is reported in Table 2.

3.2. Study population

The diagnostic criteria for MDs have changed over time. This has resulted in different criteria which have been used to define MDs within studies as well. Inclusion criteria varied widely. Most studies included patients with a genetically confirmed diagnosis of MD ($k = 45$) of which 26 studies included only patients with genetically confirmed MD, 13 studies also included patients with MD without a genetic confirmation, and 6 studies included patients with a genetically confirmed MD through self-referral. Second, patients with a confirmed diagnosis of MD according to a variety of existing criteria were included based on clinical, histo-morphological, respiratory chain, and/or genetic evidence ($k = 24$). Some diagnostic criteria distinguish between no, possible, probable and confirmed MD (e.g. Walker et al., 1996; Bernier et al., 2002; Wolf and Smeitink, 2002; Morava et al., 2006), 13 studies also included patients with a probable diagnosis of MD. Finally, several studies included patients based on self-reported diagnosis after self-referral through advertisements about the study ($k = 9$). Criteria used in studies are reported in Table 2.

Patients were most often recruited from clinics, hospitals and/or databases ($k = 28$) or through community recruitment including online patient organization platforms ($k = 7$) such as MitoAction.org and the United Mitochondrial Disease Foundation (UMDF.org). Some studies did not provide details on the recruitment process ($k = 14$). Studies included patients of different age groups and family members: children and adolescents ($k = 8$), adults ($k = 30$), or both children and/or adolescents and adults ($k = 10$). Several studies focused specifically on parents and their child with MD ($k = 10$). Sample sizes of the MD groups ranged from 6 to 231 patients, although most samples were relatively small (i.e., 40 research articles reported on sample sizes below 40).

Patients with MD were compared with healthy or typically developing controls ($k = 12$), norm scores ($k = 12$) or other patient groups ($k = 6$), such as other metabolic diseases, type 1 diabetes mellitus (T1D) or hereditary sensorimotor neuropathy (HSN). Furthermore, five studies compared symptomatic patients with MD with carriers or relatives.

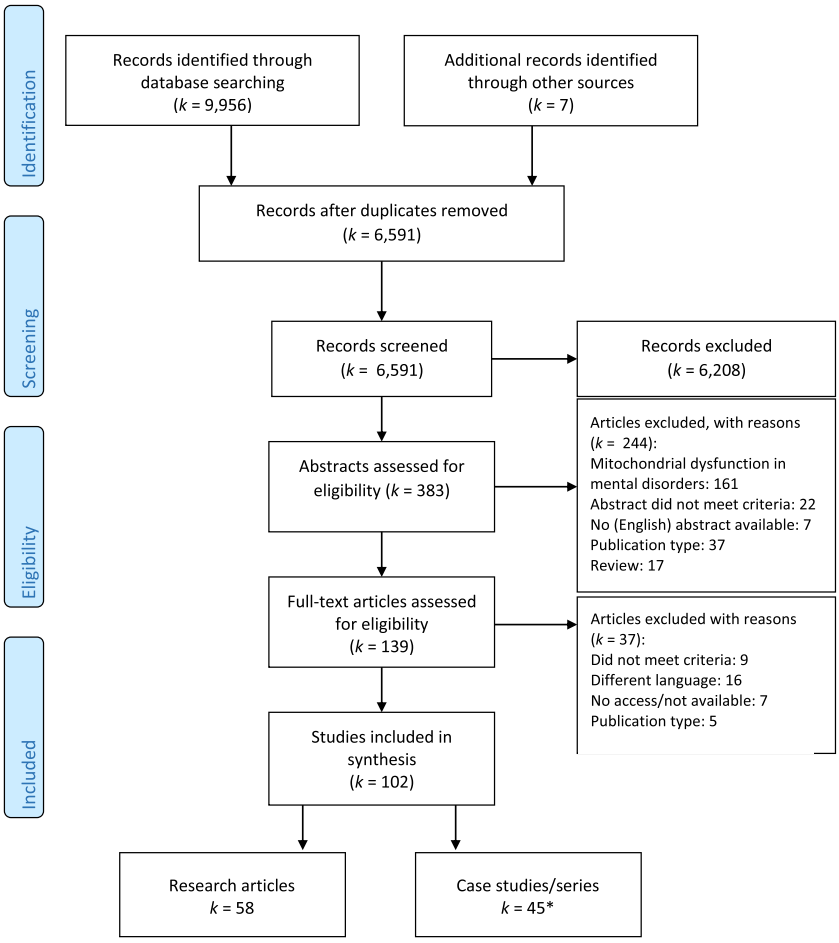

Fig. 1. Flow chart of the study selection.

Three studies specifically compared mothers of a child with MD, with mothers of a child with either epilepsy, autosomal recessive metabolic disorder (ARMD) or phenylketonuria (PKU).

Case studies focused mainly on adult patients with MD ($k = 27$), children and adolescents were described in 12 studies and six studies focused on both children and adults. In addition, four studies mainly focused on relatives. The most common MD diagnoses in patients were Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-like episodes (MELAS) spectrum disorders, genetically confirmed ($k = 15$) or without a (described) genetic mutation ($k = 5$).

3.3. Measurement instruments

Different measurement instruments were used across studies. Cognitive functioning was assessed with 42 different neuropsychological tests. Not all studies reported individual results for all tests, but used a composite score of multiple measures. Eleven studies assessed intellectual functioning using (subtests of) the Wechsler intelligence tests. Most frequently used tests to asses memory functioning were the Wechsler Memory Scale ($k = 4$) and the (Rey) Auditory Verbal Learning Test, and the Trail Making Test ($k = 3$) was often used for measuring attention/executive function.

Seven studies used unstandardized questionnaires regarding mental health, which were specifically designed for the study. Thirty-eight different validated/standardized questionnaires were used, most often used were the Hospital Anxiety and Depression Scale (HADS, including the subscale anxiety HADS-A or depression HADS-D) ($k = 6$), Research and Development-36 (RAND-36) or the general health status short form (SF-36, SF-12 or SF-Qualiveen) ($k = 13$), Beck Depression Inventory (BDI) ($k = 8$) and Beck Anxiety Inventory (BAI) ($k = 4$). The NMDAS/NPMDS (Newcastle Mitochondrial Disease Scale for Adults/Newcastle Pediatric Mitochondrial Disease Scale) was used in 10 studies, though not always the full questionnaire. Subjective fatigue was measured with five different questionnaires, most common were the Checklist Individual Strength (CIS) ($k = 6$) and Fatigue Impact Scale (FIS) ($k = 3$).

In case studies, most studies described results of a clinical and/or psychiatric assessment ($k = 32$). Cognitive functioning was measured with neuropsychological tests in 16 case studies, though three studies did not specify which neuropsychological tests were used. Furthermore, an additional 16 case studies described aspects of cognitive functioning without cognitive testing. Questionnaires measuring mental health outcomes were used in 10 case studies (see Supplementary Table 6).

3.4. Study objectives

Results of 45 research articles and 39 case studies are summarized in the following categories: 1) Cognitive functioning, including 1.1) Global cognitive functioning 1.2) Intellectual functioning 1.3) Specific cognitive domains 1.4) Cognitive functioning across repeated assessments 1.5) Influence of psychological outcomes on cognitive functioning 1.6) Relationship between disease manifestation and cognitive functioning 1.6) Case studies; 2) Mental health focusing on 2.1) Mental disorders 2.2) Psychological functioning 2.3) Social functioning 2.4) Quality of life and 2.5) Case studies; and 3) Interventions focused on cognitive function or mental health outcomes in patients with MD. In addition, studies focusing on the family or relatives are described in 4) Family-focused studies also including 4.1) Cognitive functioning 4.2) Mental health and 4.3) Case studies. For an overview of all research articles, we

Table 2
Overview table of cognitive functioning, mental disorders, psychological and social functioning, intervention and family-focused studies.

A) Cognitive functioning

Authors	MD	Criteria	(Reference) group: *n*	Age *M* ± *SD* (range)	Global functioning/ screening	Intelligence	Visuospatial/ visuo-construction	Executive functioning	Memory	Attention	Language
One specific MD based on phenotype											
Fromont et al., 2009	MIDD with mDNA 3243 A > G or mDNA 14709 T > C variants	1	MD: 11 T1D: 9 ND	MD: 53.6y (33–64) T1D: 55.9y (33–67)	**MIDD = T1D** **MIDD = ND**	**MIDD < T1D** **↓20 %**	**MIDD = T1D** **↓60 %**	**MIDD = T1D** **↓40–44.4 %^**	**MIDD < T1D (1/4 tests)** **↓0–50 %^**	NR	**MIDD = T1D** **↓ 0–30 %^**
Gramstad et al., 2009	MSCAE	1	MD: 8 ND	MD: 22.3y ± 7.8	**↓100 %** **MD < ND**	**FSIQ** ***M* = 77.4 ± 18.0** **VIQ > PIQ**	NR	NR	**↓25 %(*n* = 1)**	NR	NR
Kaufmann et al., 2004	Asymptomatic, oligosymptomatic and symptomatic carriers (MELAS, MERRF)	1	MD: 35 PR: 11 CR: 60 ND	MD: 32–42y ± 15–18 PR: 49y ± 14 CR: 37–50y ± 15–20	**MELAS < MERRF** **mDNA 3243 A > G asymp. > oligosymp. > symp.**	NR	NR	NR	NR	NR	NR
Kaufmann et al., 2009	MELAS	1	MD: 45 HC: 30 CR: 78 ND	MD: 29y ± 14 (4–60) HC: 49y ± 14 CR:38y ± 17	**MELAS < HC** **MELAS < CR** **CR = HC**	NR	NR	NR	NR	NR	NR
Kaufmann et al., 2011	MELAS	1	MD: 31 CR: 54 ND	MD: 30y ± 15 (4–61) CR: 38y ± 28 (4–76)	**MELAS ↓ over time** **CR no decline over time**	NR	NR	NR	NR	NR	NR
Kraya et al., 2019	MELAS	1	MD: 10 HC: 10 ND	MD: 43.8y (24–62)	NR	**C = ± 100** **MD = HC**	**MD = ND** **MD < HC**	**MD < ND (1/2 tests)** **MD < HC (1/2 tests)**	**MD = ND** **MD = HC**	**MD < ND** **MD < HC**	**MD < ND (1/2 subtests)** **MD< HC (2 subtest)**
Multiple mitochondrial syndromes and/or specific genetic mutation											
Bosbach et al., 2003	CPEO, KSS	2	MD: 22 HC: 20	MD: 48y ± 15 HC: matched	NR	NR	**MD < HC (2/4 tests)**	**MD < HC (1/3 outcomes)**	**MD < HC (1 outcome)** **MD = HC (2 tests)**	**MD < HC (3/4 tests)**	**MD < HC (3/5 tests)**
Lang et al., 1995	PEO, MELAS, KSS	1,2	MD: 23 ND	MD: 41.3y ± 16.1 (22–69)	**MELAS (↓84 %'abnormal') < PEO (↓37.5 %) < KSS (↓12.5 %)**	NR	NR	NR	NR	NR	NR
Majamaa-Voltti et al., 2006	Probands and relatives with mDNA 3243 A > G variant	1, 4	MD: 12 CR: 21 ND Follow-up	MD: 39y ± 13	**↓50 %** **Slight but n.s. decline over time**	NR	NR	NR	NR	NR	NR
Montirosso et al., 2002	CPEO, CPEOplus and ptosis and myopathy without CPEO	1,2	MD: 11 HC: 14 ND	MD: 49.2y ± 15.2 (30–77) HC: 40.4y ± 14.2 (23–64)	NR	**FSIQ:** ***M* = 98.4 ± 12.2** **MD = HC**	NR	NR	NR	NR	NR
Turconi et al., 1999	CPEO, CPEO plus, KSS, MERRF	1,2	MD: 16 ND	MD: 45.2y±13.0	NR	**FSIQ** ***M* = 100.4 ± 15.6** **VIQ > PIQ**	**↓70 %**	NR	**MD = ND**	NR	NR
Confirmed MD according to the used diagnostic criteria											
Inczedy-Farkas et al., 2014	MD with mDNA variants including mDNA 3243 A > G, 8344 A > G,	1,2	MD: 19 HC: 13 ND	MD: 35.3y ± 12.2	NR	**FSIQ *M* = 101 ± 23** **VIQ > PIQ**	NR	**MD=HC**	**MD < HC (2/4 outcomes)**	**MD < HC (1/2 tests)**	**MD < HC (1/2 outcomes)**

