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Definition and diagnosis of constitutional thinness: a systematic review

Mélina Bailly[1,2]*, Natacha Germain[2,3], Bogdan Galusca[2,3], Daniel Courteix[1], David Thivel[1] and Julien Verney[1]

[1]*Université Clermont Auvergne, CRNH, AME2P, F-63000 Clermont-Ferrand, France*
[2]*Eating Disorders, Addictions and Extreme Bodyweight Research Group (TAPE) EA 7423, Jean Monnet University, Saint-Étienne, France*
[3]*Division of Endocrinology, Diabetes, Metabolism and Eating Disorders, CHU Saint-Étienne, Saint-Étienne, France*

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Abstract

The existing literature about the definition and diagnostic criteria of constitutional thinness (CT) appears equivocal. The present work systematically reviewed the criteria used in the diagnosis of adult individuals with CT (PROSPERO registration number: CRD42019138236). Five electronic bibliographic databases were searched between December 2018 and November 2019: MEDLINE, Embase, CENTRAL (Cochrane Library), Google Scholar and Clinical Trials. Search terms were combined with Medical Subject Headings terms. The search strategy included any clinical trials that enrolled adults with CT. Studies were systematically excluded if the state of thinness was not due to a well-identified constitutional origin. From the 689 references after duplicate removal, 199 studies were excluded based on title and 164 based on abstract. According to the inclusion and exclusion criteria, 291 other studies were removed. Finally, thirty-five studies remained at the end of the process. The analysis of these studies showed high heterogeneity in the diagnostic criteria of CT. A real need emerged to adopt a common terminology and to systematically exclude potential non-constitutional origins of thinness such as eating disorders, associated pathology or over-exercising, with validated tools. Weight history, physiological menses and weight gain resistance are also important criteria to consider. The present systematic review revealed that our medical and scientific approaches of CT need to be harmonised in terms of terminology and diagnostic criteria. Although further studies are needed, we finally proposed recommendations and a decision tree to help in the recognition and diagnosis of CT.

Key words: **Constitutional thinness: Constitutional leanness: Diagnosis: Weight gain resistance: Underweight**

As early as 1933, the existence of constitutional thinness (CT) had already been mentioned by Erich Grafe[1], followed by the first observations of Passmore *et al.*[2] and Genest *et al.*[3] in 1955. In a French publication from 1953[4], Bernard Wissmer wondered why CT and its treatment had raised so little consideration contrary to obesity. This remark is still valid about 60 years later with obesity and its treatment being widely investigated, while CT remains poorly studied[5]. Although there is a growing preoccupation for CT among clinicians due to an increasing number of individuals presenting thinness and seeking to gain weight without apparent criteria of anorexia nervosa (AN), the prevalence of CT remains difficult to determine[5] but would be less than 0·4 % for males and less than 2·7 % for females (underweight from all causes)[6]. Despite a large proportion of concerned individuals, many of them do not consult because of a lack of recognition and diagnosis of this condition. Given this lack of interest in the literature, CT is poorly described, which can favour its misunderstanding and misdiagnosis[5], mainly with AN. Although CT and AN are both characterised by a low BMI, people with CT do not present eating disorders, food restriction, psychological disorders or hormonal signs of undernutrition, but present an equilibrated energy metabolism, stable body weight within lower percentiles of growth curve and physiological menses for females[7–11]. Despite these clinical differences, the distinction between AN and CT remains difficult. Guy-Grand & Badevant proposed a first decision tree to diagnose CT in the early 1980s[12], but its diagnosis is still debated, especially with the removal of amenorrhoea criterion from the definition of AN in the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5)[8,13]. In our modern societies, individuals

Abbreviations: AN, anorexia nervosa; C, control subjects; CT, constitutional thinness; DSM, Diagnostic and Statistical Manual of Mental Disorders; FM, fat mass.

* **Corresponding author:** Mélina Bailly, email melina.bailly@uca.fr

with CT have to face social stigmatisation similar to that of anorectic patients[14], due to their low body weight and corpulence. Unlike patients with AN, people with CT show an important desire to gain weight, which is the main reason for medical consultation[5]. As already noted in 1982[15], the demand of individuals with CT for clinical examination is stereotyped; they are concerned about their thinness and dissatisfied with their morphology usually judged for its lack of femininity for women or virility for men. CT seems then to be a natural state of underweight leading to a high self-dissatisfaction and whose causes remain unclear. While absolute resting energy expenditure was found lower[7,8,10] or similar[16–18] in CT individuals *v.* normal-weight control subjects, resting energy expenditure:fat-free mass ratio was found higher in CT *v.* control subjects in some studies[7,18] but not significantly higher in some other studies[10,17,19]. Other evidence seems to indicate a more pronounced brown fat activity in CT[20]. Despite an apparently similar energy intake (quantitatively as well as qualitatively) as normal-weight people[5,7,9,10,19], specific physiological control of appetite has been suggested in individuals with CT[9–11,21–23], with, for instance, an earlier and higher satiety onset during meals leading to reduced but more frequent intakes (more in-between meals snacking)[10]. CT subjects present no eating disorder-related traits and even have lower food restrictive behaviours compared with normal-weight people[8,10]. Despite their low BMI, they present a non-blunted fat mass (FM) percentage[7,8,10,11,17,19,23–27]. However, CT people display impairments in their bone quality: small bone sizes, low bone mass, low calculated breaking strength[28] and low bone mineral density[19,24,26,28], but, however, apparent normal bone turnover[28]. Even if the potential increased risk of osteoporosis with ageing in CT remains to be robustly demonstrated, these bone impairments could be considered as the main co-morbidity associated with CT. This public health concern might not be the only one, but issues in the recognition and diagnosis of CT likely lead to a lack of knowledge. With 2·5 thin subjects per family in CT *v.* 0·5 in AN, CT is strongly suggested to be a heritable trait likely attributable to genetic factors[7,29,30]. Moreover, the exploration of the genetic architecture of thinness demonstrated the polygenic component of CT: genome-wide association studies revealed evidence of loci that could confer susceptibility of CT and also be informative in the identification of potential anti-obesity targets[30]. While there is a growing scientific and clinical interest to better understand and characterise CT, the used inclusion and exclusion criteria remain highly heterogeneous in-between studies, making any comparison and conclusion difficult. This high variability in CT diagnosis underlines today a clear need for a common definition of CT and harmonised criteria that should be used for CT detection. According to the recent literature[8,10,18,23,30,31], parameters such as the terminology used, the characterisation and fluctuation of the level of thinness, the consideration of psychological or physiological illnesses, the weight gain resistance or the level of physical activity appear, *a priori*, to be the main parameters to focus on in this systematic review. Thus, the present paper proposed a systematic analysis of all the parameters used so far as inclusion criteria of CT individuals in the available studies, trying to suggest a clear definition and diagnostic method of CT.

Materials and methods

The systematic literature search was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and was registered in the International Prospective Register of Systematic Reviews (PROSPERO registration number: CRD42019138236).

Search strategy

The search was conducted on CT and aimed to include any clinical trials enrolling a group of adults with CT. Five electronic bibliographic databases were searched between December 2018 and November 2019: MEDLINE, Embase, CENTRAL (Cochrane Library), Google Scholar and Clinical Trials. Relevant keywords were discussed and selected between the co-authors. Search terms were also combined with Medical Subject Headings terms. The following syntax was finally used to search on the MEDLINE database: ((constitution[TI] OR constitutional[TI] OR constitutionally[TI]) AND (thinness[TI] OR leanness[TI] OR thin[TI] OR lean[TI])) OR 'constitutional thinness' [TW] OR 'constitutional leanness' [TW] OR (((resistance[TI] OR resistant[TI]) AND 'weight gain' [TI]) NOT 'insulin resistance' [TI]) OR ('thinness/physiology' [Mesh] OR ((physiological[TI] OR physiologically[TI] OR physiology[TI]) AND (thinness[TI] OR leanness[TI] OR thin[TI] OR lean[TI])) NOT 'obesity' [Mesh]) AND ('humans' [Mesh] OR 'humans' [TW] OR 'human' [TW]). Searches were carried out on articles published from 1950. Adapted syntaxes were used to perform the search on the other databases. The authors collectively discussed any discrepancies. All the selected references were then extracted to Zotero Software (5.0.21; Center for History and New Media, George Mason University).

Study eligibility

Inclusion criteria. Clinical trials had to be published in English or French languages and had to enrol constitutional thin/lean adult females or males. Any fields of study could be included in the analysis. However, experiments on animals and clinical trials on children were not eligible for the systematic review. In addition, studies were not included if not enough data were available: letters to the Editor, reviews, abstracts alone or case studies. Only thinness due to a 'constitutional' origin was considered. To do this, papers had to mention at least one of these criteria: 'constitutional thin/lean' keywords, state of thinness confirmed by measurements, absence of eating disorders, no over-exercising, no associated pathology, physiological menstruations, stable body weight and/or weight gain resistance/desire.

