



HAL
open science

Challenges of considering both extremities of the weight status spectrum to better understand obesity: insights from the NUTRILEAN project in constitutionally thin individuals

Mélina Bailly, Audrey Boscaro, Julien Verney, Angelo Tremblay, James King, Bruno Pereira, Frédéric Costes, Valérie Julian, Martine Duclos, Yves Boirie, et al.

► To cite this version:

Mélina Bailly, Audrey Boscaro, Julien Verney, Angelo Tremblay, James King, et al.. Challenges of considering both extremities of the weight status spectrum to better understand obesity: insights from the NUTRILEAN project in constitutionally thin individuals. *International Journal of Obesity*, 2023, 47 (11), pp.1171-1177. 10.1038/s41366-023-01360-y . hal-04404595

HAL Id: hal-04404595

<https://hal.science/hal-04404595>

Submitted on 25 Jun 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Challenges of considering both extremities of the weight status spectrum to better understand obesity: Insights from the NUTRILEAN Project in Constitutionally Thin Individuals.

Mélina BAILLY (✉ melina.bailly@uca.fr)

University of Clermont Auvergne <https://orcid.org/0000-0002-9202-9358>

Audrey BOSCARO

University of Clermont Auvergne

Julien Verney

Angelo Tremblay

Laval University

James King

j.a.king@lboro.ac.uk <https://orcid.org/0000-0002-8174-9173>

Bruno Pereira

<https://orcid.org/0000-0003-3778-7161>

Frédéric COSTES

University of Clermont Auvergne

Valérie JULIAN

University of Clermont Auvergne

Martine Duclos

Yves Boirie

David Thivel

Clermont-Auvergne University

Mélina BAILLY

University of Clermont Auvergne

Technical Report

Keywords:

Posted Date: April 13th, 2023

DOI: <https://doi.org/10.21203/rs.3.rs-2777415/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at International Journal of Obesity on August 8th, 2023. See the published version at <https://doi.org/10.1038/s41366-023-01360-y>.

Abstract

While the physiology of obesity has been so extensively investigated to date, only an extremely small number of studies (less than 50) have focused on the other extremity of the weight spectrum: constitutional thinness. Yet, this important state of underweight in the absence of any eating disorders provides a mirror model of obesity that might be particularly insightful in understanding obesity. Nevertheless, important methodological and recruitment-related issues appear when it comes to this complex constitutionally thin phenotype, as experienced by our research group with the realization of the ongoing NUTRILEAN clinical trial. To face this challenge, the present paper aims at identifying, analysing, and discussing the quality of such recruitment processes in publications about constitutional thinness. In this order, a group of experts collectively created a new grading system to assess the level of rigor and quality achieved by each study based on different criteria. The main results were that (i) metabolic-related biasing criteria were poorly observed despite being crucial, (ii) recruitment processes were not detailed enough and with sufficient explicitness, and (iii) recruiting among already identified patients would be associated with both higher sample sizes and better scores of quality. The present work encourages investigators to adopt a high level of rigor despite the complexity and duration of recruitment processes for this specific population, and readers to pay close attention to the quality of recruitment when interpreting the data. To better understand obesity and its physiological adaptations, it seems essential not only to compare it to normal-weight conditions, but also to the other extremity of the weight status spectrum represented by constitutional thinness.

Full Text

When it comes to weight-related disorders, hundreds of thousands of scientific articles have been published on obesity, focusing on many aspects of this condition including recruitment issues^{1,2}. While the studies conducted so far exclusively involve normal-weight people as controls when questioning the physiopathology of obesity, future studies would benefit from including participants from the other end of the weight status spectrum to better mirror obesity and improve our understanding of this chronic disease. Indeed, studying obesity by considering not only the profile of what we classify as normal weight, but also considering underweight profiles³, might help better identify new insights and potential targets when it comes to the understating of the physiological adaptations and impairments that occur in people with overweight and/or obesity. Although the integration of such participants in obesity research is of interest, their identification faces the challenge of properly diagnosing and recruiting them, carefully avoiding associated eating and hormonal disorders, and targeting then individuals with Constitutional Thinness (CT) only.