(*continued on next page*)

Table 2 (*continued*)

A) Cognitive functioning

	8993 T > C, 12770 A > G variants			(17–61) HC: 33.76y							
Moore et al., 2019	mDNA 3243 A > G and mDNA 8344 A > G variants	1	MD:49 HC: 32 ND Follow-up	MD:47.19y ± 13.59 HC:47.25y ± 14.42	NR	**FSIQ** ***M*** **= 85.08 ± 17.42 (↓22%) MD < ND, HC ↑ over time C = 93.4 ± 12.59 (↓0%) MD < ND**	NR	**MD < ND (4/6 outcomes) ↓2–25%^ MD < HC (5/6 outcomes) ↑ over time (2/6 outcomes)**	**MD < ND (3/5 outcomes) ↓10.2–14.3%^ MD = HC ↑ over time (4/7 outcomes)**	**Interaction effect of MD and HC on outcome**	**MD < ND (1/2 outcomes) ↓7–10%^ MD < HC N.s. effect over time**
Shurtleff et al., 2018	Confirmed MD, including complex I, III and/or IV deficiency, mDNA 3243 A > G, 8296 A > G, 4697 C > T variants	1,2	MD: 49 ND With vs without seizures	*Children:* 61–250 months	NR	**FSIQ Median: 85 (IQR: 50–102)**	NR	NR	NR	NR	NR
Probable and confirmed MD according to the used diagnostic criteria											
Eom and Lee, 2007	MD according to Bernier criteria	1,2,3	MD: 70 ND	MD: 1.8y ± 2.5 (0–9.9)	NR	**MDI** ***M*** **= 52.9 ± 11.3 ↓90% FSIQ** ***M*** **=64.4 ± 21.8 ↓60%**	NR	NR	NR	NR	NR
Kartsounis et al., 1992	Mitochondrial myopathy	4	MD: 36 ND	MD: 34.8y (13–63)	**↓72.3 % MD < ND**	NR	NR	NR	NR	NR	NR

< worse / = no significant difference/ > better performance compared to one of the reference groups
↓worse / ↑ better performance in percentage based on article specific criterium as reported in the article; – no significant differences found; NR: not reported.
C = crystalized intelligence; FSIQ = Full-scale Intelligence Quotient; PIQ = Performance Intelligence Quotient; VIQ = Verbal intelligence Quotient; MDI = Mental Developmental Index; IQR = interquartile range
^= depending on the (sub)test

B) Mental disorders

Authors	MD	Criteria	(Reference) group: *n*	Age *M* ± *SD* (range)	% with any mental disorder	Mood disorders	Anxiety disorders	Psychotic features	Personality disorders	Instruments
One specific MD based on phenotype										
Kaufmann et al., 2009	Symptomatic MELAS with mDNA 3243 A > G variant (see also A)	1	MD: 45 HC: 30 CR: 78 ND	MD: 29y ± 14 (4–60) HC: 49y ± 14 CR: 38y ± 17	NR	**32 % 17 %* 32 %**	NR	**18–37 %* 0–8 % 4–6 %**	NR	Structured interview/ Psychiatric history
Multiple mitochondrial syndromes and/or specific genetic mutation										
Mancuso et al., 2013	Mitochondrial myopathy, mitochondrial encephalomyopathy, and combined mitochondrial myopathy with PEO	2	MD: 24 ND	MD: 56y (24–85)	**63 %**	**50 %**	**46 %**	**17 %**	NR	Clinical interview; Standardized questionnaires
Confirmed MD according to the used diagnostic criteria										
Inczedy-Farkas et al., 2012	MD with primary mDNA variants including: mDNA 3243 A > G, 8344 A > G, 8993 T > G, 8332A > G, 12770 A > G, 2706 A > G variants	1	MD: 19 HSN: 10 ND	MD: 34y ± 8.4 HN: 40y ± 11.0	**63 % 30 %**	**47 % 30 %**	**5 % 0 %**	**5 % 0 %**	**42 % 0 %**	Clinical interview; Standardized questionnaires
Koene et al., 2009	Mitochondrial or OXPHOS disorder with a pathogenic mutation (including. PDHA1, MTND1, POLG1, del 4977 bp mtDNA, MTTK)	1	MD: 35 ND	MD: 8.7y (2–18)	**14 %**	**14 %**	NR	NR	NR	DSM-IV criteria; Standardized questionnaires.
Probable and confirmed MD according to the used diagnostic criteria										
Anglin et al., 2012	Probable or genetically confirmed MD, including MELAS, MERRF, complex I deficiency, mitochondrial cytopathy	1,3	MD: 15 HC: 15 ND	MM: 51.7y ± 8.7 HC: 50.2y ± 8.6 (ns)	**93 %** NR	**67 %** NR	**60 %** NR	NR NR	**7 %** NR	Clinical interview; Standardized questionnaires

(*continued on next page*)

Table 2 (*continued*)

B) Mental disorders

Authors	MD	Criteria	(Reference) group: *n*	Age *M* ± *SD* (range)	% with any mental disorder	Mood disorders	Anxiety disorders	Psychotic features	Personality disorders	Instruments
Fattal et al., 2007	Probable or confirmed MD: MELAS, KSS, complex I deficiency, complex IV deficiency, mitochondrial cytopathy not otherwise specified, other (criteria Bernier et al., 2002)	2,3	MD: 36 ND	MD: 41y ± 14 (18−63)	**70 %**	**11−54%**	**3−11 %**	**3 %**	NR	Clinical interview; Standardized questionnaires
Frye et al., 2013	Probable or confirmed MD (criteria Morava et al., 2006)	2,3	ASD/MD: 18 ASD: 18 ND	ASD/MD: 8.5y ± 3.0 ASD: 7.9y ± 3.2	**100 %**[a] **100 %**[a]	NR	NR	NR	NR	Standardized questionnaire

Percentages are given for number of patients of the sample with a (specific) mental disorder, e.g. mood disorders includes major depressive disorder, dysthymia, bipolar disorder and other mood-related mental disorders. NR: not reported.
[a] ASD was focus of the study

C) Psychological and social functioning

Authors	MD	Criteria	(Reference) group: *n*	Age *M* ± *SD* (range)	Mood / anxiety symptoms	Fatigue	Social impairments	Quality of life*	Other mental symptoms	Instruments
One specific MD based on phenotype										
Cui et al., 2018	LHON with mDNA 11778 G > A variant	1	MD: 55	MD: 16,3y (13.9–18.3)	NR	NR	NR	↓	NR	Standardized questionnaires
Ferguson and de Abreu, 2016	LHON	4 (1)	MD: 8	Age range 21−62y	NR	NR	NR	NR	≈ / ↑	Interview
Garcia et al., 2017	LHON	4 (1)	MD: 103	MD: 29.4y ± 13.2	**50 %**	NR	**71 %(UQ)**	NR	NR	Questionnaire
Kirkman et al., 2009	Symptomatic LHON with mDNA 3460 G > A, mDNA 11778 G > A or mDNA 14484 T > C variants	1	MD: 196 AC: 206	MD: 43.3y (13−82) AC: 47.8y (14−83)	NR	NR	NR	**MD < AC** **mDNA14484 T > C > mDNA 3460 G > A, mDNA11778 G > A**	NR	Standardized questionnaires
Fromont et al., 2009	MIDD with mDNA 3243 A > G or mDNA 14709 T > C variants (see also A)	1	MD: 11 T1D: 9 ND	MD: 53.6y (33−64) T1D: 55.9y (33−67)	–	NR	NR	NR	NR	Standardized questionnaires
Martens et al., 2014	Mitochondrial myopathy	2,3	MD: 6 HC: 10	MD: 9.8y (7−13) HC: 10.2y (8−12)	NR	**MD > HC**	**MD = HC**	**MD < HC (4/5)**	NR	(Standardized) questionnaires
Smits et al., 2011	Genetically confirmed CPEO	1	MD: 28 T1D: 28	MD: 46.9y (28−75) T1D: matched	**32 %*** **7 %**	**68 %** **MD > T1D (2/4)**	**MD > T1D**	NR	NR	Standardized questionnaires
Smits et al., 2012	Genetically confirmed CPEO	1	MD: 20	MD: 47.7y (23−65)	**25−45 %**	**75 %**	NR	NR	**35 %**	Standardized questionnaires
Multiple mitochondrial syndromes and/or specific genetic mutation										
Bosbach et al., 2003	CPEO, KSS (see also A)	2	MD: 22 HC: 20 ND	MD: 48y ± 15 HC: matched	NR	NR	**MD = ND**	**MD < ND (4/6)**	NR	Standardized questionnaires
Custers et al., 2018	MELAS spectrum disorders with mDNA 3243 A > G variant	1	MD: 76 ND	MD: 47.3y (15−69)	**25−26 %**	NR	NR	≈	**18−46 %**	Standardized questionnaires
Morava et al., 2010	OXPHOS disorders	2	MD: 18 OEIEM SOTOS ND	MD: 8,6y (3−18)	**67 %*** **MD*> OEIEM, ND**	**22 %*** **MD* > ND**	NR	NR	**22 %; 50 %**** **MD = OEIEM, ND** **MD*>OEIEM, SOTOS, ND**	Standardized questionnaire
Noorda et al., 2012	MELAS, MERRF, Leigh disease	4 (2)	MD: 16	MD: 43y	NR	NR	NR	NR	↑	Interview
		1		MD: 45y (19−67)	**26−32 %**	**78 %**	**MD > ND**	**MD < ND**	**37 %**	

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Table 2 (*continued*)