Exclusion criteria. Studies were excluded if thinness was not due to a well-identified constitutional origin, such as associated diseases, undernourishment, eating disorders, over-exercising or any 'non-constitutional' origins causing a state of thinness. Specific attention was given to the large number of studies that wrongly named their normal-weight control groups as 'lean' groups. Normal-weight 'lean' control groups were not

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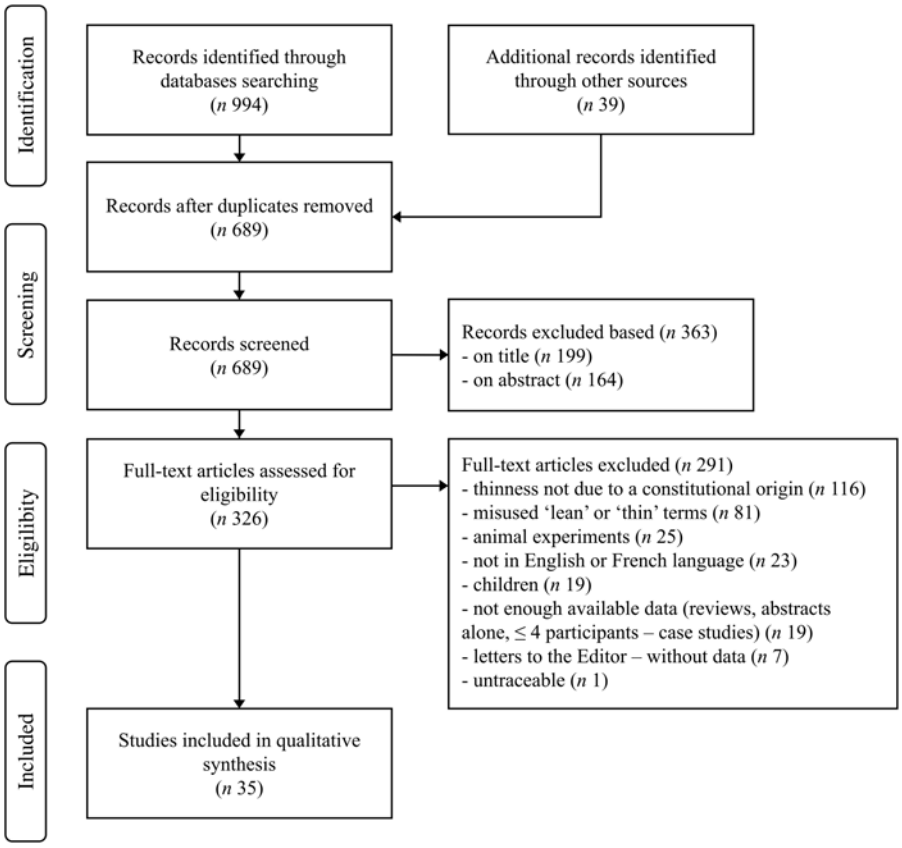

Fig. 1. Flow diagram of the description of the screening, selection and inclusion process.

considered as 'constitutional lean' groups and were therefore excluded from the systematic review.

Data extraction and synthesis of results

After the removal of duplicates, a first selection was performed on titles and abstracts of studies to assess eligibility of identified records through databases searching. Full-text articles were then screened and included according to the aforementioned inclusion and exclusion criteria. At each step of this process, a second screener assessed independently the identification, eligibility and inclusion of papers. Any disagreements about the eligibility and inclusion of papers or about the appraisal of methodological quality were solved by discussing with a third reviewer until a consensus was reached. Potentially relevant references cited in full-text read articles were also added to the initial search. Computer files containing the selected papers at each stage of the selection process were developed and made available to all the co-authors. At the end of the process, thirty-five studies were collectively included in the analysis. The flow diagram of identification, screening, eligibility and inclusion process is provided in Fig. 1. Data extraction of the thirty-five selected papers was performed using a standardised extraction spreadsheet to collect relevant information. As presented in Table 1, relevant information was summarised on established parameters chosen collectively by the authors: reference, population characteristics, definition of thinness, consideration of the absence of eating disorders, consideration of other main parameters and areas of study. We mean by 'presence of terminology' (Table 1) the explicit mention of 'constitutional(ly) thin(ness)/lean(ness)' keywords. Outcome variables were not assessed in the present work: only the inclusion criteria of the selected studies were considered. Parameters such as food questionnaires or nutritional markers do not appear in Table 1 if these parameters were used as outcomes after the constitution of groups and not as inclusion criteria. Studies are listed in Table 1 according to the publication year, from the oldest to the most recent. Since this systematic review focuses on diagnostic criteria, it was not considered appropriate to retain studies from the same cohorts (recorded as duplicates).

Risks of bias

The Cochrane Collaboration's tool[55] was used to assess the risks of bias, as presented in Table 2. Two authors estimated independently the risks of bias in each included study. The following criteria were assessed: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias) and selective reporting (reporting bias). Any disagreements were discussed with a third co-author until a consensus was reached. No study was excluded based on the risks of bias.

Table 1. Inclusion criteria used for diagnosis of constitutional thinness (CT) in the clinical trials selected in the systematic review*† (Numers; mean values and standard deviations)

References	Population characteristics (sample size, age and BMI) (mean (SD))	Definition of thinness	Consideration of the absence of eating disorders in individuals with CT	Consideration of other main parameters in individuals with CT	Areas of study
Schneider *et al.*[32]	Females: CT: *n* 53; 25·3 (SD 5·2)‡ years; NR C: *n* 100; 25·8 (SD 4·2)‡ years; NR	Presence of terminology§ Thinness threshold: at least 25 % lower than the average ideal weight defined for the height at the first prenatal consultation (first trimester of pregnancy) No apparent consideration of weight history	Considered No group of AN Not explicitly confirmed by questionnaire or interview Under-nutritional markers: NR	Amenorrhoea: NR Weight gain resistance/desire: NR Healthy, absence of associated pathology Physical activity: NR	9
van Binsbergen *et al.*[33]	Females: CT: *n* 10; 26·4‡ years; 18·4‡ kg/m^2 C: *n* 10; 25·1‡ years; 20·8‡ kg/m^2 AN: *n* 20; 24·8‡ years; 14·3‡ kg/m^2 (AN type: NR)	Absence of terminology Thinness threshold: 80–90 % of ideal body weight No apparent consideration of weight history	Considered Implicitly confirmed by the presence of a group of AN (DSM-III) Not explicitly confirmed by questionnaire or interview Under-nutritional markers: NR	No amenorrhoea Weight gain resistance/desire: NR Healthy, absence of associated pathology Physical activity: NR	3
Diaz *et al.*[34]	Males: CT: *n* 7; 26·3 (SD 4·5) years; 21·7 (SD 1·3) kg/m^2	Presence of terminology Thinness threshold: body fat ≤ 20 % (and low or normal weight) No apparent consideration of weight history	Considered No group of AN Not explicitly confirmed by questionnaire or interview Under-nutritional markers: NR	Criterion of amenorrhoea: NA (males) Weight gain resistance/desire: mentioned (they declared themselves to be good eaters and claimed to have difficulty gaining weight) Healthy, absence of associated pathology Physical activity: NR	1, 2
Scalfi *et al.*[16]	Females: CT: *n* 7; 28·6 (SD 5·6) years; 16·8 (SD 0·8) kg/m^2 C: *n* 8; 28·5 (SD 3·4) years; 22·5 (SD 2·5) kg/m^2 AN: *n* 7; 21·3 (SD 3·7) years; 15·3 (SD 2·1) kg/m^2 (AN: restrictive type)	Absence of terminology Thinness threshold: BMI < 18·5 kg/m^2 Consideration of personal weight history (stable in the 2 years before the experiment ± 1·5 kg by interview)	Considered Implicitly confirmed by the presence of a group of AN (DSM-III) Not explicitly confirmed by questionnaire or interview Under-nutritional markers: NR (but no clinical or biochemical evidence of hyperthyroidism)	No amenorrhoea Weight gain resistance/desire: mentioned (they complained of being chronically underweight and perceived themselves as normal eaters or large eaters) Healthy, absence of associated pathology Absence of over-exercising	1, 10
Hinney *et al.*[35]	Females: CT: *n* 48; 24·7 (SD 3·9) years; 17·6 (SD 0·8) kg/m^2 AN: *n* 92; 16·6 (SD 3·4) years; 14·5 (SD 1·5) kg/m^2 (AN: restrictive and binge eating/purging type) Males: CT: *n* 64; 26·1 (SD 4·1) years; 19·0 (SD 1·0) kg/m^2 AN: *n* 4; 15·3 (SD 0·9) years; 13·9 (SD 2·0) kg/m^2 (AN: restrictive and binge eating/purging type)	Absence of terminology Thinness threshold: ≤ 15th BMI percentile Consideration of personal weight history (semi-structured interview to assess weight history up to age 18 years – at ages 10, 15 and 18 years)	Considered (DSM-IV) Implicitly confirmed by the presence of a group of AN (DSM-IV) Confirmed by questionnaire and interview (TFEQ with a cognitive restraint score ≤ 5 and Composite International Diagnostic Interview[49] in accordance with DSM-IV) Under-nutritional markers: NR	Amenorrhoea: NR Weight gain resistance/desire: NR Healthy, absence of associated pathology Physical activity: NR	7

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Table 1. (*Continued*)