CT is a rare condition, characterized by an untypical but healthy thin profile, which has only recently begun to receive widespread attention. Despite a growing interest for CT, only 6 studies⁴⁻⁹ were published before 2000, 14¹⁰⁻²³ between 2000 and 2010, and 23^{3,24-45} since 2010 (last PubMed search run in February 2023). According to the World Health Organisation (WHO), the last estimation of the

prevalence of underweight in Europe (from all aetiologies) was 2.3% for women and 0.8% for men ⁴⁶. While CT represents a particular subsection of the underweight population, its specific prevalence remains unclear ⁴⁷. Interestingly, data derived from the Estonian Genome Centre of the University of Tartu (EGCUT) cohort ²⁵, with CT identified in 881 out of 47 102 participants, suggest a global prevalence of 1.9%. Despite the absence of robust data, the prevalence of CT in the general population is recognised to be extremely low, making it difficult to identify and recruit individuals with CT to studies. Furthermore, the lack of consensus in defining and diagnosing CT exacerbates heterogeneity and hampers comparability of research findings. Based on a recent systematic review of the literature conducted by our research team, a decision tree was proposed to harmonise and support the diagnosis of CT⁴⁸. This review identified the following criteria: absence of undernourishment/ malnutrition, eating disorders, associated diseases, over-exercising, presence of regular menstruations, weight gain resistance, and stable body weight throughout life ⁴⁸. Although the phenotype in CT may be very similar to anorexia ^{22,23,49,50}, many objective parameters (such as biochemical analyses) clearly distinguish these two conditions ⁴⁹. However, people with CT often experience the same weight-related stigma as people suffering from anorexia ²⁴.

Proposal of a new grading system to assess the recruitment quality in studies investigating CT

Whilst diagnostic tools exist in clinical practice ^{24,48,49,51-56}, the inclusion of participants with CT in scientific research requires more extensive inclusion and exclusion criteria. As previously mentioned, the clinical diagnosis of CT mainly relies on morphological (state of thinness, weight history), hormonal (regular cycling in women, normal levels of some markers of undernutrition), and psychological (absence of eating disorders) criteria. However, additional issues about energetic considerations should be considered within scientific research, as CT is underpinned by metabolic issues. This means that any extraneous factor influencing energy metabolism should be an exclusion criterion within research studies. For instance, as tobacco influences energy and substrate metabolism ⁵⁷⁻⁶⁰, smokers cannot be recruited in scientific research on CT even if, in absolute terms, an individual can present a CT and be a smoker. Consequently, to facilitate recruitment in scientific studies, we proposed here to divide the clinical criteria for CT into two categories entitled '*Main clinical criteria*' for a CT diagnosis and '*Metabolic-related biasing criteria*'. According to these criteria, a scale that reflects a level of quality in the recruitment processes has been collectively established (score 0 – lower grade to score 10 – upper grade) (**Table 1**). The development of such a scale has been a complex issue that required extensive and accurate considerations. To address this question appropriately, we constituted a group of experts from our research team and made different rounds of discussions based on the Delphi method until a consensus was reached and decisions made. Given the heterogeneity of the contexts and levels of detail found in the publications, some criteria could be split into many degrees of achievement while others did not have this potential. For more consistency in the scoring system, the threshold of '8 out of 10' was finally set as the minimum level for each criterion to be considered as 'appropriate' recruitment. The 'Main clinical criteria' and 'metabolic-related biasing criteria' scores are expressed in percentage (0%: lower quality, 100%: maximum quality score) after adding up the scores obtained for each criterion that respectively

belongs to each of these two main categories (**Figure 1**). A 'Global Quality' score is expressed in percentage (0%: lower quality, 100%: maximum quality score) after adding up all the scores (from both 'main clinical' and 'metabolic-related biasing' criteria). A 'Quality score per each individual criterion' is also expressed in percentage (0%: lower quality, 100%: maximum quality score) after adding up all the scores of each individual recruitment process.