C) Psychological and social functioning

Authors	MD	Criteria	(Reference) group: *n*	Age *M* ± *SD* (range)	Mood / anxiety symptoms	Fatigue	Social impairments	Quality of life*	Other mental symptoms	Instruments
Verhaak et al., 2016	MELAS spectrum with mDNA 3243 A > G variant		MD: 72 (T2: 50; T3: 48) ND							Standardized questionnaires
Confirmed MD according to the used diagnostic criteria										
Burnett et al., 2005	Probable maternally inherited (PMI) MD or probable non-maternally inherited (PnMI) MD (see also E)	4	PMI: 55 PnMI: 111	PMI: median 8y, 18+ : 27 % PnMI: median 7y, 18+: 30 %	**Probands 18−19 % (UQ)** **Probands 18−20 % (UQ)**	NR	NR	NR	≈	Questionnaire
Gorman et al., 2015	MD with genetic confirmation, including MELAS, MERRF, LHON, NARP	1	MD: 132 HC: 132 CFS: 74	MD: 52y (18−82) HC: 52y (21−77) CFS: 54y (24−80)	– **CFS > MD > HC (depressive)** **MD & CFS > HC (anxiety)**	**62 %** **MD > HC**	NR	NR	NR	Standardized questionnaires
Inczedy-Farkas et al., 2012	MD with primary mDNA variants (see also B)	1	MD: 19 HN: 10	MD: 34y ± 8.4 HN: 40y ± 11.0	**MD>HN**	NR	NR	NR	**MD>HN (10/12)**	Standardized questionnaires
Inczedy-Farkas et al., 2014	MD with mDNA variants (see also A)	1,2	MD:19 HC: 13 ND	MD: 35.3y ± 12.2 (17−61) HC: 33.8y	NR	NR	NR	NR	**?**	Standardized questionnaires
Koene et al., 2013	MD based on clinical presentation, laboratory test and/or genetic testing	2	MD: 78	MD: <3y: 6.4 %; 3−6y: 33.3%, 7−12y: 41.0%, > 13y: 19.3%	NR	**66−67 % (UQ)**	**73−87 % (UQ)**	NR	**10−55 % (UQ)**	Questionnaire
Krieg et al., 2016	Genetically confirmed MD (self-reported)	4 (1)	Genetic: 55 Probable: 146	MD: 18−60+	NR	NR	NR	NR	**≈ (UQ)**	Questionnaire
Lindenschot et al., 2019	Genetically confirmed MD	1	MD: 17	MD: 10.4y (4−18)	NR	**?**	NR	NR	NR	Standardized questionnaires
Moore et al., 2019	mDNA 3243 A > G and mDNA 8344 A > G variants (see also A)	1	MD:49 HC: 32	MD: 47.2y ± 13.6 HC: 47.3y ± 14.4	**?**	NR	NR	NR	NR	Standardized questionnaires
Parikh et al., 2019	mDNA 3243 A > G, mDNA 8344 A > G, and mDNA 10466 C > T variants, mDNA deletion; nDNA mutations	1	MD: 48	MD: 18+	**20−62 %**	**71−100 %**	NR	NR	NR	Standardized questionnaires
Poole et al., 2019	Genetically confirmed MD including mDNA 3243 A > G, 8344 A > G, 3260 A > G, 9185 T > C	1	MD: 58 C: 19	MD: 46.2y ± 14.9	NR	NR	NR	**↓59 %** **↓46 %**	NR	Standardized questionnaire
Probable and confirmed MD according to the used diagnostic criteria										
Anglin et al., 2012	Probable or genetically confirmed MD (see also B)	1,3	MD: 15 HC: 15	MD: 51.7y ± 8.7 HC: 50.2y ± 8.6 (ns)	**MD < HC**	NR	NR	NR	**MD = HC**	Standardized questionnaires
Eom and Lee, 2017	MD according to Bernier criteria (see also A and E)	1,2,3	MD: 70 ND	MD: 1.8y ± 2.5 (0−9.9)	NR	NR	**55 %**	NR	**25−43 %**	Standardized questionnaires
Fattal et al., 2007	Probable or confirmed MD: MELAS, KSS, complex I deficiency, complex IV deficiency, Mitochondrial cytopathy not otherwise specified, other (see also B)	2,3	MD: 36 With vs without mental disorder	MD: 41y ± 14 (18−63)	NR	NR	**With mental disorder > without mental disorder**	**With mental disorder < without mental disorder (5/9)**	NR	Standardized questionnaires
Read, 2003	MD, including Leigh disease, KSS, MELAS, complex I or III defiency and undetermined	2,3	MD: 29 PKU: 29	Children, MD & PKU combined: 8.8y (6 m – 18y)	NR	NR	**MD > PKU**	NR	NR	Interview, Standardized questionnaires
		1,2,3	MD: 22		NR	NR	**?**	NR	NR	

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Table 2 (*continued*)

C) Psychological and social functioning

Authors	MD	Criteria	(Reference) group: *n*	Age *M* ± *SD* (range)	Mood / anxiety symptoms	Fatigue	Social impairments	Quality of life*	Other mental symptoms	Instruments
Rogac et al., 2011	Definite MD according to Mitochondrial Disease Criteria			MD: 7.3y (0.5−18.5)						Standardized questionnaires
Schreiber, 2012	MD (self-reported)	4 (1,3)	MD: 14	MD: 12−18y (*n* = 9); 19−21y (*n* = 5)	**?**	NR	NR	NR	**?**	Standardized questionnaires

Clinically relevant symptoms in % of sample; + symptoms present (mean above clinical cut-off as defined in the article); - not present (below clinical cut-off); n/a not mentioned or studied;
Outcomes: ↓ ≈ ↑ : Relatively low/mild – moderate – high/severe symptoms or impairments (compared with norms or controls);? : implications of scores were not clearly described or compared with reference groups; NR: not reported
Equations: MD scores significantly worse (<), similar (=) or better (>) than controls, numbers between () following the equation describes the number of tests or subscales for which the equation applies, when differences per test/subscale were present.
*Quality of life is only shown if standardized measures were used measuring these specific outcomes. Quality of life: ↑ ≈ ↓: Relatively good – moderate – worse functioning (compared with norms or controls);? : implications of scores were not clearly described or compared with reference groups; NR: not reported.
Social functioning is shown when (sub)scales of standardized questionnaires were used.
(UQ) Symptoms and/or impairments reported in unstandardized, study-designed questionnaires or qualitative studies.

D) Intervention studies

Authors	MD	Criteria	(Reference) group: *n*	Age *M* ± *SD* (range)	Cognitive functioning	Mood symptoms	Quality of life	Fatigue	Other	Instruments
One specific MD based on phenotype										
Martinelli et al., 2012	Genetically confirmed Leigh syndrome	1	MD: 10 Literature: 115	MD: 6.3y (1−13)	NR	NR	+	NR	NR	Standardized questionnaires
Murphy et al., 2008	CPEO with sporadic, heteroplasmic, single, large-scale deletion of mDNA	1	MD: 8	MD: 39y ± 9 (25−48)	NR	NR	–	NR	NR	Standardized questionnaire
Taivassalo et al., 2006	CPEO with a sporadic single, large-scale deletion of mDNA	1	MD: 8	MD: 40.8y (25−60)	NR	NR	+	NR	NR	Standardized questionnaire
Multiple mitochondrial syndromes and/or specific genetic mutation										
Bates et al., 2013	MD with mDNA 3243 A > G variant	1	MD: 10 HC: 10	MD: 42.4y ± 10.5 HC: 39.0y ± 11.8	NR	NR	–	–	NR	Standardized questionnaires
Janssen et al., 2019	MELAS spectrum with mDNA 3243 A > G variant	1	Intervention: 11 Placebo: 9	Intervention: 44y (21−54) Placebo: 43y (22−61)	+	+	–	–	NR	Standardized questionnaires
Mancuso et al., 2010	PEO, PEO + proximal myopathy, mitochondrial myopathy	1	MD: 27 HC: 42	MD: 55,3y ± 12.9 HC: 55.9y ± 16.5	NR	NR	–	NR	NR	Standardized questionnaires
Taivassalo et al., 1998	Mitochondrial myopathy including CPEO + myopathy and KSS	1,2	MD: 10	MD: 36y ± 9	NR	NR	+	NR	NR	Standardized questionnaire
Zweers et al., 2020	MD with mDNA 3243 A > G variant	1	Intervention: 20 Waitlist: 18	Intervention: 47y ± 13 Waitlist: 47y ± 14	NR	NR	+ / -	+ / -	NR	Standardized questionnaires
Confirmed MD according to the used diagnostic criteria										
Fiuza-Luces et al., 2018	MD including CPEO, MELAS, progressive myopathy	1	MD: 12	MD: 46y ± 12 (19−59)	NR	NR	+ / -	NR	NR	Standardized questionnaire
Glover et al., 2010	MELAS, CPEO, mitochondrial myopathy, NARP, LHON, mDNA 9035 T > C variant	1,2	MD: 30	MELAS: 48y ± 3 Other: 56y ± 3	NR	NR	–	NR	NR	Questionnaire

Treatment effects are visualized: - no effect, + improvement on outcome, + / - an effect on some subscales or time points, but not all. NR: not reported.

E) Family-focused studies

Authors	Diagnosis	Criteria	(Reference) group: *n*	Age *M* ± *SD* (range)	Cognitive impairments	Mental disorders	Mood/ anxiety symptoms	Stress	Other	Instruments
Multiple mitochondrial syndromes and/or specific genetic mutation										
Kim et al., 2010	Mother of child with MD with complex I defect: MELAS, Leigh, nonspecific encephalopathy	2	MD: 33 IE: 32	MD: 37.7y ± 5.2 (29−55) IE: 35.4y ± 4.6	NR	NR	**39−42 %*** **3−9 %**	NR	**MD > IE (6/12)**	Standardized questionnaires

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Table 2 (*continued*)

E) Family-focused studies

Authors	Diagnosis	Criteria	(Reference) group: *n*	Age *M* ± *SD* (range)	Cognitive impairments	Mental disorders	Mood/ anxiety symptoms	Stress	Other	Instruments
Probable and confirmed MD according to the used diagnostic criteria										
Boles et al., 2005	Mothers and matrilineal relatives of child with presumed maternally inherited MD	1,3	MD: 15 ARMD: 17	Children: MD: 9.8y ± 5.7 ARMD: 6.9y ± 4.4 p = 0.1	NR	**87 %*** **18 %**	**MD > ARMD (5/8)**	NR	NR	(Standardized) questionnaires
Burnett et al., 2005	PMI and PnMI (see also C)	4	PMI: 55 PnMI: 111	Median: MD: 7−8y, 18+ : 27 %–30 %	NR	**maternal: 38–51 %*** **paternal: 9–12 %** **(UQ)** **maternal: 10–12 %** **paternal: 10–12 %** **(UQ)**	NR	NR	≈	Questionnaire
Eom and Lee, 2017	Mothers of child with MD according to Bernier criteria (see also A and C)	1,2,3	MD: 70 ND	MD: 1.8y ± 2.5 (0−9.9)	NR	NR	**65 %**	**75 %**	NR	Standardized questionnaires
Read, 2003	Mothers of child with MD including Leigh disease, KSS, MELAS, complex I or III defiency and undetermined	2,3	MD: 29 PKU: 29	Mothers MD & PKU combined: 38y (20−58)	NR	NR	NR	**MD > PKU**	**MD > PKU**	Interview, Standardized questionnaires
Senger et al., 2016a	Parents of child with possible, probable or definite MD	4 (1,2,3)	MD: 231	Mothers: 42y ± 8,3; Children MD: 9.9y ± 5.2	NR	NR	NR	**?**	↑	Standardized questionnaires
Senger et al., 2016b (same sample as Senger et al., 2016a)	Parents of child with possible, probable or definite MD	4 (1,2,3)	MD: 231	Mothers: 42y ± 8,3 Children MD: 9.9y ± 5.2	NR	NR	NR	**?**	**?**	Standardized questionnaires
Varvogli and Waisbren, 1999	Mothers of a child with suspected or confirmed MD	1,2,3	MD: 42	Mothers: 34.7y ± 5.4 (23−49) Children MD: 6.3y ± 4.7 (8 months-22y)	NR	NR	NR	NR	**56 %**	Standardized questionnaires

Clinically relevant symptoms in % of sample; + symptoms present (mean above clinical cut-off as defined in the article); - not present (mean below clinical cut-off); n/a not mentioned or studied;
Outcomes: ↓ ≈ ↑ : Relatively low/mild– moderate – high/severe symptoms or impairments (compared with norms or controls);? : implications of scores were not clearly described or compared with reference groups; NR: not reported.
Equations: MD scores worse (>), similar (=) or better (<) than reference group, numbers between () following the equation describes the number of tests or subscales for which the equation applies, when differences per test/subscale were present.
(UQ) Symptoms and/or impairments reported in unstandardized, study-designed questionnaires or qualitative studies.