References	Population characteristics (sample size, age and BMI) (mean (SD))	Definition of thinness	Consideration of the absence of eating disorders in individuals with CT	Consideration of other main parameters in individuals with CT	Areas of study
Petretta *et al.*[36]	Females: CT: *n* 10; 22 (SD 3) years; 16·6 (SD 1·1) kg/m^2 C: *n* 10; 21 (SD 3) years; 23·4 (SD 2·4) kg/m^2 AN: *n* 13; 20 (SD 2) years; 15·7 (SD 2·4) kg/m^2 (AN: restrictive type)	Presence of terminology Thinness threshold: BMI < 20 kg/m^2 Consideration of personal weight history (history of leanness throughout life)	Considered Implicitly confirmed by the presence of a group of AN (DSM-IV) Confirmed by questionnaire (normal scores on food questionnaire – not further defined) Under-nutritional markers: NR	No amenorrhoea Weight gain resistance/desire: NR Healthy, associated pathology: NR Physical activity: NR	1, 3, 12
Slof *et al.*[37]	Females: CT: *n* 80; 42·4 (SD 7·2) years; 20·3 (SD 1·5) kg/m^2 C: *n* 881; 43·0 (SD 7·7) years; 26·8 (SD 6·2) kg/m^2	Presence of terminology (but 'persistent thinness' preferentially used) Thinness threshold: 1–3 (1: very thin, 9: very large) on silhouette ratings Consideration of personal weight history (persistent thinness with consideration of childhood, adolescence and adulthood)	Considered (DSM-III-R and DSM-IV) No group of AN Confirmed by interview (Structured Clinical Interview for DSM-III-R by trained interviewers – 40 h of training) Under-nutritional markers: NR	Amenorrhoea: NR Weight gain resistance/desire: NR Healthy, associated pathology: NR Physical activity: NR	11
Tolle *et al.*[11]	Females: CT: *n* 8; 23·3 (SD 3·1)‡ years; 15·7 (SD 0·4)‡ kg/m^2 C: *n* 10; 23·2 (SD 1·1)‡ years; 21·5 (SD 0·7)‡ kg/m^2 AN: *n* 9; 17·2 (SD 0·9)‡ years; 14·6 (SD 0·4)‡ kg/m^2 (AN: restrictive type)	Presence of terminology Thinness threshold: NR (but BMI similar to the AN group before renutrition) No apparent consideration of weight history	Considered Implicitly confirmed by the presence of a group of AN (DSM-IV) Not explicitly confirmed by questionnaire or interview Under-nutritional markers: NR	No amenorrhoea Weight gain resistance/desire: NR Healthy, associated pathology: NR Physical activity: NR	2, 3, 4
Bosy-Westphal *et al.*[38]	CT (12 females): *n* 12; 26·4 (SD 6·8) years; 16·9 (SD 0·9) kg/m^2 C (12 females and 13 males): *n* 25; 25·4 (SD 2·4) years; 22·3 (SD 2·0) kg/m^2	Absence of terminology Thinness threshold: BMI < 18·5 kg/m^2 Consideration of personal weight history (stable for at least 1 week)	Considered (DSM-IV) No group of AN Not explicitly confirmed by questionnaire or interview Under-nutritional markers: NR (but blood glucose and lipid profile assessed)	Amenorrhoea: NR Weight gain resistance/desire: NR Healthy, associated pathology: NR Physical activity: NR	1, 2, 5
Mazzeo *et al.*[39]	Males: CT: *n* 158; NR but probably 29–69 years; 22·5 (SD 2·1) kg/m^2 C: *n* 915; NR but probably 29–69 years; 27·6 (SD 4·2) kg/m^2	Presence of terminology (but 'persistent thinness' preferentially used) Thinness threshold: 1–4 (1: very thin, 9: very large) on silhouette ratings Consideration of personal weight history (persistent thinness with consideration of childhood, adolescence and adulthood)	Considered (DSM-III-R) No group of AN Confirmed by interview (Structured Clinical Interview for DSM-III-R) Under-nutritional markers: NR	Criterion of amenorrhoea: NA (males) Weight gain resistance/desire: NR Healthy, associated pathology: NR Physical activity: NR	11

Table 1. (*Continued*)

References	Population characteristics (sample size, age and BMI) (mean (SD))	Definition of thinness	Consideration of the absence of eating disorders in individuals with CT	Consideration of other main parameters in individuals with CT	Areas of study
Tagami *et al.*[40]	Females: CT: *n* 6; 27·5 (SD 4·2) years; 17·7 (SD 0·5) kg/m^2 C: *n* 16; 25·7 (SD 2·9) years; 20·3 (SD 1·5) kg/m^2 AN: *n* 31; 25·5 (SD 8·1) years; 14·0 (SD 2·5) kg/m^2 (AN: probably restrictive type)	Presence of terminology Thinness threshold: BMI < 18·0 kg/m^2 No apparent consideration of weight history	Considered Implicitly confirmed by the presence of a group of AN (DSM-IV) Not explicitly confirmed by questionnaire or interview Under-nutritional markers: NR	No amenorrhoea Weight gain resistance/desire: NR Healthy, absence of associated pathology Physical activity: NR	2, 3
Miljic *et al.*[41]	Females: CT: *n* 10; 22·5 (SD 4·4) years; 17·6 (SD 1·3) kg/m^2 AN: *n* 9; 25·1 (SD 5·1) years; 12·0 (SD 1·2) kg/m^2 (AN: restrictive and binge eating/purging type)	Presence of terminology Thinness threshold: NR (but subnormal body weight 51·4 (SD 7·6) kg (45–60 kg) and BMI 17·6 (SD 1·3) kg/m^2 (16·6–19·3 kg/m^2)) Consideration of personal weight history (without history of weight loss)	Considered Implicitly confirmed by the presence of a group of AN (DSM-IV) Not explicitly confirmed by questionnaire or interview Under-nutritional markers: NR	No amenorrhoea Weight gain resistance/desire: NR Healthy, associated pathology: NR Physical activity: NR	3, 4
Bossu *et al.*[7]	Females: CT: *n* 7; NR but 18–26 years; 16·1 (SD 0·6) kg/m^2 C: *n* 7; NR but 18–26 years; 21·2 (SD 0·8) kg/m^2 AN: *n* 6; NR but 18–26 years; 15·8 (SD 0·8) kg/m^2 (AN: restrictive type)	Presence of terminology Thinness threshold: BMI: 14·5–16·5 kg/m^2 Consideration of personal weight history (stable throughout the post-pubertal period and weight history retrospectively reconstituted from birth to 18 years)	Considered Implicitly confirmed by the presence of a group of AN (DSM-IV) Not explicitly confirmed by questionnaire or interview Under-nutritional markers: NR	No amenorrhoea Weight gain resistance/desire: mentioned (desire for weight gain as a main reason for medical consultation) Healthy, absence of associated pathology Absence of over-exercising	1, 2, 3, 11
Germain *et al.*[9]	Females: CT: *n* 10; 20·2 (SD 3·8) years; 15·7 (SD 0·6) kg/m^2 C: *n* 7; 23 (SD 2·1) years; 20·4 (SD 0·8) kg/m^2 AN: *n* 12; 20·7 (SD 4·2) years; 15·2 (SD 1·4) kg/m^2 (AN: probably restrictive type)	Presence of terminology Thinness threshold: BMI: 14·5–16·5 kg/m^2 Consideration of personal weight history (stable throughout the post-pubertal period)	Considered Implicitly confirmed by the presence of a group of AN (DSM-IV) Not explicitly confirmed by questionnaire or interview Under-nutritional markers: NR	No amenorrhoea Weight gain resistance/desire: mentioned (desire for weight gain as a main reason for medical consultation) Healthy, absence of associated pathology Physical activity: NR	1, 2, 3, 4
Marra *et al.*[17]	Females: CT: *n* 20; 22·5 (SD 5·8) years; 17·2 (SD 1·0) kg/m^2 C: *n* 20; 22·0 (SD 3·7) years; 21·7 (SD 2·4) kg/m^2 AN: *n* 20; 18·8 (SD 3·4) years; 15·1 (SD 1·6) kg/m^2 (AN: restrictive type)	Presence of terminology Thinness threshold: NR Consideration of personal weight history (body weight that has always been in the lower percentiles for age, sex and ethnicity)	Considered Implicitly confirmed by the presence of a group of AN (DSM-IV) Not explicitly confirmed by questionnaire or interview Under-nutritional markers: NR (but normal thyroid functions seem to be assessed)	No amenorrhoea Weight gain resistance/desire: NR Healthy, absence of associated pathology Absence of over-exercising	1, 2

Table 1. (*Continued*)