Quality assessment of recruitment strategies in previous studies enrolling participants with CT

The studies presented in the **Figure 1** have been identified by an update (last bibliographic research run in February 2023) of the systematic reviews of the literature in CT completed in 2020 and 2021 ^{48,49} (for further details in the research strategies, see these references ^{48,49}). From these previous works, 4 new studies have been identified ^{26,42-44}. In the present work, we refer to 'recruitment processes' instead of 'studies' as a single recruitment process sometimes led to several studies ^{13,14,18,19,39,40,43,44} (**Figure 1**).

Out of the 36 recruitment processes ³⁻⁴⁵, only one ⁴⁵ succeeded to have the minimal grade (8/10 – acceptable) for all of the 8 parameters considered, with only one other ³⁹⁻⁴⁴ that reached 7 out of these 8 parameters (**Figure 1**). When calculating a global quality score, it appeared that only 6 recruitment processes ^{22,23,37-45} reached at least the global mark of 80%. **Figure 1** also shows that the 'metabolic-related biasing criteria' has been less considered by studies than the 'main clinical criteria'. Indeed, 69%, 50%, 69%, and 14% of the recruitment processes respectively reached the minimal acceptable grade (8 out of 10) for 'thinness' ^{3,8,9,11,15,16,18-27,30-32,34-45}, 'weight history' ^{3,7,8,10,12,20-24,33-45}, 'physiological menses' ^{5-7,13-25,28,30-33,35-45}, and 'eating disorders' ^{7,9,32,39-45} criteria that belong to 'main clinical criteria'. On the other hand, only 67%, 39%, 14%, and 17% of the recruitment processes respectively reached the minimal acceptable grade for 'pathology' ^{3-5,8,9,16-25,29,30,32,33,35-45}, 'medication' ^{6,17,20-25,34-36,38-45}, 'tobacco' ^{18,19,34,35,37,45}, and 'physical activity level' ^{3,28,31,38-45} that belongs to 'metabolic-related biasing criteria' (further details about each criterion **Table 1**). According to these results, it is noticeable that the 'eating disorders' criterion has not been considered rigorously enough. A more robust approach necessarily requires that validated eating behaviour questionnaires are employed as screening tools, along with biomarkers such as cortisol, free T3, IGF-1, or leptin (as supported by a detailed methodology published in 2017 ²⁴ and meta-analytical approaches ⁴⁹). Of the 8 recruitment processes published since 2017 ^{3,25-29,34,39-42,44}, only one ^{39-42,44} however combined both eating behaviours and undernutrition marker evaluations. Beyond these two approaches, a medical evaluation by a suitably qualified eating disorder specialist is also highly recommended. While many published studies referred to a visit to a health or general practitioner ^{7,9,15,16,20-24,29,32,33,36-42,44,45}, a specialized physician should be consulted. However, the methodological sections of published manuscripts often lack the details necessary to confirm whether or not the aforementioned visits specifically involved screening for eating disorders.

When calculating a global quality score per each individual criterion rather than counting the number of recruitment processes that reached a minimal grade, data once more shows that 'metabolic-related biasing criteria' were less considered by studies than the 'main clinical criteria' (last line **Figure 1**).

Graphically illustrated by **Figure 2A**, these results highlight that four criteria did not reach a global quality score of 50%: 'tobacco' (score: 22%), 'physical activity level' (score: 30%), 'medication' (score: 46%), and 'eating disorders' (score: 46%). While 'tobacco' and 'eating disorders' criteria have already been discussed in this article, these results also highlight the necessity to more rigorously evaluate screening criteria for medication use and physical activity within CT studies.