MD diagnosis:
1: Genetically confirmed MD.
2: Definite MD based on existing diagnostic criteria using a combination of clinical, biochemical, histomorphologic, neuroimaging, respiratory chain, and/or genetic evidence.
3: Probable based on existing diagnostic criteria using a combination of clinical, biochemical, histomorphologic, neuroimaging, respiratory chain, and/or genetic evidence.
4: Other: self-reported, (asymptomatic) carriers, no description of used diagnostic criteria. When self-reported, the included (self-reported) diagnoses are between brackets.
Abbreviations reference groups:
AC: asymptomatic carriers; ARMD: autosomal recessive metabolic disorder; CFS: chronic fatigue syndrome; CR: carrier relatives (matrilineal, asymptomatic, oligosymptomatic or *symptomatic* carriers); HC: healthy controls; HSN: hereditary sensorimotor neuropathy; IE: intractable epilepsy; ND: normative data, age/ education adjusted; OIEM: other inborn errors of metabolism; PKU: phenylketonuria; PMI/PnMI: probable maternally inherited / probable non-maternally inherited; PR: paternal relatives; T1D: Type 1 diabetic patients.

refer to Table 2, more detailed results are described in Supplementary Tables 2−5. Results of case studies are described in Supplementary Table 6.

3.4.1. Cognitive functioning

For a global overview of the results, we refer to Table 2. Detailed description of the individual studies and test results, see Supplementary Table 2.

3.4.1.1. Global cognitive functioning. Six studies reported global cognitive functioning in adults, indicating the more general cognitive functioning as assessed by composite scores of multiple neuropsychological tests or a cognitive screener. Five studies reported a worse functioning in patients with different types of MD, that is, 1) Mitochondrial Spinocerebellar Taxia and Epilepsy (MSCAE), 2) mitochondrial myopathy, 3) MELAS, 4) asymptomatic, symptomatic and oligosymptomatic carriers of MELAS and Myoclonic Epilepsy with Ragged-red Fibers (MERRF), and 4) Progressive External Ophthalmoplegia (PEO), MELAS and Kearns–Sayre Syndrome (KSS), compared to either normative data, other patient groups or healthy controls (Gramstad et al., 2009; Kartsounis et al., 1992; Kaufmann et al., 2009, 2004; Lang et al., 1995). A 6th study reported scores in the normal range on a dementia screener in patients with MIDD (mDNA 3243 A > G and mDNA 14709 T > C variants) (Fromont et al., 2009).

3.4.1.2. Intellectual functioning. Five studies examined intellectual functioning in adult patients with a variety in MD, with the Wechsler intelligence tests (Gramstad et al., 2009; Inczedy-Farkas et al., 2014; Montirosso et al., 2002; Moore et al., 2019; Turconi et al., 1999), and two studies focused on children (Eom and Lee, 2017; Shurtleff et al., 2018). Results on the Full-Scale Intelligence Quotient (FSIQ) were mixed. Four studies reported lower scores (ranging from intellectual disability to scores in the below-average range) compared to normative data (Eom and Lee, 2017; Gramstad et al., 2009; Moore et al., 2019; Shurtleff et al., 2018) or healthy controls (Moore et al., 2019), while two studies reported scores in the normal range (Montirosso et al., 2002; Turconi et al., 1999), and one study in the normal range but more variable compared with healthy controls (Inczedy-Farkas et al., 2014).

Regarding specific intelligence profiles (using Wechsler's Index Scores), four studies reported a higher verbal than performance IQ (Eom and Lee, 2017; Gramstad et al., 2009; Inczedy-Farkas et al., 2014; Turconi et al., 1999). In two studies verbal versus performance IQ scores were not analyzed (Montirosso et al., 2002; Shurtleff et al., 2018). Moore et al. (2019) reported a better functioning on the perceptual reasoning index compared with the processing speed index. Results of Shurtleff et al. (2018) reported worse performance in children with versus those without seizures, in which the latter had an average intelligence.

One study assessed non-verbal intelligence with the Raven's Progressive Matrices (Raven's PM-38) and reported in twenty percent of the Maternally Inherited Diabetes and Deafness (MIDD) patients an impaired score (z-score < -1.65) (Fromont et al., 2009).

Two studies investigated premorbid cognitive intelligence (estimated intelligence level, a measure for crystallized intelligence, which is less susceptible for changes after cerebral dysfunctions due to a disease or illness) as an indication of comparability between the patient group and control group. Results showed functioning in the normal range (Kraya et al., 2019), and mild to moderate premorbid cognitive difficulties (impairments 1 SD = 27 %; 1.5SD = 18 %, 2 SD = 0 %) (Moore et al., 2019). Another study reported a moderate to severe discrepancy between estimated levels of premorbid ability and performance on an intelligence test, indicating intellectual deterioration (Kartsounis et al., 1992).

3.4.1.3. Specific cognitive domains. In seven studies multiple cognitive domains were tested, all focusing on adults with a variety in MD (Bosbach et al., 2003; Fromont et al., 2009; Gramstad et al., 2009; Inczedy-Farkas et al., 2014; Kraya et al., 2019; Moore et al., 2019; Turconi et al., 1999). Results are summarized for the different cognitive domains.

Visuospatial perception was assessed in two studies using different tests. One study reported that 70 % of the MD patients showed impairments (score <1 SD) as compared with the norms (Turconi et al., 1999) while another study found no differences compared with healthy controls (Bosbach et al., 2003).

Four studies investigated *visuoconstructive skills* with the Rey's Complex Figure Test (copy trial). Two studies reported a worse functioning of patients with MD as compared with healthy controls (Bosbach et al., 2003; Kraya et al., 2019). Two studies reported a worse functioning compared with normative data; one study reported a z-score of <1 SD below the mean in 70 % of the patients (Turconi et al., 1999), and one reported z < -1.65 in 60 % the patients (Fromont et al., 2009). One study analyzed visuoconstructive skills with another test, and reported a worse performance compared with healthy controls (Bosbach et al., 2003).

Executive functioning was assessed in three studies with the Trail Making Test part B (TMT B). One study reported a worse performance on this task in patients with MD compared with healthy controls (Kraya et al., 2019), and one a below average performace (Inczedy-Farkas et al., 2014). Fromont et al. (2009) detected an impaired performance in 44 % of the patients (z < -1.65). The remaining studies examined executive functioning with a range of tests, of which two studies did not report any differences in performance of MD patients compared to healthy controls (Inczedy-Farkas et al., 2014; Kraya et al., 2019). Three other studies reported mixed results on different tests, that is, a worse functioning on some but not all subtests compared with normative data and/or healthy controls (Bosbach et al., 2003; Fromont et al., 2009; Moore et al., 2019).

A total of 7 studies assessed one or more domains of *auditory/ verbal memory functioning*. Regarding verbal-auditory working memory, one study showed an impaired score in 40 % of the patients (standard score <6, mean = 8−12) (Fromont et al., 2009). Another study reported a below-average performance as compared to normative data, and a non-significant trend towards worse performance compared with healthy controls (Kraya et al., 2019). The verbal auditory episodic memory was assessed in five studies, three of which used the Rey Auditory Verbal Learning Test (RAVLT). Regarding the immediate recall measure of this task, two studies reported average scores and no difference with healthy controls (Bosbach et al., 2003; Kraya et al., 2019), and one study reported a below average performance compared with healthy controls (mean z-score = -1.8) (Inczedy-Farkas et al., 2014). Performance on the short and long delayed recall conditions of the RAVLT were in the average range in one study (Bosbach et al., 2003), while another study reported impaired scores as compared to healthy controls (short delayed recall mean z-score = -2.5, long delayed recall mean z-score = -2.4) (Inczedy-Farkas et al., 2014). One study did not assess the delayed recall conditions (Kraya et al., 2019). Moore et al. (2019) used an extensive memory battery, the WMS-IV, to assess verbal auditory episodic memory, and reported a worse performance on 3/5 of the subtests as compared with normative data, but no differences compared with healthy controls matched on age and premorbid cognition. Performance on 4/7 subtests (also including two recognition tasks) improved over time, possibly reflecting a practice effect. Fromont et al. (2009) also used an extensive battery, the Free and Cued Selective Reminding Test (FCSRT), and reported average scores in patients, except on the three trials of recall condition (each trial consisting of a free, and when indicated, a cued condition), each consisting of a free recall and when indicated a cued recall, in which 22 % of the patients had a z-score<-1.65.

Non-verbal/visual memory was assessed with the Rey-Osterrieth Complex Figure Test (ROCFT) in 4 studies. Compared to normative data, one study reported a score of <1 SD below the mean on the recall

condition in 70 % of the patients (Turconi et al., 1999), another study reported a z-score < - 1.65 on immediate recall in 50 % of the patients (Fromont et al., 2009), and a third study reported scores in the average range on delayed recall (Kraya et al., 2019). Two studies compared the performance to healthy controls and did not find any differences (Bosbach et al., 2003; Kraya et al., 2019). Fromont et al. (2009) used the visual subtests of the WMS-R and reported impairment rates of 20 % (standard score <6, mean = 8−12) on immediate and 30 % on delayed recall.

There were other two studies using an extensive memory battery, investigating multiple domains of episodic memory performance. Turconi et al. (1999) reported no difference in verbal or visual memory performance using the Memory Assessment Scale, but found a worse performance on immediate memory compared with normative data. Gramstad et al. (2009) used the WMS-R for memory assessment and reported, based on individual test results, a tendency towards lower visual than verbal memory performance.

Attention and concentration was assessed in 4 studies, using in total 7 different (sub)tests, of which only the TMT part A was examined in more than 1 study. Patients with MD performed worse compared with healthy controls on all tests (Bosbach et al., 2003; Inczedy-Farkas et al., 2014; Kraya et al., 2019), except one (Bosbach et al., 2003).

Regarding *verbal skills/ language performance*, four studies reported impairments regarding verbal fluency on one or more (sub)test compared with healthy controls and/or normative data (Bosbach et al., 2003; Fromont et al., 2009; Inczedy-Farkas et al., 2014; Kraya et al., 2019; Moore et al., 2019). Results on 4 other (sub)tests were mixed; on 2 tests, patients performed worse than controls, but on the other two no differences were found (Bosbach et al., 2003; Fromont et al., 2009).

3.4.1.4. Cognitive functioning across repeated assessments. Three studies investigated cognitive functioning across repeated assessments. One of these, the study by Kaufmann et al. (2011), reported a worsening in neuropsychological global score over time (from baseline to 1 and 4 years follow-up) in patients with fully symptomatic MELAS spectrum disorders (defined as having evidence of focal brain involvement in addition to lactic acidosis), aged 30 ± 15 years, while no decline was observed in symptomatic or asymptomatic relatives (who represent obligate carriers by pedigree analysis).

Two studies did not report a significant decline in cognitive functioning over time. Majamaa-Voltti et al. (2006) tested adult patients aged 39 ± 13 with the mDNA 3242A > G mutation at baseline and after a 3-year follow-up. 16 patients (50 %) showed a cognitive impairment at baseline (5/7 domains z-score < 1.65), and repeated assessment over three years showed a slight, but non-significant decline. The study by Moore et al. (2019) reported an increase in Full Scale Intelligence Quotient (FSIQ), as well as on some but not all executive functioning and memory tests, from baseline to 6- and 18-month follow-up in patients with the mDNA 3243A > G and mDNA 8344A > G mutations as well as in the control group. The authors suggest that this is likely due to "practice effects caused by familiarity, and indicative of normal learning ability" (Moore et al., 2019, p. 834).