References	Population characteristics (sample size, age and BMI) (mean (SD))	Definition of thinness	Consideration of the absence of eating disorders in individuals with CT	Consideration of other main parameters in individuals with CT	Areas of study
Galusca *et al.*[28]	Females: CT: *n* 25; 23·1 (SD 6·0) years; 15·8 (SD 0·5) kg/m^2 C: *n* 28; 23·9 (SD 7·4) years; 20·7 (SD 2·1) kg/m^2 AN: *n* 44; 23·4 (SD 8·0) years; AN: 15·5 (SD 0·7) kg/m^2 (AN: restrictive type)	Presence of terminology Thinness threshold: BMI: 12·0–16·5 kg/m^2 Consideration of personal weight history (stable throughout the growth period until the age of 18)	Considered Implicitly confirmed by the presence of a group of AN (DSM-IV) Not explicitly confirmed by questionnaire or interview Under-nutritional markers: NR	No amenorrhoea Weight gain resistance/desire: mentioned (desire for weight gain as a main reason for medical consultation) Healthy, absence of associated pathology Absence of over-exercising	2, 3, 5
Fernández-García *et al.*[24]	Females: CT: *n* 22; 19·7 (SD 5·3) years; 16·7 (SD 1·0) kg/m^2 C: *n* 20; 19·3 (SD 1·6) years; 22·3 (SD 1·6) kg/m^2 AN: *n* 25; NR for restrictive type; 16·1 (SD 1·5) kg/m^2 (AN: restrictive type)	Absence of terminology Thinness threshold: BMI < 18·5 kg/m^2 No apparent consideration of weight history (but after 5 years of follow-up, none presented any criteria for eating disorders)	Considered Implicitly confirmed by the presence of a group of AN (DSM-IV) Not explicitly confirmed by questionnaire or interview Under-nutritional markers: NR	No amenorrhoea Weight gain resistance/desire: NR Healthy, associated pathology: NR Physical activity: NR	2, 3, 5
Germain *et al.*[21]	Females: CT: *n* 9; 24·1 (SD 3·6) years; 16·1 (SD 0·3) kg/m^2 C: *n* 10; 23·1 (SD 4·4) years; 20·5 (SD 1·3) kg/m^2 AN: *n* 15; 20·4 (SD 5·0) years; 14·8 (SD 0·4) kg/m^2 (AN: restrictive type)	Presence of terminology Thinness threshold: BMI < 16·5 kg/m^2 Consideration of personal weight history (stable throughout the growth period)	Considered Implicitly confirmed by the presence of a group of AN (DSM-IV) Not explicitly confirmed by questionnaire or interview Under-nutritional markers: NR	No amenorrhoea Weight gain resistance/desire: mentioned (a stated desire for weight gain) Healthy, absence of associated pathology Physical activity: NR	2, 3, 4
Marra *et al.*[25]	Females: CT: *n* 10; 19·4 (SD 2·4) years; 16·8 (SD 1) kg/m^2 C: *n* 30; 20·0 (SD 2·1) years; 22·5 (SD 2·8) kg/m^2 AN: *n* 30; 19·0 (SD 2·0) years; 16·7 (SD 0·5) kg/m^2 (AN type: NR)	Presence of terminology Thinness threshold: BMI < 18·5 kg/m^2 No apparent consideration of weight history	Considered Implicitly confirmed by the presence of a group of AN Not explicitly confirmed by questionnaire or interview Under-nutritional markers: NR	No amenorrhoea Weight gain resistance/desire: NR Healthy, absence of associated pathology Absence of over-exercising	2
Hasegawa *et al.*[26]	Females: CT: *n* 20; 23·2 (SD 2·3) years; 17·6 (SD 0·8) kg/m^2 C: *n* 20; 23·1 (SD 2·1) years; 21·9 (SD 1·2) kg/m^2	Presence of terminology (but 'lean' term preferentially used) Thinness threshold: BMI < 18·5 kg/m^2 No apparent consideration of weight history	Considered No group of AN Not explicitly confirmed by questionnaire or interview Under-nutritional markers: NR	No amenorrhoea Weight gain resistance/desire: NR Healthy, absence of associated pathology Physical activity: NR	1, 2, 3
Galusca *et al.*[22]	Females: CT: *n* 14; 23·7 (SD 6)‡ years; 16·0 (SD 0·4)‡ kg/m^2 C: *n* 10; 23·1 (SD 5)‡ years; 20·8 (SD 0·6)‡ kg/m^2 AN: *n* 19; 23·2 (SD 8)‡ years; 15·3 (SD 0·4)‡ kg/m^2 (AN: restrictive type)	Presence of terminology Thinness threshold: BMI < 16·5 kg/m^2 Consideration of personal weight history (stable throughout the growth period)	Considered Implicitly confirmed by the presence of a group of AN (DSM-IV) Not explicitly confirmed by questionnaire or interview Under-nutritional markers: NR	No amenorrhoea Weight gain resistance/desire: mentioned (a stated desire for weight gain) Healthy, absence of associated pathology Absence of over-exercising	2, 3, 4

Table 1. (*Continued*)

References	Population characteristics (sample size, age and BMI) (mean (SD))	Definition of thinness	Consideration of the absence of eating disorders in individuals with CT	Consideration of other main parameters in individuals with CT	Areas of study
Santonicola *et al.*[42]	Females and males (not clearly reported): CT: *n* 9; 24·9 (SD 6·6) years; NR C: *n* 22; 23·7 (SD 3·3) years; NR AN: *n* 20; 22·5 (SD 4·2) years; NR (AN: probably restrictive type)	Presence of terminology Thinness threshold: NR (but severely underweight) Consideration of personal weight history (stable throughout the post-pubertal period)	Considered (DSM-IV) Implicitly confirmed by the presence of a group of AN (DSM-IV) Confirmed by interview (to detect potential lifetime eating disorders in accordance with the criteria of the DSM-IV) Under-nutritional markers: NR	No amenorrhoea Weight gain resistance/desire: mentioned (desire for weight gain as a main reason for medical consultation) Healthy, absence of associated pathology Physical activity: NR	13
Pasanisi *et al.*[20]	Females: CT: *n* 7; 21·7 (SD 3·6) years; 16·2 (SD 0·9) kg/m^2 C: *n* 20; 25·6 (SD 3·9) years; 21·7 (SD 2·4) kg/m^2 AN: *n* 7; 23·4 (SD 4·5) years; 15·3 (SD 0·8) kg/m^2 (AN: restrictive type)	Presence of terminology Thinness threshold: NR No apparent consideration of weight history	Considered Implicitly confirmed by the presence of a group of AN (DSM-IV) Not explicitly confirmed by questionnaire or interview Under-nutritional markers: NR (but normal thyroid function)	No amenorrhoea Weight gain resistance/desire: NR Healthy, absence of associated pathology Physical activity: NR	1, 2, 10
Paschalis *et al.*[43]	Females: CT: *n* 8; 21·4 (SD 1·1) years; 17·3 (SD 0·6) kg/m^2 C: *n* 12; 20·2 (SD 1·4) years; 22·0 (SD 1·0) kg/m^2	Absence of terminology Thinness threshold: NR (but groups constituted according to BMI) Consideration of personal weight history (stable at their anthropometric characteristics for at least the last 2 years)	NR No group of AN Not explicitly confirmed by questionnaire or interview Under-nutritional markers: NR	No amenorrhoea Weight gain resistance/desire: NR Healthy, absence of associated pathology Absence of over-exercising (≤ 1 h per week on sport activities)	6
Germain *et al.*[10]	Females: CT: *n* 8; 21·6 (SD 5·4) years; 17·1 (SD 0·8) kg/m^2 C: *n* 8; 22·1 (SD 2·3) years; 22·1 (SD 0·8) kg/m^2	Presence of terminology Thinness threshold: BMI: 13–17·5 kg/m^2 Consideration of personal weight history (stable throughout the post-pubertal period)	Considered No group of AN Confirmed by questionnaires (DEBQ[50] and EDE[51] – no reported thresholds) Normal nutritional markers (normal IGF-1, oestradiol, FT_3, mean cortisol and non-blunted leptin)	No amenorrhoea Weight gain resistance/desire: mentioned (recruited among outpatients consulting for body weight gain desire) Healthy, absence of associated pathology Absence of over-exercising (according to the MOSPA questionnaire)	1, 2, 3, 4, 7, 11
Galusca *et al.*[23]	Females: CT: *n* 22; 23·2 (SD 2·3) years; 15·9 (SD 0·5) kg/m^2 C: *n* 14; 22·6 (SD 6·0) years; 21·6 (SD 1·1) kg/m^2 AN: *n* 23; 22·5 (SD 6·2) years; 14·6 (SD 2·4) kg/m^2 (AN: restrictive type)	Presence of terminology Thinness threshold: BMI < 16·5 kg/m^2 Consideration of personal weight history (stable throughout the growth period)	Considered Implicitly confirmed by the presence of a group of AN (DSM-IV) Not explicitly confirmed by questionnaire or interview Under-nutritional markers: NR	No amenorrhoea Weight gain resistance/desire: mentioned (a stated desire for weight gain) Healthy, absence of associated pathology Absence of over-exercising (according to the MOSPA questionnaire)	2, 3, 4
Germain *et al.*[27]	Females: CT: *n* 10; 20·6 (SD 6·6) years; 15·9 (SD 0·9) kg/m^2 C: *n* 10; 22·7 (SD 1·6) years; 21·4 (SD 1·6) kg/m^2 AN: *n* 10; 21·6 (SD 4·7) years; 15·1 (SD 2·5) kg/m^2 (AN: restrictive type)	Presence of terminology Thinness threshold: BMI < 17 kg/m^2 Consideration of personal weight history (stable throughout the growth period)	Considered Implicitly confirmed by the presence of a group of AN (DSM-IV) Not explicitly confirmed by questionnaire or interview Under-nutritional markers: NR	No amenorrhoea Weight gain resistance/desire: mentioned (a stated desire for weight gain) Healthy, absence of associated pathology Physical activity: NR	2, 3

Table 1. (*Continued*)