NUTRILEAN experiment – an example of difficult recruitment

The realization of the ongoing NUTRILEAN clinical trial conducted by our research group raised all the methodological and recruitment-related issues discussed in the present paper and led our group to deepen the question and conduct the present analysis. The NUTRILEAN study specifically questioned the potential functional, metabolic, hormonal, nutritional, and energetic specificities that might help better understand and characterize CT. The aims of the study obviously impose on us a strict and careful recruitment process. As highlighted by **Figure 2B**, we strive to follow the previously discussed criteria to the best of our ability. Yet, we would like to catch scientific attention that striving for an important level of rigour in the inclusion process of participants with CT really represents a tremendous challenge. From our 2-years-long experience of active recruitment, multiplying advertisement strategies (solicitations of general practitioners, specialized physicians, nutritionists, dieticians, nutrition centres, and naturopaths, articles in local newspapers, online publications, mailing to large lists of students and employees and recruitment brochures in shops/street/university campus), only 11 participants with CT finally ended the protocol while the study information has been spread to about 30 000 people (crude estimation). A rate of recruitment relative to the total number of canvassed people has been calculated as 0.03% and relative to participants with a presumed CT before the inclusion process 7.0% (**Figure 2B**).

Practical considerations when recruiting participants with CT

Such rates of recruitment raise an important question: why is it so difficult to recruit participants with CT? Beyond the low prevalence of CT and the need to consider metabolic-related biasing criteria, we thought that the sample size would be strongly explained by the level of recruitment quality reached by the studies. We hypothesised that the higher the recruitment quality, the lower the sample size. For instance, we indeed had to exclude dozens of people because of smoking according to our experience in the NUTRILEAN Study. Contrary to our expectations, the data did not provide a clear relationship between recruitment quality and sample size. This led to the consideration of other factors, more particularly the type of recruitment (**Figure 3**). As presented in **Figure 1**, recruitment processes were divided into three main categories: (C) existing cohorts or databases without physical contact with patients, (F) medical files of already known patients or participants, and (N) new recruitment through advertising campaigns. After setting aside large existing cohorts or data without physical contact with patients (C), **Figure 3** reveals that the type of recruitment (F vs. N) appears as a strong discriminating factor. To recruit among already known patients/participants (F) (yellow bars) would be related to both a higher sample size and a higher score of quality in the inclusion process compared with the recruitment of new patients/participants through advertising campaigns (N) (grey bars) (**Figure 3**). To have access to a pool

of medical cases of patients/participants already identified seems therefore to be associated with recruitment strategies of higher quality but also with larger numbers of participants with CT.

To conclude, while this seems of high interest for both a better consideration of CT itself and also when it comes to obesity research, the present commentary highlights and discusses the considerable challenge to recruit individuals presenting a rare condition such as CT, especially when recruiting new patients/participants. Through the example of CT in the lower extremity of the bodyweight spectrum, present data showed that metabolic-related biasing criteria (such as 'medication', 'tobacco', and 'physical activity level') remain poorly observed while the main clinical criteria were found quite well-considered in the inclusion processes. Metabolic-related biasing criteria however seem crucial given that metabolic issues are inherent to the atypical physiology of CT. Another important point emphasised here was that many methodological sections of the included studies contain implicit information that would benefit from being more explicitly detailed. Finally, the present work invites readers to always be cautious with the interpretation of the data provided in the literature and to consider them in light of the observance of all the aforementioned inclusion criteria. Indeed, only a few studies were found to rigorously observe all these criteria, which should encourage investigators to be as rigorous as possible in the diagnosis and inclusion of participants with CT in clinical trials, even if it would constrain the timelines of the studies. Although challenging, we believe that future researchers conducted in the field of overweight and obesity should not only consider normal-weight people as natural controls but should enlarge their analysis to individuals from the other extremity of the weight status spectrum, for a better understanding of obesity itself and of its associated complications.

Declarations

Author Contributions: AB and MB contributed to writing the original draft and the review & editing. AB performed data curation. JAK and DT provided feedback in the writing review and editing process. MB DT JV and AT conducted the conceptualization, investigation, and project administration. DT JV and MB were responsible of the funding acquisition. BP was implied in formal analysis and methodological aspects. AT FC BJ MD and YB contributed to supervision, validation, resources and visualization.

Data availability statement: Data generated or analysed during this study are available from the corresponding author upon request.