3.4.1.5. Influence of psychological outcomes on cognitive functioning. Two studies investigated the influence of psychological outcomes on cognitive functioning. Moore et al. (2019) reported both anxiety and depressive symptoms negatively influenced scores on several subtests of cognitive functioning and anxiety negatively influenced FSIQ. In contrast, Inczedy-Farkas et al. (2014) examined general psychopathology, which did not correlate with cognitive performance. Several other studies investigated or reported on both cognitive and psychological outcomes, but did not investigate whether a relationship existed between these domains (e.g. Eom and Lee, 2017; Kaufmann et al., 2009; Koene et al., 2013; Lindenschot et al., 2018; Rogac et al., 2011; Smits et al., 2011).

3.4.1.6. Relationship between disease manifestation and cognitive functioning. Seven studies included one or more disease-specific variables in relation to cognitive functioning in *adults*. Two studies did not find significant correlations with amongst others age of onset, disease duration or grade of heteroplasmy (Bosbach et al., 2003; Turconi et al., 1999).

The remaining five studies did report significant correlations with one or more disease-specific measures. First, one study reported significant negative correlations between duration of disease and functional disability with most measures of cognitive functioning as assessed in patients with primary mDNA alterations (Inczedy-Farkas et al., 2014). Kraya et al. (2019) reported significant correlations between disease severity (high scores in NMDAS) as well as lesion load in MRI, with some but not all cognitive tasks measured. Furthermore, Kaufmann et al. (2004) reported a correlation between cognitive impairment and MRS ventricular lactate levels in matrilineal 3243 A> G subjects. Within MERRF families, the ventricular lactate levels of clinical groups were not significantly different, but there was a trend toward higher lactate values in more symptomatic individuals. Authors suggest that neuropsychological and neurological deficits are not merely the consequences of stroke-like episodes, but rather caused by ventricular lactate levels. They found differences *'not only between patients with or without clinical CNS involvement, but also between individuals and groups without clinical CNS involvement'* (Kaufmann et al., 2004, p. 1300). The fourth study reported that patients with mitochondrial myopathies and encephalomyopathies with severe cognitive deficits all had cerebral atrophy, and the majority of the patients with generalized and/or focal cognitive deficits showed abnormalities on computed tomographic (CT) scans and/or on electroencephalograms (ECG) (Kartsounis et al., 1992). Authors conclude that the incidence of cognitive dysfunction is 50 % higher than that predicted by clinical assessment. Finally, the study by Moore et al. (2019) described repeated measurements over an 18-month follow-up period, and reported premorbid cognitive ability and disease severity as consistent predictors of cognitive functioning in patients. However, disease severity remained stable over the 18-month follow-up period and was therefore unlikely to trigger further cognitive decline. They reported no genotypic differences in cognitive functioning, while anticonvulsant medication and mood negatively predicted some measures of cognitive functioning.

Two studies focused on *children*. In young children with MD, higher levels of cognitive development were found in children without versus those with diffuse brain atrophy, and in children without versus those with intractable epilepsy (Eom and Lee, 2017). No differences were found regarding diffuse brain atrophy or intractable epilepsy in intelligence levels as assessed in children of 'adequate age' to perform an intelligence test. Results of Shurtleff et al. (2018) reported worse performance on an intelligence test in children with versus those without seizures.

Five studies compared *cognitive functioning between different types of MD*. Two of these studies used a cognitive screener. One reported a worse performance of patients with MELAS compared with patients with MERRF (Kaufmann et al., 2004). The second study showed that patients with MELAS performed worst, followed by patients with PEO and KSS (Lang et al., 1995). Another study also compared patients with chronic PEO (CPEO) with patients with KSS on multiple tests, but reported no differences between these groups on cognitive functioning (Bosbach et al., 2003). This is in line with results of a study reporting no differences in cognitive functioning in a small sample of 12 patients with CPEO, 3 patients with KSS, and 1 with MERRF (Turconi et al., 1999). Finally, one study (Fromont et al., 2009) compared cognitive functioning of patients with MIDD with patients with type 1 diabetes (T1D). Patients with MIDD performed worse compared with T1D on non-verbal intelligence and verbal working memory, but there were no differences regarding visuo-constructive functioning, executive functioning, and auditory/verbal or visual/non-verbal memory. Overall, five out of ten MIDD patients and two out of nine T1D controls had at least on two tests

an unsuccessful performance.

3.4.1.7. Case studies. Thirty-four out of forty-five case studies/series included some aspect of cognitive functioning. Results of one or more neuropsychological tests were described in 15 studies ($n = 23$). The remaining studies did not specify the assessment of cognitive functioning or only reported self-reported impairments or cognitive complaints (see Supplementary Table 6 for specific details). We used the terminology of impairment as described in the articles, in absence of specific scores in some of the studies.

Reported intellectual functioning ranged widely (FSIQ scores 40–114, n =11). Three patients had a significantly higher verbal than performance IQ. Five out of seven patients had impaired verbal fluency, and one patient had a below-average performance. Five out of six patients had deficits in one or more types of attention. Furthermore, patients showed deficits in motoric speed (n =3), motoric slowing ($n = 1$). Regarding working memory, seven patients were impaired, one had a low-average performance and one performed in the average range. With regard to episodic memory, three out of eight patients had impairments in the visual domain, whereas five out of ten patients had verbal memory impairments. Impairments in visuoconstruction were reported ($n = 6$), while there were no impairments in visuospatial functioning ($n = 4$). Nine patients had executive functioning deficits on one or more domains (e.g. planning) ($n = 4$).

Three case studies assessed *functioning over time,* reporting heterogeneous results. Neargarder et al. (2007) reported intraindividual variability in performance over an 8-month period, that is, an increase in some and a decrease in others, in two children with mitochondrial cytopathy with a genetic mutation at nt 15,924. Sartor et al. (2002) tested a patient with the diagnosis of MELAS syndrome over a 4-year follow-up period and reported that all cognitive functions which were impaired at baseline (the domains of fluency, verbal short term memory, and spatial orientation), remained impaired at follow-up. Verbal learning, working memory and recognition remained unimpaired. There was a deterioration in, amongst other, phasic alertness and tactile functions. Finally, Anglin et al. (2012a) reported an increase in IQ (99 instead of 88) over a 10-year period in a patient with a MELAS 3271 mutation.

3.4.2. Mental health

The concept of mental health was divided into the following subcategories: mental disorders, psychological functioning and social functioning.

3.4.2.1. Mental disorders. Six studies used psychiatric interviews to diagnose mental disorders, one study described the psychiatric history reported by patients (Kaufmann et al., 2009). Detailed outcomes of these studies are described in Supplementary Table 3. Four research articles focused on adults with MD and provided an overview of the presence of mental disorders in general. One study described several mental disorders commonly seen in the psychiatric history of the patients (Kaufmann et al., 2009), whereas two research articles focusing on children studied a specific mental disorder, namely major depressive disorder or autism spectrum disorder.

Current and past diagnosed mental disorders in adult patients with MD were described in five studies which included samples ranging from 15 to 45 (symptomatic) patients (Anglin et al., 2012b; Fattal et al., 2007; Inczedy-Farkas et al., 2012; Mancuso et al., 2013). Mental disorders were highly prevalent: 63−93 % of the patients had been diagnosed with at least one current and/or past psychiatric disorder (Anglin et al., 2012b; Fattal et al., 2007; Inczedy-Farkas et al., 2012). Furthermore, Mancuso et al. (2013) performed neuropsychiatric interviews in patients with MD but without a known diagnosis of a mental disorder and reported that more than 60 % of their sample ($n = 15$ / 24) met the criteria for a mental disorder. They did not find an association between disease manifestation as measured by the NMDAS and the presence of a mental disorder.

Mood disorders were most often observed. Overall, major depressive disorder was most common, followed by anxiety disorders (Anglin et al., 2012b; Fattal et al., 2007; Inczedy-Farkas et al., 2012; Kaufmann et al., 2009; Mancuso et al., 2013). An estimated lifetime prevalence of 54 % for major depressive disorder has been reported in MD patients (Fattal et al., 2007). Psychotic features were present in 3–37 % of the patients (Fattal et al., 2007; Inczedy-Farkas et al., 2012; Kaufmann et al., 2009; Mancuso et al., 2013), whereas diagnosed personality disorders varied between 6–42 % (Anglin et al., 2012b; Inczedy-Farkas et al., 2012). Differences in observed psychotic features may be related to the different included MD subtypes and the scope of the individual studies. Kaufmann et al. (2009) reported a prevalence of 18 % for delusions and 37 % for hallucinations in patients with MELAS. In contrast, the studies of Fattal et al. (2007) and Inczedy-Farkas et al. (2012) included a wide variety of mitochondrial disorders and found that psychotic symptoms were only present in 3–5 % of patients. Personality disorders were uncommon (or not reported) in most studies. In contrast, Inzedy-Farkas et al. (2012) reported that 42 % of their MD patients with a mDNA mutation were diagnosed with a personality disorder.

In children with MD, two studies focused on a specific mental disorder. Koene et al. (2009) found that five out of 35 children and adolescents with oxidative phosphorylation (OXPHOS) disorder presented with major depressive disorder according the DMS-IV criteria before their MD diagnosis. In all children, major depression presented within a year after fatigue complaints had started. Furthermore, both patients with a maternal carrier showed a family history of depression whereas the other three patients did not. Frye et al. (2013) investigated differences between patients with MD and comorbid autism spectrum disorders (ASD) and patients with ASD only. The group with MD scored lower on communication and daily living skills. No differences were found on autistic behavior and social dysfunction.

3.4.2.2. Self-reported psychological symptoms. Twenty-eight research articles mentioned aspects of psychological functioning, including negative emotions such as depressive and anxiety symptoms in adults ($k = 13$), behavioral problems in children ($k = 4$) and subjective fatigue ($k = 11$). These outcomes were self-reported on questionnaires or part of qualitative studies focusing on patient experiences. The details of these studies are described in Supplementary Table 4.

In adults, results on self-report questionnaires measuring negative emotions, clinically relevant distress was present in 36–46 % of patients with MELAS spectrum disorders (Custers et al., 2018; Verhaak et al., 2016). Elevated or clinically relevant depressive and anxiety symptoms were present in 25−45 % of patients with MELAS spectrum disorders or CPEO (Custers et al., 2018; Smits et al., 2011, 2012; Verhaak et al., 2016) and 18.4 % scored high on fear of progression of the disease (Custers et al., 2018). In contrast, two other studies did not find (clinically) elevated scores of depressive (Fromont et al., 2009; Gorman et al., 2015a) and anxiety symptoms (Gorman et al., 2015a) in patients with MD on a group level. However, scores on depressive and anxiety symptoms were higher in patients with MD compared with healthy controls in all studies comparing scores of MD patients with healthy controls or norm scores (Anglin et al., 2012b; Gorman et al., 2015a; Verhaak et al., 2016).

Compared with other patient groups, patients with MD reported more mental health problems, including depressive symptoms, compared with patients with HSN (Inczedy-Farkas et al., 2014) and T1D (Smits et al., 2011). Comparing norm scores of a general hospital population, patients with MD reported more depressive symptoms, but less symptoms related to anxiety (Custers et al., 2018). In contrast, patients with Myalgic Encephalopathy/Chronic Fatigue Syndrome (ME/CFS) reported more depressive symptoms than patients with MD (Gorman et al., 2015a).

