

Supplementary file 1.

Table S1. Search strategy and main literature results considered in the perspective.

Database Searched	Search Terms	Exclusion criteria	Main research topic	N° of papers	Concerning adults	Concerning pediatric patients and adolescents	Study type
MEDLINE, Up To Date, Google Scholar	("Fatigue" OR "weakness" OR "tiredness" OR "weariness" OR "drowsiness") AND ("child" OR "pediatric" OR "paediatric" OR "children" OR "kid" OR "toddler"). "Tired child"; "child with fatigue"; "paediatric fatigue"; "pediatric fatigability"; ("chronic fatigue" AND "children"); ("medication" OR "drugs" AND "fatigue" AND "children"); ("sleep disturbances" AND "children")	- Articles addressing fatigue related to COVID-19 pandemic - Fatigue in patients with chronic diseases - Duplicates - Case reports, case series	Chronic Fatigue Syndrome/ Myalgic Encephalomyelitis (CSF/ME)	26	4	22	10 review articles, 1 systematic review, 4 guidelines from metanalysis, 11 observational studies
			Fatigue as a clue of psychological/psychiatric problem or Somatic Symptom Disorder	20	6	14	1 systematic review, 5 review articles, 5 commentaries, 9 observational studies
			Fatigue as the main complaint expression of several subtended condition	19	12	7	13 review articles, 3 systematic reviews and 3 observational studies
			Fatigue as the main complaint 'per se'	12	6 - Approach to the adult patient with fatigue. (UpToDate) - Approach to the patient with muscle weakness (UpToDate) - Approach to the patient with excessive daytime sleepiness (Uptodate) - Finsterer et al. (2004) - Nijrolder et al. (2009) - Sharpe (2002)	6* Farmer et al. (2004) Haines et al. (2005) ter Wolbeek et al. (2006) Saidi et al. (2006) Fisher et al. 2013 Cárdenas Villamil et al. (2017)	7 clinical review articles, 5 observational studies

*Such literature results are reported in table 3.

Table S2. Literature results concerning fatigue as the main complaint among children and young adults.

Abbreviations: CSF, chronic fatigue syndrome; GP, general practitioner; CSF/ME, chronic fatigue syndrome/myalgic encephalomyelitis; ESR/CRP, erythrocyte sedimentation rate, C- reactive protein; EBV, Epstein Barr virus; ANA, anti-nuclear antibodies; RF, rheumatoid factor; CI, confidence interval; MRC, Medical Research Council.

Citation (Author/Date)	Framework	Research hypotheses	Study type - Methods	Results	Conclusions
Farmer et al. (2004)	Epidemiology of chronic fatiguing illnesses in young people	To estimate the lifetime prevalence of different definitions of chronic fatigue in 8- to 17-year-olds.	Observational study. Participants came from two population-based twin series. Parents completed self-report questionnaires that enquired whether either child had ever experienced more than a few days of disabling fatigue. Telephone interviews were undertaken for individuals who had experienced such an episode.	Questionnaires were returned by 1468 families (65% response rate) and telephone interviews were undertaken regarding 99 of the 129 subjects (77%) who had experienced fatigue. The lifetime prevalence estimates ranged from 2.34% (95% CI 1.75^2.94) for disabling fatigue lasting 3 months to 1.29% (95% CI 0.87^1.71) for a disorder resembling adult operationally defined chronic fatigue syndrome.	From the age of 11 years, young people have similar rates and types of chronic fatiguing illnesses to adults. Chronic fatigue causes considerable impairment in young people, to both social development and time missed from school. Operational criteria for chronic fatigue syndrome (CFS) should require only 3 months' symptom duration in young people and not 6 months as in adults.
Haines et al. (2005)	Prevalence of severe fatigue in primary care pediatric patients	To report cases of severe disabling fatigue of over three months in 5–19 year old in primary care and the diagnoses given by the GP	Retrospective cross-sectional study. A postal survey of 1024 UK General Practitioner (GP) practices was undertaken. The number of subjects with disabling fatigue for at least three months with a pre-morbid level of activity significantly reduced or impaired was reported.	These cases were grouped as: fatigue diagnoses (n = 281; 62%) (chronic fatigue, CFS, fatigue/severe fatigue syndrome, fatigue, lethargy, malaise, ME, CFS/ME, fibromyalgic CFS, and fibromyalgia); viral diagnoses (viral infection, post-viral fatigue) (n = 154; 34%); and psychosocial diagnoses (depression, bullying, family factors) (n = 20; 4%).	The prevalence of medically unexplained severe fatigue over three months in 5–19 year old was 62/100 000. Cases were predominantly adolescent girls and were more likely to come from practices in less deprived areas, which could reflect consulting behaviors.