Corresponding author: Audrey BOSCARO, University of Clermont Auvergne, Laboratory of the Metabolic Adaptations to Exercise under Physiological and Pathological Conditions (AME2P), UPR 3533, CRNH Auvergne, Clermont-Ferrand, France, audrey.boscaro@uca.fr

Conflict of interest statement. The authors report that there are no conflicts of interest.

References

1. Griffin HJ, O'Connor HT, Rooney KB, Steinbeck KS. Effectiveness of strategies for recruiting overweight and obese Generation Y women to a clinical weight management trial. *Asia Pac J Clin Nutr* 2013; **22**: 235–240.
2. Bergmann S, Keitel-Korndörfer A, Herfurth-Majstorovic K, Wendt V, Klein AM, von Klitzing K *et al.* Recruitment strategies in a prospective longitudinal family study on parents with obesity and their toddlers. *BMC Public Health* 2017; **17**: 145.
3. Riveros-McKay F, Mistry V, Bounds R, Hendricks A, Keogh JM, Thomas H *et al.* Genetic architecture of human thinness compared to severe obesity. *PLoS Genet* 2019; **15**: e1007603.
4. Diaz EO, Prentice AM, Goldberg GR, Murgatroyd PR, Coward WA. Metabolic response to experimental overfeeding in lean and overweight healthy volunteers. *Am J Clin Nutr* 1992; **56**: 641–655.
5. Schneider L, Heard I, Bréart G, Henrion R. [Maternal thinness and pregnancy]. *Arch Fr Pediatr* 1979; **36**: 1068–1074.
6. van Binsbergen CJ, Coelingh Bennink HJ, Odink J, Haspels AA, Koppeschaar HP. A comparative and longitudinal study on endocrine changes related to ovarian function in patients with anorexia nervosa. *J Clin Endocrinol Metab* 1990; **71**: 705–711.
7. Petretta M, Bonaduce D, Scalfi L, de Filippo E, Marciano F, Migaux ML *et al.* Heart rate variability as a measure of autonomic nervous system function in anorexia nervosa. *Clin Cardiol* 1997; **20**: 219–224.
8. Hinney A, Barth N, Ziegler A, von Prittwitz S, Hamann A, Hennighausen K *et al.* Serotonin transporter gene-linked polymorphic region: allele distributions in relationship to body weight and in anorexia nervosa. *Life Sci* 1997; **61**: PL 295-303.
9. Scalfi L, Coltorti A, Borrelli R, Contaldo F. Postprandial thermogenesis in leanness and anorexia nervosa. *Ann Nutr Metab* 1992; **36**: 48–54.
10. Mazzeo SE, Slof RM, Tozzi F, Kendler KS, Bulik CM. Characteristics of men with persistent thinness. *Obes Res* 2004; **12**: 1367–1369.
11. Bosy-Westphal A, Reinecke U, Schlörke T, Illner K, Kutzner D, Heller M *et al.* Effect of organ and tissue masses on resting energy expenditure in underweight, normal weight and obese adults. *Int J Obes Relat Metab Disord* 2004; **28**: 72–79.
12. Slof R, Mazzeo S, Bulik CM. Characteristics of women with persistent thinness. *Obes Res* 2003; **11**: 971–977.
13. Miljic D, Pekic S, Djurovic M, Doknic M, Milic N, Casanueva FF *et al.* Ghrelin has partial or no effect on appetite, growth hormone, prolactin, and cortisol release in patients with anorexia nervosa. *J Clin Endocrinol Metab* 2006; **91**: 1491–1495.
14. Miljic D, Djurovic M, Pekic S, Doknic M, Stojanovic M, Milic N *et al.* Glucose metabolism during ghrelin infusion in patients with anorexia nervosa. *J Endocrinol Invest* 2007; **30**: 771–775.
15. Fernández-García D, Rodríguez M, García Alemán J, García-Almeida JM, Picón MJ, Fernández-Aranda F *et al.* Thin healthy women have a similar low bone mass to women with anorexia nervosa. *Br J Nutr* 2009; **102**: 709–714.