Almost half of the patients with Leber's hereditary optic neuropathy (LHON) met the criteria for major depressive disorder after their vision loss, measured with a self-report questionnaire (Garcia et al., 2017). Interviews showed negative emotions were most pronounced at the start of the vision loss, which seemed to improve over time as patients developed new coping skills (Ferguson and de Abreu, 2016).

Patients with MD mainly worried about the future, disease course, and the hereditary nature of the disease, as described in both quantitative and qualitative studies (Custers et al., 2018; Krieg et al., 2016; Noorda et al., 2012). In addition, they experienced an increased dependence on others, the disease may impact on their personal identity and they need to cope with symptoms such as fatigue (Noorda et al., 2012).

Several studies show fatigue is a common symptom in patients with MD. Around 60 % of patients reported severe fatigue in the studies of Verhaak et al. (2016) and Gorman et al. (2015a). Even higher percentages of severe fatigue were found by Parikh et al. (2019), ranging between 71−100 % depending on the questionnaires used. Parikh et al. (2019) reported 20–26 % of patients with genetically confirmed MD and severe fatigue also experienced clinically significant depressive symptoms and 57.5–61.8 % reported clinically significant anxiety symptoms.

The relationship between disease manifestation and mental health outcomes and subjective fatigue was reported in five studies, with varying results. Patients with MELAS showing more severe disease manifestation, also reported more mental health problems (Verhaak et al., 2016) and fear of progression (Custers et al., 2018). Disease severity indicated by the NMDAS score correlated positively with fatigue complaints in all studies focusing on this symptom (Gorman et al., 2015a; Parikh et al., 2019; Verhaak et al., 2016). Parikh et al. (2019) did not find disease severity was related to depressive and anxiety symptoms, but both mental health symptoms correlated with fatigue. In contrast, Morava et al. (2010) did not find a relationship between disease severity and major depressive behavior in children with MD (Morava et al., 2010). They did not investigate the possible influence of fatigue within this relationship.

Studies focusing on children investigated the presence of behavioral problems ($k = 4$) and fatigue complaints ($k = 5$), and the impact of these complaints on their daily functioning. Psychological symptoms measured in children were mainly based on parent reports. Children with MD experienced psychological symptoms, such as behavioral problems and negative emotions (Eom and Lee, 2017; Koene et al., 2009; Morava et al., 2010; Schreiber, 2012). Two studies assessed behavioral problems with the widely used Child Behavior Checklist (CBCL) (Eom and Lee, 2017; Morava et al., 2010). Behavioral problems have been observed in 43 % of the children assessed by Eom and Lee (2017), with 25 % showing clinical levels of internalizing problems reflecting problems related to negative emotions.

Morava et al. (2010) specifically investigated withdrawn/depressive behaviors, which they observed in 50 % of the children with MD (score >65, i.e. significantly higher than norms scores). This corresponds with Eom and Lee (2017), who reported 46 % of children score in the clinical range (score >70) on the withdrawn behaviors subscale. Combined anxious and depressive behavior did not differ between groups. Moreover, depressive behavior was unrelated to the clinical severity of the disease (Morava et al., 2010). Koene et al. (2013) reported behavioral problems as well, which were considered one of the most burdensome complaints for the parents.

Fatigue was the most common complaint in children with MD in the study of Koene et al. (2013) ranging between 57.7–73.3 % depending on age, tiredness and lack of energy were present in 67 an 66 % of the children, respectively. Fatigue was also the most burdensome for both children and parents. Other studies show higher levels of fatigue in children with MD compared with healthy children (Martens et al., 2014; Morava et al., 2010).

3.4.2.3. Social functioning. Results on social functioning, described in 11 research articles, were based on self-report questionnaires and interviews in adults ($k = 7$) and children ($k = 4$).

In adults, inconclusive results were seen regarding social functioning. On subscales of the quality of life measures, adults with MELAS spectrum disorders were less satisfied in the social domain compared with healthy norms in the study of Verhaak et al. (2016), but not in patients with CPEO or KSS in the study by Bosbach et al. (2003). The presence of a mental disorder negatively impacted social functioning in the study of Fattal et al. (2007). Compared with patients with T1D, patients with CPEO reported more severe functional impairments related to social interactions (Smits et al., 2011).

Between 70 and 74 % of patients with LHON experienced a negative impact of their vision loss on their interpersonal interactions and career goals. Patients between 31 and 65 years of age were affected more severely on these social domains compared with younger patients (Garcia et al., 2017). In a qualitative study by Ferguson and de Abreu (2016), LHON patients also describe social problems, which were mainly related to missing non-verbal communication due to their vision loss (Ferguson and de Abreu, 2016).

Patients with MD report receiving social support from several groups. Most often, patients received social and emotional support from relatives and friends, but contact with other patients with MD and (online) support groups were also reported as valuable (Garcia et al., 2017; Krieg et al., 2016). However, some patients did report a lack of appropriate (local) support resources (Krieg et al., 2016). Patients also reported receiving emotional support from health care professionals. Almost 18 % of patients reported they only received emotional support from their health-care professionals (Garcia et al., 2017). In a qualitative study including patients with several MDs, patients reported a loss of meaningful activities and social contacts including their partner, children, relatives and friends (Noorda et al., 2012). Furthermore, most patients also experienced a lack of understanding and social support from others. However, some patients also acquired new meaningful contacts with fellow patients with MD (Noorda et al., 2012).

In children, social problems were also present. Koene et al. (2013) described social problems in several subgroups of children with MD. Many children (87 %) between 13 and 18 years of age reported problems forming and keeping social relationships. Looking at mitochondrial syndromes, social problems were mentioned as a main problem for children with encephalopathy (68.8 %). Overall, 73 % of children of all ages had difficulties related to others and 74 % of children up to 12 years old had problems related to playing with others. The percentage of children experiencing social problems in the study of Eom and Lee (2017) was somewhat lower (55 %), but shows clinically relevant social problems, measured with the CBCL. Compared with children with PKU, children with MD scored lower on both social functioning scales, communication and socialization (Read, 2003). In contrast, Martens et al. (2014) did not find a difference in social integration between children with mitochondrial myopathy and healthy controls.

Rogac et al. (2011) examined caregiver assistance needed in several domains of daily life. Most children with MD in this study experienced some level of developmental delay (91 %). They were relatively independent in areas related to social functioning, compared with self-care and mobility. The children were most capable on areas such as comprehension, expression and problem solving. However, in most cases caregiver assistance was still needed, especially on joint problem solving, peer play and safety (Rogac et al., 2011).

3.4.2.4. Quality of life. Quality of life was investigated in several mitochondrial syndromes ($k = 10$), including LHON, MELAS spectrum disorders and mitochondrial cytopathies. In patients with LHON vision-related quality of life was studied ($k = 2$).

Quality of life in adult patients with MD was lower in several domains compared with the healthy population (Bosbach et al., 2003; Verhaak

et al., 2016). Patients with MELAS spectrum disorders, including classical MELAS and MIDD syndromes and mixed phenotypes, scored lower on all domains assessed with the RAND36/SF-36. Overall, patients experienced negative emotions and limitations in daily life (Verhaak et al., 2016). Fattal et al. (2007) reported lower scores on physical and general health, physical role functioning, and social functioning in patients with MD with a mental disorder versus without a mental disorder. Furthermore, Poole et al. (2019) looked at quality of life related specifically to lower urinary tract symptoms, common in patients with MD (83.7 %). In 58.5 % of patients with MD these symptoms affected their quality of life, yet no patients received treatment for these symptoms.

Quality of life in patients with LHON was investigated in two studies, which measured vision-related quality of life with the VF-14 (Visual Function Index) (Cui et al., 2018; Kirkman et al., 2009). Symptomatic LHON patients rated their quality of life significantly lower on this questionnaire compared with asymptomatic carriers. Moreover, taking genetic mutation in LHON into account, patients with mDNA 14484 T > C mutation reported a higher quality of life than patients with other mutations (mDNA 3460 G > A and mDNA 11778 G > A variants). Cui et al. (2018) showed improvement in vision-related quality of life over three year follow-up in all patients but improved more in patients younger than 14 years old (Cui et al., 2018). Overall, adolescents reported a higher quality of life than older patients (Garcia et al., 2017).

3.4.2.5. Mental health described in case studies. Mood disorders were most often observed in case studies describing patients with MD. Eighteen patients had a depressive disorder ($k = 7$), including major depressive disorder, depressive episodes with catatonic features, and psychotic depression. A total of 21 patients experienced psychotic symptoms such as hallucinations and delusions ($k = 15$). Psychotic features were related to MDD ($n = 4$), bipolar disorder ($n = 1$), ASD ($n = 1$), and a form of schizophrenia was diagnosed in 4 cases. Seven patients with psychotic symptoms were not diagnosed with a mental disorder ($k = 6$). Other described mental disorders were bipolar disorders ($n = 3$), anxiety disorders ($n = 7$), obsessive-compulsive disorder (OCD) ($n = 5$), ASD ($n = 5$), and personality disorders ($n = 3$).

Case studies also described aspects of psychological functioning in patients with MD. In eight case studies subjective fatigue complaints were present in a total of nineteen patients. Depressive symptoms were reported in three cases, and anxiety in one case. Other described psychological symptoms included emotional instability ($n = 3$) and internalizing problems ($n = 1$). Social problems were often related to the mental disorders of patients. Only one case study described some social difficulties in a patient without a diagnosed mental disorder (Born et al., 2015).

3.4.3. Interventions focused on cognitive function or mental health outcomes in patients with MD

No research articles were found focusing on interventions specifically targeting mental health or cognitive functioning. One study by Janssen et al. (2019) performed an exploratory phase 2a study into the effects of a new pharmacological agent in patients with mDNA 3243A > G variant, and found improvements on depressive and anxiety symptoms and the cognitive domain of attention, but not on quality of life or subjective fatigue measures.

Nine intervention studies included quality of life as an outcome measure. Interventions included physical exercise training ($k = 5$) which all showed effect on physical parameters, whereas effects on quality of life were mixed. Martinelli et al. (2012) investigated the effects of an existing pharmacological agent in children with Leigh syndrome. All children showed an arrested or reversal in disease progression and an improvement on quality of life measures. Two studies investigating supplements did not show changes in quality of life (Glover et al., 2010; Mancuso et al., 2010), but a dietary intervention in patients with mDNA 3243 A > G variant showed (temporary) improvements in vitality and subjective fatigue (Zweers et al., 2020). All relevant psychological outcomes of the intervention studies are described in Supplementary Table 5.

Pharmacological treatment of mental disorders and symptoms has been described more often in case studies. Treatment of mood disorders including psychotic depressive disorder, depressive episode with catatonic features and bipolar I disorder was described in seven cases. Four cases showed clinical improvement (Cozart et al., 2018; Ju Seok et al., 2009; Kannan et al., 2006; Verhoeven et al., 2011), whereas depressive symptoms persisted in two cases (Anglin et al., 2012c; Magner et al., 2014). One case did improve over time, but only after the treatment had been discontinued (Anglin et al., 2012a). In addition, one case study described deep transcranial magnetic stimulation (dTMS) in a patient with anxious-depressive symptoms who did not respond to pharmacological treatment. The dTMS treatment improved both depressive and cognitive symptoms, but not the anxiety symptoms (Rapinesi et al., 2015).

Eight case studies described the pharmacological treatment of psychotic symptoms. In some cases the psychotic symptoms resolved and did not return, whereas other cases had recurring or persistent psychotic symptoms. Kaufman et al. (2010) described the normalization of biochemical abnormalities, which corresponded with improvement of the psychotic symptoms in the patient.