References	Population characteristics (sample size, age and BMI) (mean (SD))	Definition of thinness	Consideration of the absence of eating disorders in individuals with CT	Consideration of other main parameters in individuals with CT	Areas of study
Gunes *et al.*[44]	CT (16 females, 8 males): *n* 24; 22·1 (SD 3·7) years; 17·4 (SD 1·2) kg/m^2 C (9 females, 15 males): *n* 24; 23·5 (SD 4·0) years; 22·1 (SD 2·4) kg/m^2	Presence of terminology Thinness threshold: BMI < 18·5 kg/m^2 Consideration of personal weight history (stable during the post-pubertal period)	NR No group of AN Not explicitly confirmed by questionnaire or interview Under-nutritional markers: NR	No amenorrhoea Weight gain resistance/desire: mentioned (desire for weight gain as a main reason for medical consultation) Healthy, absence of associated pathology Absence of over-exercising	8
Ling *et al.*[31]	Females: CT: *n* 15; NR (design) but 18–35 years; NR (design) 13–17·5 kg/m^2 C: *n* 15; NR (design) but 18–35 years; NR (design) but 20–25 kg/m^2 Males: CT: *n* 15; NR (design) but 18–35 years; NR (design) 13–18·5 kg/m^2 C: *n* 15; NR (design) but 18–35 years; NR (design) but 20–25 kg/m^2	Presence of terminology Thinness threshold: BMI: 13–17·5 kg/m^2 (females), 13–18·5 kg/m^2 (males) Consideration of personal weight history (stable for post-pubertal and at least 3 months)	Considered (DSM-IV) No group of AN Confirmed by questionnaires (DEBQ, EDE, Eating Disorder Inventory Questionnaire[53], and Body Shape Questionnaire[47] – no reported thresholds) Normal nutritional markers (normal IGF-1, oestradiol, FT_3, mean cortisol and non-blunted leptin)	No amenorrhoea Weight gain resistance/desire: mentioned (recruited among outpatients consulting for body weight gain desire) Healthy, absence of associated pathology Absence of over-exercising (according to the MOSPA questionnaire and ≤ 3 sessions per week)	1, 2, 3, 4, 5, 6, 7, 11
Estour *et al.*[8]	Females: CT: *n* 56; 26·9 (SD 7·6) years; 16·5 (SD 0·9) kg/m^2 C: *n* 54; 23·4 (SD 4·1) years; 20·9 (SD 2·2) kg/m^2 AN: *n* 40; 25·0 (SD 6·5) years; 16·0 (SD 0·8) kg/m^2 (AN: restrictive type)	Presence of terminology Thinness threshold: BMI < 17·5 kg/m^2 Consideration of personal weight history (when available (26/56 CT), weight history from birth to at least 18 years old was retrospectively reconstituted)	Considered Implicitly confirmed by the presence of a group of AN (DSM-IV) Not explicitly confirmed by questionnaire or interview Under-nutritional markers: NR	No amenorrhoea Weight gain resistance/desire: mentioned (desire for weight gain as a main reason for medical consultation) Healthy, absence of associated pathology Physical activity: NR	1, 2, 3, 5, 11
Galusca *et al.*[19]	Females: CT: *n* 10; 22·1 (SD 5·1) years; 17·0 (SD 0·9) kg/m^2 C: *n* 10; 22·2 (SD 2·5) years; 21·7 (SD 1·3) kg/m^2	Presence of terminology Thinness threshold: BMI < 17·5 kg/m^2 Consideration of personal weight history (stable throughout the post-pubertal period)	Considered No group of AN Not explicitly confirmed by questionnaire or interview Normal nutritional markers (normal IGF-1, oestradiol, FT_3)	Amenorrhoea: NR Weight gain resistance/desire: NR Healthy, absence of associated pathology Physical activity: NR	1, 2, 3, 5, 6, 7
Florent *et al.*[45]	Females: CT: *n* 10; 22·4 (SD 2·5) years; 17·1 (SD 0·9) kg/m^2 C: *n* 10; 21·8 (SD 2·2) years; 21·9 (SD 1·3) kg/m^2 AN: *n* 10; 26·4 (SD 6·0) years; 15·3 (SD 1·9) kg/m^2 (AN: restrictive type)	Presence of terminology Thinness threshold: BMI < 18·5 kg/m^2 No apparent consideration of weight history	Considered (DSM-IV) Implicitly confirmed by the presence of a group of AN (DSM-IV) Confirmed by questionnaire (TFEQ with a cognitive restraint score ≥ 13) Under-nutritional markers: NR	No amenorrhoea Weight gain resistance/desire: NR Healthy, absence of associated pathology Physical activity: NR	11, 14

Table 1. (*Continued*)

References	Population characteristics (sample size, age and BMI) (mean (SD))	Definition of thinness	Consideration of the absence of eating disorders in individuals with CT	Consideration of other main parameters in individuals with CT	Areas of study
Margaritelis *et al.*[46]	Females: CT: *n* 12; 21·2 (SD 1·4) years; 17·8 (SD 0·8) kg/m^2 C: *n* 14; 20·4 (SD 1·8) years; 22·4 (SD 1·1) kg/m^2	Absence of terminology Thinness threshold: BMI < 20 kg/m^2 and body fat: 10–20 % Consideration of personal weight history (body weight did not change more than ± 3 kg the last 2 years prior to participation in the study)	NR No group of AN Not explicitly confirmed by questionnaire or interview Under-nutritional markers: NR	No amenorrhoea Weight gain resistance/desire: NR Healthy, absence of associated pathology Absence of over-exercising (≤ 1 h per week on sport activities)	1, 3, 6
Marra *et al.*[18]	Males: CT: *n* 15; 23·3 (SD 5·2) years; 17·9 (SD 0·6) kg/m^2 C: *n* 18; 22·3 (SD 3·7) years; 22·3 (SD 1·7) kg/m^2 AN: *n* 17; 22·3 (SD 5·3) years; AN: 17·1 (SD 1·2) kg/m^2 (AN: probably restrictive type)	Presence of terminology Thinness threshold: NR Consideration of personal weight history (stable on time)	Considered Implicitly confirmed by the presence of a group of AN (DSM-5) Not explicitly confirmed by questionnaire or interview Under-nutritional markers: NR	Criterion of amenorrhoea: NA (males) Weight gain resistance/desire: NR Healthy, absence of associated pathology Physical activity: NR	1, 2
Riveros-McKay *et al.*[30]	Females: CT: *n* 1325; 36·6 (SD 14·3) years; 17·6 (SD 0·9) kg/m^2 C: *n* 5837; 52·0 (SD 16·7) years; 27·0 (SD 7·9) kg/m^2 AN type: NR Males: CT: *n* 297; 35·2 (SD 14·5) years; 17·6 (SD 1·1) kg/m^2 C: *n* 4596; 52·7 (SD 17·3) years; 26·9 (SD 7·8) kg/m^2 AN type: NR	Presence of terminology (but 'persistent/healthy thinness' preferentially used) Thinness threshold: BMI < 18 kg/m^2 (but a small number of individuals with a BMI of 19·0 kg/m^2 were included as they had a strong family history of thinness) Consideration of personal weight history (persistently thin/always thin throughout life)	Considered Implicitly confirmed by the presence of a group of AN Confirmed by questionnaire (SCOFF questionnaire – no reported thresholds) Under-nutritional markers: NR	Amenorrhoea: NR Weight gain resistance/desire: NR Healthy, absence of associated pathology Absence of over-exercising (excluded if they exercised more than three times a week or with an intensity exceeding six metabolic equivalents for any duration or frequency)	7

NR, not reported; C, control subjects; AN, anorexia nervosa; DSM, Diagnostic and Statistical Manual of Mental Disorders; NA, not applicable; TFEQ, Three-Factor Eating Questionnaire[48]; DEBQ, Dutch Eating Behaviour Questionnaire; EDE, Eating Disorder Examination Questionnaire; IGF-1, insulin-like growth factor-1; FT_3, free triiodothyronine; MOSPA, Monica Optional Study of Physical Activity[52].

* SCOFF questions, Do you make yourself sick because you feel uncomfortably full? Do you worry you have lost control over how much you eat? Have you recently lost more than one stone in a 3 month period? Do you believe yourself to be fat when others say you are too thin? Would you say that food dominates your life?[54].

† Areas of study: 1: Energy balance, 2: Body composition, 3: Hormonal, biochemical assays, 4: Appetite-regulating hormones, 5: Bone tissue/Bone markers, 6: Muscle tissue/Muscle function, 7: Genetics or omics approaches, 8: Ophthalmology, 9: Pregnancy, 10: Thermogenesis/Brown adipose tissue, 11: Psychological profile, 12: Cardiology, 13: Functional dyspepsia, 14: Neurology.

‡ Type of values dispersion (SD or SEM) not clearly reported.

§ 'Terminology presence' means the mention of 'constitutional(ly) thin(ness)/lean(ness)' crucial keywords.