ter Wolbeek et al. (2006)	Prevalence of severe fatigue in adolescents	To determine the prevalence of severe fatigue in adolescents; to explore the role of lifestyle factors in fatigue; to investigate whether severe fatigue in a healthy population is associated with depression, anxiety, and comorbid factors also observed in chronic fatigue syndrome patients.	Observational study. In a sample of 1718 boys and 1749 girls, fatigue severity and duration were measured using a multidimensional questionnaire (Checklist Individual Strength). In addition, self-reports of depressive symptoms, anxiety, chronic fatigue syndrome-related symptoms, and lifestyle characteristics were assessed. Prevalence rates of severe fatigue and severe fatigue for >1 month, based on a clinical cutoff score of the Checklist Individual Strength, were determined for boys and girls separately, and gender-specific predictors of fatigue were identified by multiple regression analysis.	Data showed high prevalence rates of severe fatigue in adolescents. 20.5% of girls and 6.5% of the boys scored above the clinical cutoff score on the Checklist Individual Strength. Of the examined lifestyle characteristics, only sleep characteristics and the participation in sports played a role in predicting fatigue in both genders. Moreover, in girls, fatigue was associated with higher age, an early menarche, medication use, and the absence of an additional job. Overall, girls scored higher on depression, anxiety, and chronic fatigue syndrome-related symptoms. In both girls and boys, the duration of fatigue was positively related to fatigue severity, severity of depression and anxiety, and the number of chronic fatigue syndrome-related symptoms.	Adolescent girls seem to be more vulnerable to symptoms of fatigue and comorbidity than boys. Interestingly, despite a female predominance in complaints, the relation between fatigue and depression, anxiety, and chronic fatigue syndrome-related symptoms was not gender specific and emerged as a cluster. It has been hypothesized that enduring severe fatigue may form a risk factor for the development of chronic fatigue syndrome.
Saidi et al. (2006)	Management of chronic fatigue syndrome in primary care among pediatric patients	To describe characteristics of patients aged 5–19 years with CFS-like illness in primary care and to examine how GPs investigate and manage patients.	Descriptive retrospective study. 62 UK GP practices in the MRC General Practice Research Framework (GPRF) were included. 116 patients consulting a GP with severe fatigue lasting over 3 months were identified. Practice nurses and GPs completed questionnaires from medical notes and patients completed postal questionnaires.	94 patients were considered to meet the Oxford CFS criteria with a fatigue duration of 3 months. 73% were girls, 94% white, mean age was 12.9 years and median illness duration 3.3 years. GPs had principal responsibility for 62%. A diagnosis of CFS/ME was made in 55%, 30% of these within 6 months. Pediatric referrals were made in 82% and psychiatric referrals in 46% (median time of 2 and 13 months respectively). Advice given included setting activity goals, pacing, rest and graded exercise.	Patient characteristics are comparable to those reported in tertiary care, although fewer are severe cases. GPs have responsibility for the majority of patients, are diagnosing CFS/ME within a short time and applying a range of referral and advice strategies. The most ordered lab tests by the GP included: Hemoglobin, White cell count, thyroid, kidney and liver function, Monospot, ESR/CRP, Urine test, Bone profile, Blood glucose, Immunoglobulins, Creatine kinase.

Fisher. (2013)	Fatigue in pediatrics can be a complaint of an underlying medical condition, psychological or psychiatric condition or a specific sleep disorder.	To provide a framework for evaluating the complaint of fatigue in adolescents offering approaches to management.	Mini-review. It is a communication based on author's personal experience in the clinical management of fatigue in adolescents. They consider: adolescent sleep patterns, psychological and medical causes of fatigue.	A thorough list of possible organic causes of fatigue is considered, along with sleep disorders, psychological causes and medications. Also they underline the need of performing a basic laboratory screening including complete blood count and metabolic panel, as well as thyroid function test. Other possible tests to perform are ESR, EBV antibodies, RF, ANA, pulmonary function tests, chest X-ray or tuberculin test if signs are consistent. Chronic Fatigue syndrome as an exclusion diagnosis is also mentioned.	The evaluation of CFS in adolescents, which applies to the evaluation of fatigue in teenagers in general, incorporates a physical examination that most often demonstrates no abnormalities, as well as basic laboratory tests, which likewise usually demonstrate no abnormalities. In those rare instances in which either the examination or laboratory testing do reveal abnormalities, they may be the clue to a specific diagnosis.
Cárdenas Villamil et al. (2017)	Evaluation and management of the tired adolescent in the family practice	To provide a tool for approaching the adolescent complaining of fatigue.	Narrative review. A total of 33 articles obtained for the diagnostic and therapeutic approach of the tired adolescent in Primary Care were analyzed .	Prevalence of fatigue in adolescence vary from 0.7 to 7.4%. The main cause of fatigue in adolescence was excessive daytime sleepiness and drowsiness for insufficient or inadequate sleep. Other causes to investigate are mentioned.	A sleep assessment should be a routine component of the clinical evaluation of adolescents and the initial approach to exclude secondary causes.

List of the main papers evaluated but not all included in the reference list:

CHRONIC FATIGUE SYNDROME/MYALGIC ENCEPHALOMYELITIS (26)

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FATIGUE AS A CLUE OF PSYCHIATRIC/PSYCHOLOGICAL/SOMATIC DISORDERS (20)

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