Lacey and Salzberg (2008) focused on the treatment of OCD in two cases. Standard treatment of OCD in both patients consisted of pharmacological treatment and one patient received additional cognitive behavior therapy. However, the symptoms persisted in both patients (Lacey and Salzberg, 2008). Another study investigated cognitive training to improve cognitive functioning. Combined computerized cognitive training and motor training improved cognitive functioning more than only computerized cognitive training or traditional cognitive training (De Luca et al., 2016). Pharmacological treatment for myoclonus in a patient described by Mancuso et al. (2006) did not improve cognitive function, but did improve quality of life.

Lastly, two case studies described the effect of coenzyme Q10 and other supplements used for treatment of MD complaints on autism (Guevara-Campos et al., 2013; Tsao and Mendell, 2007). Tsao and Mendell (2007) did not find any effect whereas Guevara-Campos et al. (2013) described a slight improvement in language in one case and the second case seemed more sociable. Galan et al. (2015) described a positive effect of riboflavin and thiamine on fatigue, muscle symptoms and cognitive functioning. The interventions and their effects are also described in Supplementary Table 6.

3.4.4. Family-focused studies

A total of 11 studies focused on cognitive functioning or mental health in relatives of patients with MD. The details of these studies are described in Supplementary Table 2 and 5.

3.4.4.1. Cognitive functioning in relatives. Three studies assessed cognitive functioning in carrier relatives, all reporting worse functioning of fully symptomatic patients compared to carrier relatives. Kaufmann et al. (2004), reported a worsening of neuropsychological impairments in asymptomatic, oligosymptomatic and symptomatic mDNA 3243 A> G mutation carriers. High MRS ventricular lactate values were correlated to worse cognitive functioning (see also 3.4.1.5). The second study by Kaufmann et al. (2009) used a modified version of the MMSE and reported a worse performance in patients with fully symptomatic MELAS (with clear evidence of focal brain involvement in addition to lactic acidosis), compared with carrier relatives (matrilineal carrier relatives without focal seizures or strokes) and controls. Carrier relatives showed 'mildly' reduced performance compared with controls. Finally, Kaufmann et al. (2011), reported a worsening in their neuropsychological global score over time (from baseline to a 1- and 4-year follow-up) in fully symptomatic MELAS patients (defined as having

evidence of focal brain involvement in addition to lactic acidosis), aged 30 ± 15 years, while no decline was observed in symptomatic or asymptomatic relatives (who represent obligate carriers by pedigree analysis).

3.4.4.2. Mental health in relatives. Mental disorders were common in matrilineal relatives of patients with MD (Boles et al., 2005; Burnett et al., 2005). Compared with matrilineal relatives of children with autosomal recessive metabolic disorders (ARMD), mental disorders were more common in matrilineal relatives in the MD group (Boles et al., 2005). Secondly, Burnett et al. (2005) investigated the presence of mental disorders in relatives of possible maternally inherited MD compared with probable non-maternally inherited MD. A higher percentage of mothers and maternal aunts, uncles and grandmothers had a depressive and/or anxiety disorder when maternally inherited MD was suspected, compared to the relatives of patients with probable non-maternally inherited MD or paternal relatives (Burnett et al., 2005).

Psychological symptoms, such as depressive and anxiety symptoms, were experienced by a substantial proportion of mothers of children with MD. Percentages of clinically relevant depressive symptoms ranged between 42 and 65 % (Eom and Lee, 2017; Kim et al., 2010) and elevated anxiety was observed in 39 % (Kim et al., 2010). This was significantly higher compared with mothers of children with intractable epilepsy, in whom depressive and anxiety symptoms were present in only 3 and 9 %, respectively (Kim et al., 2010). Boles et al. (2005) described differences in the presence of anxiety and depressive symptoms related to the severity of the child's illness in mothers of a child with either MD or ARMD. There were no differences in anxiety or depressive symptoms in mothers of a child with MD based on severity of the disease. This contrasts with mothers of children with ARMD: mothers with a mildly affected child scored significantly lower than mothers of a severely affected child (Boles et al., 2005).

Varvogli and Waisbren (1999) investigated personality profiles and possible psychopathology in mothers with a child with MD. More than 50 % scored elevated on areas such as hypochondriasis, hysteria, paranoia and psychopathic deviate, domains as measured on the Minnesota Multiphasic Personality Inventory (MMPI-2). The authors argue that these outcomes can be explained by the presence of many stressful situations related to their child's illness, or intrinsic features that may be linked to their possible carrier status.

Parental stress and coping related to caring for a child with MD has been investigated in several studies (Kim et al., 2010; Senger et al., 2016a, 2016b). Senger et al. (2016a and 2016b) reported elevated illness-related concerns. Parents most often worried about their child's future and worsening of the disease. Illness-related concerns, as well as certain coping behaviors and demographic characteristics correlated with the stress of parents regarding their child's illness (Senger et al., 2016a, 2016b). Furthermore, compared with mothers of children with intractable epilepsy, mothers of children with MD experience higher caregiver burden and lower quality of life (Kim et al., 2010).

3.4.4.3. Case studies describing cognitive functioning and mental health in relatives. Three studies reported on cognitive functioning in family members of a patient diagnosed with MD. First, a family of two teenagers and a mother, all with diagnosed MD, did not show any signs of depression and had unimpaired daily functioning (Neargarder et al., 2007). Their intellectual functioning was in the average to high average range, but all showed cognitive deficits on some but not all domains. One study assessed a patient with LOHN and six family members. Neuropsychological testing revealed scores ranging from mild intellectual disability to borderline intellectual functioning. Finally, 5 out of 25 relatives of a patient with CPEO showed mental retardation or cognitive dysfunction (Kasamo et al., 2020).

Three case studies specifically focused on the mental health of relatives of a patient with a diagnosed MD. A variety of mental disorders was described. Campos et al. (2001) showed similar psychiatric disorders in four maternal relatives: episodes of (manic-)depression, psychoses and fatigue. In paternal relatives, no mental disorders were diagnosed.

Four cases were diagnosed with an ASD (Brown and Rais, 2015; Connolly et al., 2010; Graf et al., 2000). Two relatives of a patient with MELAS were diagnosed with autism in the study of Connolly et al. (2010). Brown and Rais (2015) described the teenage son of a mother with MD, who was diagnosed with ASD as well as oppositional defiant disorder (ODD), attention deficit/hyperactivity disorder (ADHD), major depressive disorder and anxiety problems (Brown and Rais, 2015). The last case, described by Graf et al. (2000), was the brother of a girl with Leigh syndrome. He experienced symptoms related to his autism: lack of emotional control, impaired attention/concentration, lack of social interaction. Both siblings had some form of cognitive regression (mild to severe). One of the two maternal half-sisters experienced specific learning disabilities and oppositional behavior.

4. Discussion

This scoping review is the first to provide an overview of research into cognitive functioning and mental health in patients with MD. Results indicated considerable problems in all domains, reflecting serious impairments in daily life. However, interpretation of the results is hampered by heterogeneity regarding the included patients, with samples ranging from one specific mitochondrial syndrome to groups including a range of probable and genetically confirmed MDs. Furthermore, the used measurement instruments and comparison groups were heterogeneous. This heterogeneity illustrates the need for scrutinizing cognitive (dys)function and mental health in mitochondrial medicine. Results are summarized and discussed below.

Studies focusing on *cognitive functioning* reported impairments in multiple cognitive domains, which is in line with the thorough systematic review by Moore et al. (2020) on cognitive deficits in adults with MD. The present scoping review added detailed information on the results of the specific subdomains of cognitive functions, enabling comparisons across studies and more insight in specific characteristics of cognitive impairments. Overall, results of this review regarding cognitive functioning highlighted serious impairments in patients with MD. Results suggested global cognitive deficits, a large variability in intellectual functioning, and in most studies a superior verbal to performance functioning. Furthermore, deficits were observed in the areas of visuospatial/ visuocontruction, executive functioning, memory, language, and attention. Other reviews on case studies in MD frequently reported cognitive impairments, sometimes as severe as meeting the criteria for dementia (Finsterer, 2008, 2009). In this review, only 15 (= 44 %) case-studies included objective neuropsychological tests, while the remaining described clinical or subjective reports of cognitive impairments. Results from the included case-studies support evidence of the wide range in intellectual functioning and also report focal deficits, globally in line with results from the included research articles.

Regarding *mental health*, this review shows that *mental disorders* are highly prevalent in patients with MD (60–93 %), of which major depressive disorder was most commonly reported. The prevalence of mood disorders in MD was comparable or even higher as described in literature on other chronic diseases (Clarke and Currie, 2009; Marrie et al., 2015a). Previous reviews on case-reports in MD underlined the high prevalence of mental disorders in patients with MD (Fattal et al., 2006; Rosebush et al., 2017). This is in line with results from case-studies included in this review, in which mood disorders were highly prevalent. In addition, psychotic features were frequently reported, while this was more variable in the research articles.

Results on self-reported *psychological and social functioning* also showed less favorable results in patients with MD compared to healthy controls and/or normative data, especially regarding symptoms of depression and anxiety and quality of life in adults, and withdrawn/ depressed behavior in children. The prevalence of psychological

symptoms in MD are comparable as or even higher than described in the literature on other chronic diseases, such as multiple sclerosis (MS), Duchenne Muscular Dystrophy (DMD), and Cystic Fibrosis (CF) (Marrie et al., 2015b; Pangalila et al., 2015; Quittner et al., 2014). The vast majority of the adult patients as well as children reported severe fatigue (Gorman et al., 2015a; Koene et al., 2013; Parikh et al., 2019; Verhaak et al., 2016). Fatigue is a common symptom in many chronic diseases. The high prevalence in MD patients is comparable to the ones reported in patients with diseases such as MS, amyotrophic lateral sclerosis and advanced cancer (e.g. Finsterer and Mahjoub, 2014). It is considered a burdensome complaint in many chronic diseases (e.g. Harris, 2008), and consequently an important problem to map and address in clinical practice. Results on satisfaction with social support and social functioning varied, but most qualitative studies showed problems in the social domain. In children, social problems were frequently reported, as well as a need for care-giver assistance in many areas of social functioning. The few existing case studies describing psychological functioning also reported depressive symptoms, fatigue and social problems in patients with MD, in line with the research articles.

Interventions primarily focusing on cognitive functioning and mental health were only investigated in case studies and showed mixed results. Few studies in patients with MD have focused on the effects of treatment on mental health outcomes. Exercise studies often include measures of quality of life, with mixed results. In contrast, interventions targeting mental health have only been described in case reports. As secondary outcome in a phase 2a pharmacological clinical trial, one study showed a positive effect on cognitive functioning and mental health in terms of both attention and depression (Janssen et al., 2019).

Results from *family-focused studies* showed evidence of impaired cognitive functioning in carrier relatives, though less severe compared to fully symptomatic patients. Furthermore, more depressive and anxiety problems in relatives and family members of patients in which maternally inherited MD was suspected compared to non-(maternally) inherited MD. Furthermore, parenting stress, illness-related concerns, caregiver burden, and a lower quality of life are reported in parents of children with MD.