Table 2. Risks of bias

References	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Schneider *et al.*[32]	Moderate risk	NR	Low risk	Moderate risk	Moderate risk	Moderate risk
van Binsbergen *et al.*[33]	Low risk	NR	High risk	Low risk	NR	Low risk
Diaz *et al.*[34]	Low risk	NR	High risk	High risk	High risk	Low risk
Scalfi *et al.*[16]	Low risk	NR	High risk	Moderate risk	NR	Low risk
Hinney *et al.*[35]	Low risk	NR	High risk	Low risk	Low risk	Low risk
Petretta *et al.*[36]	Low risk	NR	High risk	Low risk	NR	Low risk
Slof *et al.*[37]	Moderate risk	NR	High risk	High risk	Low risk	Low risk
Tolle *et al.*[11]	Moderate risk	NR	High risk	Low risk	Moderate risk	Low risk
Bosy-Westphal *et al.*[38]	Low risk	NR	High risk	Low risk	High risk	Low risk
Mazzeo *et al.*[39]	Moderate risk	NR	High risk	High risk	Low risk	Low risk
Tagami *et al.*[40]	Low risk	NR	High risk	Low risk	Moderate risk	Low risk
Miljic *et al.*[41]	Moderate risk	NR	High risk	Low risk	Moderate risk	Low risk
Bossu *et al.*[7]	Low risk	NR	High risk	Moderate risk	NR	Low risk
Germain *et al.*[9]	Low risk	NR	High risk	Low risk	NR	Low risk
Marra *et al.*[17]	Moderate risk	NR	High risk	Low risk	NR	Low risk
Galusca *et al.*[28]	Low risk	NR	High risk	Low risk	NR	Low risk
Fernández-García *et al.*[24]	Low risk	NR	High risk	Low risk	Moderate risk	Low risk
Germain *et al.*[21]	Low risk	NR	High risk	Low risk	Moderate risk	Low risk
Marra *et al.*[25]	Low risk	NR	High risk	Low risk	NR	Low risk
Hasegawa *et al.*[26]	Low risk	NR	High risk	Low risk	NR	Low risk
Galusca *et al.*[22]	Low risk	NR	High risk	Low risk	NR	Low risk
Santonicola *et al.*[42]	Moderate risk	NR	High risk	High risk	NR	Low risk
Pasanisi *et al.*[20]	Moderate risk	NR	High risk	Low risk	Moderate risk	Low risk
Paschalis *et al.*[43]	Moderate risk	NR	High risk	Moderate risk	NR	Low risk
Germain *et al.*[10]	Low risk	NR	High risk	Moderate risk	NR	Low risk
Galusca *et al.*[23]	Low risk	NR	High risk	Low risk	NR	Low risk
Germain *et al.*[27]	Low risk	NR	High risk	Low risk	NR	Low risk
Gunes *et al.*[44]	Low risk	NR	High risk	Low risk	NR	Low risk
Ling *et al.*[31]	Low risk	NR	High risk	Moderate risk	NA	NA
Estour *et al.*[8]	Low risk	NR	High risk	Low risk	NR	Low risk
Galusca *et al.*[19]	Low risk	NR	High risk	Low risk	NR	Low risk
Florent *et al.*[45]	Low risk	NR	High risk	Moderate risk	Moderate risk	Low risk
Margaritelis *et al.*[46]	Low risk	NR	High risk	Moderate risk	NR	Low risk
Marra *et al.*[18]	Moderate risk	NR	High risk	Low risk	NR	Low risk
Riveros-McKay *et al.*[30]	Low risk	NR	High risk	Low risk	Low risk	Low risk

NR, not reported.

Results

The initial database search yielded a total of 994 studies, and thirty-nine additional studies were also identified. In total, 689 studies remained after the removal of duplicates. After the review of titles and abstracts, 363 studies were excluded: 199 based on title and 164 based on abstract. Thus, 326 full-text articles were scrutinised for eligibility according to inclusion and exclusion criteria. Finally, thirty-five studies were considered for analysis (Fig. 1). The risks of bias were estimated with the Cochrane Collaboration's tool[55] as presented in Table 2.

Population characteristics

Of the thirty-five studies selected in the systematic review, twenty-six[7–11,16,17,19–28,32,33,36,37,40,41,43,45,46] enrolled females exclusively, three[18,34,39] enrolled males exclusively and six[30,31,35,38,42,44] enrolled both females and males (Table 1). Of these thirty-five studies, thirty-two[7–11,16–28,30–33,36–40,42–46] included a normal-weight control group and twenty-three[7–9,11,16–18,20–25,27,28,30,33,35,36,40–42,45] included a group of individuals with AN (eighteen[7–9,11,16–18,20–24,27,28,36,40,42,45] of restrictive type, two[35,41] of both restrictive and binge eating/purging type and three[25,30,33] did not report the type of AN). Selected studies included sample sizes ranging from six[40] to 1622[30] (both sex) in individuals with CT, from seven[7,9] to 10 433[30] (both sex) in normal-weight control people and from six[7] to ninety-six[35] (both sex) in patients with AN. Studies enrolled participants from 19·4[25] to 42·4[37] years old in people with CT, from 19·3[24] to 52·3[30] years old (both sex) in normal-weight people and from 15·3[35] to 26·4[45] years old in patients with AN. BMI ranged from 15·7[9,11] to 22·5[39] kg/m^2 in individuals with CT, from 20·3[40] to 27·6[39] kg/m^2 in normal-weight controls and from 12·0[41] to 17·1[18] kg/m^2 in patients with AN.

Definition of thinness

The 'constitutional(ly) thin(ness)/lean(ness)' keywords were mentioned in twenty-eight[7–11,17–23,25–28,30–32,34,36,37,39–42,44,45] of the thirty-five studies and were therefore not mentioned in the seven remaining studies[16,24,33,35,38,43,46]. Of the thirty-five included studies, thinness threshold was reported through absolute BMI value in twenty-one studies[7–10,16,19,21–28,30,31,36,38,40,44,45] (ranging from 16·5[7,9,21–23,28] to 20·0 kg/m^2[36]), through BMI percentile in one study (≤ 15th BMI percentile)[35], through

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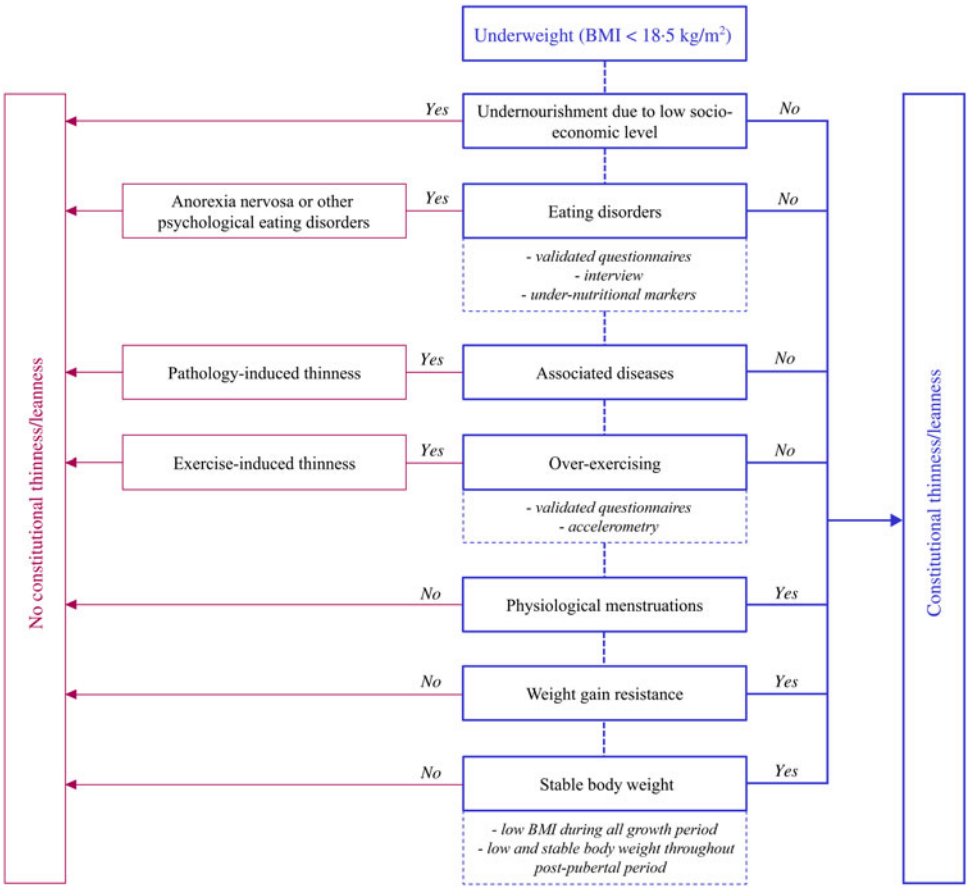

Fig. 2. Decision tree in the diagnosis of constitutional thinness.

percentage of ideal body weight in two studies (at least 25 % lower than the average ideal body weight[32] or 80–90 % of ideal body weight[33]), through silhouette ratings (1: very thin, 9: very large) in two studies (ranging from 1 to 3 for thin females[37] and from 1 to 4 for thin males[39]), through FM percentage in one study[34] (body fat ≤ 20 % and low or normal weight) and through both BMI (< 20 kg/m²) and FM percentage (between 10 and 20 %) in one study[46]. Thinness threshold was not clearly reported in seven[11,17,18,20,41–43] of the thirty-five studies. Weight history was considered in twenty-five[7–10,16–19,21–23,27,28,30,31,35–39,41–44,46] of the thirty-five studies: four studies[16,38,43,46] reported a stable body weight for a certain period of time before the experiment (ranging from 1 week[38] to 2 years[16,43,46]), and twenty-one studies[7–10,17–19,21–23,27,28,30,31,35–37,39,41,42,44] reported it for a longer period throughout the growth period and/or the post-pubertal period. Weight history was not considered in the ten[11,20,24–26,32–34,40,45] remaining studies.

Consideration of the absence of eating disorders in individuals with constitutional thinness

Of the thirty-five studies, thirty-two[7–11,16–28,30–42,45] considered the absence of eating disorders in the inclusion criteria of CT and three[43,44,46] did not consider it. The absence of eating disorders was implicitly confirmed by the presence of a group of patients with AN in twenty-three studies[7–9,11,16–18,20–25,27,28,30,33,35,36,40–42,45]. This absence of eating disorders was confirmed using questionnaires in five studies[10,30,31,36,45], interviews in three studies[37,39,42] and both in one study[35]. Different questionnaires and thresholds were used: the Three-Factor Eating Questionnaire[48] for two studies[35,45] with a cognitive restraint score ≤ 5[35] or ≥ 13[45] using their respective version of the Three-Factor Eating Questionnaire, a food questionnaire with normal scores not further defined for one study[36], the Dutch Eating Behaviour Questionnaire[50] and the Eating Disorder Examination Questionnaire[51] without reported thresholds for two studies[10,31], the Eating Disorder Inventory Questionnaire[53] and the Body Shape Questionnaire[47] without reported thresholds for one study[31], and the SCOFF questionnaire[54] without reported thresholds for one study[30]. The Composite International Diagnostic Interview[49] was used for one study[35], the Structured Clinical Interview for DSM-III-R was used for two studies[37,39] and an interview to detect potential lifetime eating disorders in accordance with the criteria of the DSM-IV was used for one study[42]. The twenty-six remaining studies[7–9,11,16–28,32–34,38,40,41,43,44,46] did not mentioned the use of questionnaires or interviews. Three studies[10,19,31] presented

the following criteria as inclusion criteria: normal insulin-like growth factor-1, oestradiol and free triiodothyronine. Among them, two studies[10,31] also added normal mean cortisol and non-blunted leptin as inclusion criteria. Under-nutritional markers were not assessed in the thirty-two remaining studies[7–9,11,16–18,20–28,30,32–46].

Consideration of other important parameters in individuals with constitutional thinness

Of the thirty-five studies, twenty-six[7–11,16,17,20–28,31,33,36,40–46] mentioned the presence of menses in their group of CT, six[19,30,32,35,37,38] did not mention it and three studies[18,34,39] did not enrol females but only males (not applicable criterion). Weight gain resistance/desire was taken into consideration in fourteen articles[7–10,16,21–23,27,28,31,34,42,44] and was not reported in the twenty-one other selected studies[11,17–20,24–26,30,32,33,35–41,43,45,46]. Among them, twelve studies[7–10,21–23,27,28,31,42,44] specifically referred to the idea of a 'desire' to gain weight, one study[16] reported a complaint about being chronically underweight and one study[34] identified a difficulty in gaining weight. No studies used the term 'resistance' to weight gain. The absence of associated pathology was considered in twenty-eight[7–10,16–23,25–28,30–35,40,42–46] of the thirty-five studies but was not reported in the seven remaining studies[11,24,36–39,41]. Physical activity was reported in thirteen studies[7,10,16,17,22,23,25,28,30,31,43,44,46] and was consequently not reported in the twenty-two remaining studies[8,9,11,18–21,24,26,27,32–42,45]. Ten articles[7,16,17,22,25,28,30,43,44,46] just mentioned the absence of over-exercising without questionnaire-based assessment. Among them, two articles[43,46] specified that participants did not spend more than 1 h per week on sport activities and one article[30] excluded all participants who stated that they exercised more than three times a week or with an intensity exceeding six metabolic equivalents for any duration or frequency[56]. Three articles[10,23,31] used the Monica Optional Study of Physical Activity questionnaire[52] to assess the absence of over-exercising, and one[31] of them added intensive physical activity (more than three sessions of physical activity per week) as an exclusion criterion.

Areas of study

Various fields of study were investigated in the selected articles. Of the thirty-five studies included in the systematic review, twenty-one[7–11,17–28,31,34,38,40] investigated body composition, nineteen[7–11,19,21–24,26–28,31,33,36,40,41,46] assessed hormonal or biochemical parameters and fifteen[7–10,16–20,26,31,34,36,38,46] studied energy balance of individuals with CT. Investigations were carried out in a total of eight studies[9–11,21–23,31,41] on appetite-regulating hormones, six studies[8,19,24,28,31,38] on bone tissue or bone markers, seven studies[7,8,10,31,37,39,45] on psychological profile, five studies[10,19,30,31,35] on genetics or omics approaches, four studies[19,31,43,46] on muscle tissue or muscle function, two studies[16,20] on thermogenesis or brown adipose tissue, one study[44] on ophthalmology, one study[32] on pregnancy, one study[36] on cardiology, one study[42] on functional dyspepsia and one study[45] on neurology.

Discussion

The literature shows a growing number of clinical trials enrolling underweight participants without apparent disorders in their energy balance, suggesting a constitutional origin of thinness. These studies, however, reveal a high heterogeneity when it comes to the employed definition and diagnosis of CT, as well as a high diversity in the fields of study. In that context, we proposed here a systematic analysis of the clinical trials that enrolled participants with CT in order to propose a better definition and diagnosis of CT.

The need for a clear terminology

The lack of consensus and visibility concerning CT is probably due to the lack of common terminology. Among the thirty-five studies considered in the present systematic review, seven[16,24,33,35,38,43,46] did not used the key terms 'constitutional thinness' or 'constitutional leanness'. This makes highly probable that people might not detect those references while conducting simple scientific or systematic researches. For example, Farooqi and her research team who conducted a very interesting genetic research on CT[30] preferentially used the 'persistent/healthy thinness' expression even if 'constitutional thinness' is still found once[30]. In addition, studies enrolling 'lean' or 'underweight' groups need to be particularly screened. Most of the time, the 'lean' term refers to normal-weight individuals and 'underweight' term to undernourishment, but confusingly, these terms also remain found in the literature to designate CT individuals. Thus, we would privilege a common terminology, such as 'constitutional thinness' or 'constitutional leanness' designations. Since CT individuals do not seem to be characterised by a very low body fat percentage despite their low BMI[8,10,11,17,19,23–27], we would favour the terminology of 'constitutional thinness' which therefore seems more appropriate than 'constitutional leanness'. A common terminology would drastically facilitate the referencing of CT in research databases and increase its visibility.

Thinness threshold

As underlined in different studies, dealing with thinness first requires to properly set a threshold for this thinness[8,15,57]. The WHO defines different thresholds, based on BMI cut-offs: grade 1 – mild thinness (17·00–18·49 kg/m^2), grade 2 – moderate thinness (16·00–16·99 kg/m^2) and grade 3 – severe thinness (< 16·00 kg/m^2)[57,58]. Thus, the WHO uses the BMI measurement to provide demarcation points. Of the thirty-five included studies, twenty-two[7–10,16,19,21–28,30,31,36,38,40,44–46] also used BMI cut-offs and one study[35] used a threshold of BMI percentile (≤ 15th BMI percentile). BMI cut-offs ranged from 16·5[7,9,21–23,28] to 20·0[36,46] kg/m^2 for studies using a BMI threshold and mean BMI ranged from 15·7[9,11] to 22·5[39] kg/m^2 in individuals with CT, revealing a high heterogeneity in BMI values. Two studies[34,46] used percentages of FM to define a thinness cut-off. From an etymological point of view, 'leanness' defines a low body fat content and interestingly, Maffetone *et al.* proposed the use of the 'underfat' term instead of 'underweight'[59]. Nevertheless, Maffetone *et al.* proposed this terminology considering thinness due to a chronic illness or eating disorders, not

thinness due to a constitutional origin[59]. Despite their low BMI, CT individuals have been suggested to present a non-blunted FM percentage[7,8,10,11,17,19,23–27], unlike AN individuals whose FM seems significantly lower compared with CT people[7,8,11,17,23,24]. The use of a body fat percentage threshold does not seem yet adequate to diagnose CT and could, on the contrary, lead to misdiagnosis. While we therefore suggest that 'underfat' might not be an appropriate term in the context of CT, further studies using similar inclusion criteria and methodologies are required to provide more evidence about body composition in CT. Two studies[32,33] focused their definition of thinness on a percentage of ideal body weight, and two studies[37,39] argued that silhouette ratings were a better choice to base their definition of thinness. Nevertheless, silhouette ratings led to the inclusion of individuals with a relatively high BMI of 20·3 kg/m^2[37] in females and 22·5 kg/m^2[39] in males, whose CT diagnosis was therefore highly debatable. Seven studies[11,17,18,20,41–43] did not clearly report any threshold for their definition of thinness. Thus, the systematic review revealed that studies do not systematically point out a cut-off to define thinness. In addition, large variability in both the used criteria and cut-off values was observed. In that context, it seems complex to propose specific recommendations concerning a thinness threshold. However, given the BMI cut-offs of the WHO[57,58], we would recommend not to enrol CT individuals with a BMI exceeding 18·49 kg/m^2.

Weight history

Weight fluctuation and duration of fluctuations are other important parameters that should accompany consideration of the thinness degree. The present systematic review showed that weight history was well taken into consideration with twenty-five studies[7–10,16–19,21–23,27,28,30,31,35–39,41–44,46] reporting this criterion. However, there was a high heterogeneity in modalities: four studies[16,38,43,46] reported a stable weight for a certain period of time before the experiment (ranging from 1 week[38] to 2 years[16,43,46]) and twenty-one studies[7–10,17–19,21–23,27,28,30,31,35–37,39,41,42,44] reported it for a longer period throughout the growth period and/or the post-pubertal period. In 1982, Apfelbaum and Sachet already stressed the need to consider the weight history of CT patients and to differentiate between slimness and slimming[15]. Indeed, weight history opposes CT from AN[5,7,8]. Contrary to AN that is characterised by a curve break at the onset of anorexic tendencies, the diagnosis of CT should be supported by a low BMI (approximately the 3rd percentile) during all the growth period and by a stable body weight throughout the post-pubertal period[5,7,8]. In addition, CT seems to be a heritable trait[29,30], leading to CT families[7]. For three generations, an average of 2·5 thin subjects per family is found in CT for only 0·5 per family in AN[7]. Thus, the presence of other thin individuals in familial history can also reinforce a CT diagnosis.