Overall results of this scoping review highlighted the importance of the impairments in patients with MD in the multiple domains of cognitive functioning as well as mental health. The etiology of cognitive dysfunction and mental disorders in MD is, however, still unclear. Cognitive and mental health impairments can be 1) inherent to the disease, that is a direct consequence of mitochondrial dysfunctioning, or 2) an indirect consequence of the disease, such as sequaelae related to symptoms such as lack of energy or loss of health. For example, there is evidence pointing into the direction of genes affecting mitochondrial functioning contributing to the etiology of depression and to impaired cognitive functioning (Petschner et al., 2018). This seems supported by the high prevalence of mental disorders and cognitive problems of carrier relatives. However, mental health problems could also be the consequence of impairments caused by the disease, for instance, symptoms of depression because of the loss of functioning. These symptoms of depression could also impact cognitive functioning. Although direct and indirect consequences are difficult to disentangle, we summarize information regarding possible explanations from studies of this scoping review below.

Regarding cognitive functioning, impairments can be caused directly by the disease due to, for example, mitochondrial dysfunctioning, or an indirect consequence of the disease, such as a consequence of brain damage by epileptic activity (Shurtleff et al., 2018), or fatigue (Bol et al., 2009). Included studies investigating these relations reported varying results regarding the influence of factors such as disease severity, levels of heteroplasmy, age of onset, and disease duration. As reported in the review of Moore et al. (2020) evidence on genotype-specific cognitive profiles is scarce. However, two studies reported worse cognitive performance of MELAS patients compared to MERRF patients (Kaufmann et al., 2004; Lang et al., 1995). Authors suggested that this could be caused by differences in spatial cerebral lactic acid concentrations, given its correlation with phenotype and cognitive functioning, and are less likely caused by stroke-like episodes given the different brain areas involved in the cognitive functioning versus affected areas by stroke like episodes (Kaufmann et al., 2004). Contradictory, the study by Moore et al. (2019), reported no genotypic differences in cognitive fuctioning between mDNA 3243A > G and mDNA 8344A > G mutations, while disease severity, premorbid cognitive abilities, anticonvulsant medication and mood were predictors. In young children with MD, diffuse brain atrophy, intractable epilepsy, and seizures were related to worse cognitive functioning (Eom and Lee, 2017; Shurtleff et al., 2018). In general, evidence is scarce regarding, amongst other, the specific effects of mitochondrial dysfunction, lactate levels, disease manifestation and severity, and brain functioning on cognitive functioning. Research is furthermore lacking on MD-related neuropathology compared with (normal) sex differences or aging-related changes in the brain, for example increased oxidative stress affecting the mitochondrial functioning in older adults (Grimm and Eckert, 2017). There is emerging evidence that mitochondria are crucial for neurodevelopment and adult neurogenesis, and that "*Inherited mutations and accumulated damage to mitochondria over the course of ageing serve as key factors underlying cognitive defects in neurodevelopmental disorders and neurodegenerative diseases, respectively*" (Kacho et al., 2019, p. 34). The exact sequence of events from mitochondrial oxidative phosphorylation defects towards e.g. cognitive decline remains enigmatic. Systematic assessment of cognitive functioning, starting from diagnosis, monitoring the natural disease course across the lifespan, and inclusion of brain specific biomarkers could provide more insight into these relations. Surprisingly, in children there were only two studies focusing on intellectual functioning, while no studies exist on specific cognitive domains. Research in adults showed evidence for specific cognitive deficits, but there is no evidence that these deficits are congenital or acquired through the years. Information on the development of cognitive deficits during the course of the disease could provide information about relationship between indicators of disease severity and cognitive functionig. In adults, only three studies investigated cognitive functioning over time with repeated assessment, of which only one reported a decline over a 4-year period (Kaufmann et al., 2011), which is remarkable given the progressive disease course of MD (Gorman et al., 2015b). When interpreting these results, it is important to keep in mind the drop-out rates of 15–37 % (Kaufmann et al., 2011; Moore et al., 2019), which may have biased the results. Finally, when testing cognitive functioning, it is important to be aware of factors influencing the test performance, like mental health (Moore et al., 2019) and MD specific factors, ataxia, fatigue and variability in functioning from day-to-day. In MD, research on this area is scarce and more focus on interaction effects, for example between cognitive functioning, fatigue and mental health, is needed.

Research focusing on direct or indirect consequences of MD on mental disorders is also scarce. No studies have investigated differences in mental disorders related to genetic mutations, or biochemical results such as levels of heteroplasmy. Only one study reported a relation between disease severity and mental disorders (Mancuso et al., 2013). In the etiology of psychiatric disorders, literature described suggestions of mitochondrial dysfunction as being a factor in the development or manifestation of mental disorders such as autism (Babinska et al., 2017; Rossignol and Frye, 2012) or depressive disorder (Allen et al., 2018; Bansal and Kuhad, 2016; Iwata, 2019; Zvěřová et al., 2019). In our review focusing on patients with primary MD, this relationship could not be confirmed due to limited studies and a lack of designs to asses this relation. However, given the high prevalence of mental disorders reported in patients with primary MD, an important role of mitochondrial dysfunction in the etiology of mental disorders is suspected. The variety in the prevalence estimates, can partly be explained by the variety in MDs in the different studies. Research in specific mitochondrial syndromes is important to unravel the differences in mental disorders between the different syndromes.

Studies regarding the relation between disease specific measures and psychological function also show ambiguous results. Unraveling the relation between chronic disease, fatigue and mental health is a complex puzzle. It is often an interplay of disease-related and psychological factors such as lack of energy, less active behavior, less social interaction and more depressive symptoms (Afari and Buchwald, 2003; Bol et al., 2009). In MD, three of the included studies in this review reported a positive correlation between disease severity and fatigue complaints, and between fatigue and mental health (Gorman et al., 2015a; Parikh et al., 2019; Verhaak et al., 2016). Only one of the included studies supported the relation between disease severity, and mental health outcomes (Verhaak et al., 2016), while two other studies did not find a relation (Morava et al., 2010; Parikh et al., 2019). Fatigue as explained by more indirect effects could be identified by controlling for disease progression in terms of genetics, biochemical factors and clinical symptoms, in predicting the course of fatigue.

From results of the family-focused studies, one could hypothesize that mental health problems in matrilineal relatives may be higher due to maternally inherited MD and related to the mutations in the mDNA, and are therefore a direct cause of mitochondrial functioning. However, anxiety and depression in parents could (also) be influenced indirectly by factors such as parenting stress, coping with the illness of the child, maternal depression, or anxiety. More research is needed on this subject. Overall, the family-focused studies suggest an important role of the genetical vulnerability in the development of cognitive and mental impairments, as well as illness-related concerns in mothers of children with MD. Furthermore, these results stress the need for help in family members of patients with MD.

Research regarding the effects of (a combination of) physical and psychological interventions and pharmacological treatments on cognitive functioning and mental disorders is necessary. In addition, it is important to establish which treatments are most effective in specific MD genotypes or phenotypes. In other diseases, physical exercise has had positive effects on brain functioning and cognition (Bernardo et al., 2016; Hillman et al., 2008), and on depression (Barbour and Blumenthal, 2005; Dinas et al., 2011; Knapen et al., 2015). Furthermore, cognitive behavioral therapy for treating mental disorders and improve coping with the consequences of the disease is promising (e.g. Hofmann et al., 2012). Studies on such interventions in patients with MD, however, are lacking altogether, making this an important area for future research.

A strength of this scoping review is the inclusion of studies with all types of MD. By investigating MD in its broadest definition, we were able to identify the comorbid cognitive and mental health problems. Mapping these problems is a first step to systematically describe the impact of MD on cognitive functioning and mental health. As the results show, the impact is considerable and more thorough research is needed. Based on the included studies, we could not identify differences in cognitive functioning and mental health between patients with specific mitochondrial syndromes. MDs such as LHON, MELAS and CPEO have been studied in specific research articles, but too little research exist on specific syndromes to systematically compare possible differences between the MDs. A limitation is that we did not include grey literature or articles in other languages than English, German and Dutch. Furthermore, articles focusing on secondary mitochondrial dysfunction in relation to mental health and cognitive functioning were not included. This area could also provide valuable insights to guide future research in patients with MD.

Following guidelines and discussions on scoping reviews, a formal quality assessment is not required (Arksey and O'Malley, 2005; Pham et al., 2014), but we described several quality-related criteria. Assessment of these criteria showed a high variability in diagnostic criteria of MD (genetically based, based on different guidelines, self-reported, etc.), patient groups (age, genetic etiology, MD criteria, symptom severity, organ involvement, disease progression), lack of standardized comparison groups, small sample sizes, and large variability in measurement instruments. This indicates a need for standardization in diagnostic criteria for MD, and cognitive and mental health assessment. Despite this variability, the included studies show evidence of specific cognitive deficits and mental disorders in patients with MDs.

Summarized, more focused and systematic research is needed to unravel the complex interplay between the direct and indirect pathways between MD and outcomes in terms of cognitive functioning and mental health. By focusing on the specific influences of mitochondrial dysfunction, lactate levels, disease manifestation and severity, and brain functioning on cognitive functioning and mental health, more insight is gathered into the nature of this relation. The use of standardized and validated tests and relevant comparison groups is necessary. Longitudinal, natural-history studies following children from the onset of the disease into adulthood provides more information regarding causes and consequences of the disease.

Translating our scoping review into clinical recommendations, it is crucial to provide patients and their relatives information on cognitive functioning and mental health to enhance coping and to provide adequate support. Potentially, standardized screening on a regular basis is important for prevention of developing complaints and symptoms and provides important information for therapeutic strategies. Based on results from this review and in line with recommendations by Parikh et al. (2017), given the high risk of cognitive impairments, we recommend an age-appropriate standardized baseline neuropsychological assessment at diagnosis to screen for (development of) cognitive impairments. Monitoring and repeated testing of cognitive functioning is recommended based on indication of complaints/limitations or changes in functioning or disease deterioration. Regarding mental disorders and psychological functioning, we recommend regular monitoring of depressive and anxiety symptoms, again in line with recommendations of Parikh et al. (2017), using standardized questionnaires or a structured psychiatric interview. As discussed above, symptoms of fatigue are important to take into account given the high comorbidity with both MD and depression. Given the reported cognitive impairments and psychological problems in relatives, we advise to be aware of these and actively ask or screen for limitations or complaints. An overview of all recommendations and gaps in de literature is described in Table 3.

In conclusion, this scoping review shows a paucity of systematic research on the cognitive and mental health morbidity; despite this shortcoming it is clear that serious issues are present in the MD population. More structured systematic assessments are needed to provide insights into the relationship between MD geno/phenotypes and, disease course on the one hand and cognitive functioning and mental health on the other. With this knowledge we can provide tailored management to

Table 3
Gaps and clinical and research recommendations based on the scoping review.

Gaps in the literature
Studies on natural disease course
Relationship between disease activity, cognitive functioning, and mental disorders
Research on focal cognitive functioning in children
Prevalence of mental disorders in children with MD: depression, anxiety, ASD, ADHD, ODD
Intervention studies on cognitive functioning or mental health as primary outcome measure
Relationship between cognitive functioning, fatigue and mental health in MD
Clinical recommendations
Systematic assessment of patient on different domains of functioning as well as on patient reported outcomes/ complaints, including cognitive functioning and screening for depression and anxiety.
Integrate psychiatric assessment in positively screened patients.
Recommendations future research
Intervention studies regarding the effects of (a combination of) physical and psychological treatment and pharmacological treatments on cognitive functioning and mental health.
Longitudinal assessment form start of diagnosis with repeated assessment to unravel the complex relation of cognitive functioning and mental health outcomes in relation with the disease course and manifestation.

patients with MD, ultimately to improve their outcomes and wellbeing.

Declaration of Competing Interest

JS is the Founding CEO of Khondrion BV, a mitochondrial medicine company. All other authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neubiorev.2021.02.004.

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