Absence of eating disorders, associated pathology and over-exercising

Potential eating disorders and associated diseases, as well as an energy imbalance caused by a high-energy expenditure through physical activity, need to be taken into account to properly identify CT[5,8,10,19,21,28,31]. In the thirty-five included papers, the absence of eating disorders was well considered: only three papers[43,44,46] did not consider this criterion. Although well considered, this absence of eating disorders is most of the time simply mentioned or implicitly suggested without any details regarding its assessment. Only 26 %[10,30,31,35–37,39,42,45] of the included studies used specific tools, like questionnaires or interviews, to confirm the absence of eating disorders, and only two studies[10,31] have associated questionnaires with the assessment of the following nutritional biomarkers: normal insulin-like growth factor-1, oestradiol, free triiodothyronine, mean cortisol and non-blunted leptin. In addition, questionnaires and interviews used were highly heterogeneous, using different versions, rarely reporting thresholds, and if so, with different thresholds. This observation shows the real need to adopt harmonised and common methods to robustly detect eating disorders. Concerning the absence of associated pathology, this criterion was well considered in the selected papers: only seven studies[11,24,36–39,41] did not report it. Since some studies may have taken into account some diagnostic parameters without explicitly detailing them in their inclusion process, we assume that some diagnostic parameters may have been slightly underestimated. Regarding physical activity, 63 %[8,9,11,18–21,24,26,27,32–42,45] of the included studies did not report any physical activity level in their inclusion criteria. Ten articles[7,16,17,22,25,28,30,43,44,46] simply mentioned the absence of high physical activity level and only three articles[10,23,31] actually assessed physical activity level, using the Monica Optional Study of Physical Activity questionnaire[52]. Importantly, the relevance of the Monica Optional Study of Physical Activity questionnaire[52] should be discussed. This questionnaire has been validated[52] among fifty pregnant women only, and several limitations in the methodological approaches of its validation need to be recognised[52]. The thresholds used to define the different physical activity levels differ: two articles[43,46] specified that participants did not spend more than 1 h per week in sport activities, one article[31] considered the practice of more than three sessions of physical activity per week as an exclusion criterion and one article[30] excluded all participants who stated that they exercised more than three times a week or with an intensity exceeding six metabolic equivalents for any duration or frequency[56]. Altogether, these observations raised a real need to precisely describe the population in terms of type, duration, frequency and intensity of physical activity, not only with validated questionnaires but also with a more objective method such as accelerometry. Interestingly, spontaneous repeated muscle contractions in daily life, like fidgeting, were also suggested to be a relevant parameter to evaluate in CT for future studies[10,17,20,31].

Weight gain resistance/desire

Of the included articles, less than half of them[7–10,16,21–23,27,28,31,34,42,44] mentioned weight gain resistance/desire in their inclusion criteria of CT people, and most of these articles have been written by members of the same research team[7–10,21–23,27,28,31]. Of the fourteen articles[7–10,16,21–23,27,28,31,34,42,44] mentioning this weight gain resistance/desire, twelve[7–10,21–23,27,28,31,42,44] used the idea of a 'desire' to gain

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weight, one study[16] mentioned a complaint about being chronically underweight, another study[34] reported difficulty in gaining weight and no studies used the term 'resistance' to weight gain. Even if the desire to gain weight is actually, most of the time, the main reason for medical consultation in CT[5] and definitely differentiates CT from AN, we suggest here that an individual with CT might not present a strong desire to gain weight despite a physiological weight gain resistance, to the same extent that obesity is not defined as the subject's 'willingness' to lose weight. In the case of CT, it may seem more accurate to define it as a 'resistance' to gain weight, which can result in a desire to gain weight – but not necessarily. Indeed, CT was found to be the first human model of physiological weight gain resistance[10], and several publications proposed supplements and treatments to help CT people gain weight, a few decades earlier[3,4,15,60] or more recently[10,31]. Bulik & Allison even proposed the following definition of CT: 'constitutional protection against the need to diet in order to maintain a low body weight'[29].

Female sex predominance and amenorrhoea

A female sex predominance was observed with twenty-six studies[7–11,16,17,19–28,32,33,36,37,40,41,43,45,46] that were conducted among females exclusively, six studies[30,31,35,38,42,44] on both sex and three studies[18,34,39] in males exclusively. As the systematic review was performed on clinical studies, it seems to us that this observation probably only illustrates the lower consultation rate in men, and we encourage further researches in both sex, as CT is not a sex-specific condition. The presence of menses in the diagnosis of CT was widely taken into account: only six studies[19,30,32,35,37,38] did not mention this criterion of the thirty-two studies[7–11,16,17,19–28,30–33,35–38,40–46] enrolling females. Although the absence of amenorrhoea was well considered in the studies, the removal of this criterion from the revised DSM-5[13] can lead to new difficulties in the differential diagnosis between AN and CT[8]. It seems, however, relevant to us to verify the absence of amenorrhoea in the diagnosis of CT.

Recommendations in the diagnosis of constitutional thinness

The systematic review of clinical trials that enrolled participants with CT definitely revealed the real need to adopt both a common terminology and a well-defined diagnosis of CT. Based on the present results, we collectively propose here the key term 'constitutional thinness' to be used. Using the 'constitution' term to refer to the innate and natural cause of thinness seems of particular interest since it also helps clarify the distinction with other behavioural or pathological origins of thinness. In this respect, it seems essential to systematically exclude energy imbalance caused by inappropriately low energy intake (eating disorders) and/or inappropriately high exercise-induced energy expenditure, using validated tools. Ideally, eating behaviour should be evaluated not only with common validated questionnaires or interviews using specific thresholds but also with the assessment of nutritional biomarkers. If possible, the absence of over-exercising should not only be declarative but also measured with robustly validated questionnaires or even by accelerometry technique. Although amenorrhoea has been removed from the definition of AN in the DSM-5[13], it seems relevant to consider the presence of physiological menstruations in the diagnosis of CT. In addition, weight gain resistance and weight history also need to be taken into consideration in the diagnosis. Finally, the question of defining a strict threshold for thinness remains complex and arbitrary. Even though BMI assessment is associated with various limitations[59], we would tend to favour this measurement as long as it is very common and simple to perform. Conversely, we recommend not to use the percentage of body fat as a maximal threshold since CT does not seem to be characterised by a low body fat percentage[8,10,11,17,19,23–27]. Given the BMI cut-offs of the WHO[57,58], we propose that CT should not be discussed with a BMI exceeding the value of 18·49 kg/m^2. Beyond these essential criteria for CT diagnosis, some studies seem to suggest certain common characteristics in CT groups. In comparison to people with AN, CT individuals might display higher resting energy expenditure and resting energy expenditure to fat-free mass ratio[7,17,18] (although it does not seem significant in two studies[8,16]), non-blunted FM percentages despite their low BMI[7,8,11,17,23,24], and different profiles of appetite-regulating hormones[9,11,21–23]). If these types of results were supported by a substantial number of studies and clinical evidence, they could be used as new criteria for the distinction of CT from AN in the future, which remains to be robustly demonstrated. In order to visually synthesise the potential actual recommendations in CT diagnosis, based on this systematic analysis, a decision tree is proposed in Fig. 2.

On top of the inclusion criteria used by the selected studies, their methodologies must also be considered when interpreting our results as analysed and presented in our risks of bias table (Table 2). Indeed, as reported in Table 2, thirty-four out of the thirty-five included studies present a high risk for the 'blinding of participants and personnel', which might affect the obtained results when it comes, for instance, to the evaluation of energy intake, eating profiles or physical activity that could be influenced by the non-blinding of participants or personnel. This interpretation of our analyses must also consider the high proportion of studies presenting a moderate-to-high risk regarding the attrition bias, or even unreported data.

Conclusion

The present review used a systematic approach to identify any clinical trials that enrolled individuals with CT, particularly focusing on the methods used to define and diagnose CT. The employed methodology led us to identify thirty-five clinical trials enrolling a group of participants with CT. This clearly pointed out a relatively reduced number of studies interested in this condition. In addition, the definition and the diagnostic features of CT were found highly heterogeneous in these studies. Terminology and thinness thresholds do not reach consensus, and a high heterogeneity was also observed regarding the assessment of weight history, weight gain resistance and the presence of physiological menses. The absence of eating disorders, associated pathology or over-exercising was not systematically verified and if so, with various methodological approaches.

This systematic review points out the essential need not only to be aware of the existence of CT but also to harmonise our medical and scientific practices in the definition and diagnosis of CT. Altogether, the present results led us to propose a decision tree that could help practitioners and researchers better define and diagnose CT, in a potentially more harmonised way. Importantly, not only the proposed decision tree has been elaborated based on clinically relevant indicators that have to be considered for the diagnosis of CT, but it also proposes different alternative evaluations (from self-reported eating questionnaires to under-nutritional physiological markers for instance), guaranteeing its clinical feasibility and applicability.

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