16. Tagami T, Satoh N, Usui T, Yamada K, Shimatsu A, Kuzuya H. Adiponectin in anorexia nervosa and bulimia nervosa. *J Clin Endocrinol Metab* 2004; **89**: 1833–1837.
17. Tolle V, Kadem M, Bluett-Pajot M-T, Frere D, Foulon C, Bossu C *et al.* Balance in ghrelin and leptin plasma levels in anorexia nervosa patients and constitutionally thin women. *The Journal of Clinical Endocrinology & Metabolism* 2003; **88**: 109–116.
18. Marra M, Pasanisi F, Montagnese C, De Filippo E, De Caprio C, de Magistris L *et al.* BMR variability in women of different weight. *Clin Nutr* 2007; **26**: 567–572.
19. Marra M, Caldara A, Montagnese C, De Filippo E, Pasanisi F, Contaldo F *et al.* Bioelectrical impedance phase angle in constitutionally lean females, ballet dancers and patients with anorexia nervosa. *Eur J Clin Nutr* 2009; **63**: 905–908.
20. Germain N, Galusca B, Le Roux CW, Bossu C, Ghatei MA, Lang F *et al.* Constitutional thinness and lean anorexia nervosa display opposite concentrations of peptide YY, glucagon-like peptide 1, ghrelin, and leptin. *The American journal of clinical nutrition* 2007; **85**: 967–971.
21. Germain N, Galusca B, Grouselle D, Frere D, Tolle V, Zizzari P *et al.* Ghrelin/obestatin ratio in two populations with low bodyweight: constitutional thinness and anorexia nervosa. *Psychoneuroendocrinology* 2009; **34**: 413–419.
22. Bossu C, Galusca B, Normand S, Germain N, Collet P, Frere D *et al.* Energy expenditure adjusted for body composition differentiates constitutional thinness from both normal subjects and anorexia nervosa. *American Journal of Physiology Endocrinology and Metabolism* 2007; **292**: E132-137.
23. Galusca B, Zouch M, Germain N, Bossu C, Frere D, Lang F *et al.* Constitutional thinness: unusual human phenotype of low bone quality. *J Clin Endocrinol Metab* 2008; **93**: 110–117.
24. Estour B, Marouani N, Sigaud T, Lang F, Fakra E, Ling Y *et al.* Differentiating constitutional thinness from anorexia nervosa in DSM 5 era. *Psychoneuroendocrinology* 2017; **84**: 94–100.
25. Orthofer M, Valsesia A, Mägi R, Wang Q-P, Kaczanowska J, Koziaradzki I *et al.* Identification of ALK in Thinness. *Cell* 2020; **181**: 1246-1262.e22.
26. Bang EB, Ko JK, Kwag KH, Lee GY, Kim Y-R. A comparison of patients with anorexia nervosa and women who are constitutionally thin. *Eur Eat Disord Rev* 2020; **28**: 633–642.
27. Florent V, Baroncini M, Jissendi-Tchofo P, Lopes R, Vanhoutte M, Rasika S *et al.* Hypothalamic structural and functional imbalances in anorexia nervosa. *Neuroendocrinology* 2019; **110**: 552–562.
28. Margaritelis NV, Theodorou AA, Kyparos A, Nikolaidis MG, Paschalis V. Effect of body composition on redox homeostasis at rest and in response to exercise: the case of underfat women. *J Sports Sci* 2019; **37**: 1–8.
29. Marra M, Sammarco R, De Filippo E, De Caprio C, Speranza E, Contaldo F *et al.* Resting energy expenditure, body composition and phase angle in anorectic, ballet dancers and constitutionally lean males. *Nutrients* 2019; **11**: 502.
30. Hasegawa A, Usui C, Kawano H, Sakamoto S, Higuchi M. Characteristics of body composition and resting energy expenditure in lean young women. *J Nutr Sci Vitaminol* 2011; **57**: 74–79.

31. Paschalis V, Nikolaidis MG, Theodorou AA, Deli CK, Raso V, Jamurtas AZ *et al.* The effects of eccentric exercise on muscle function and proprioception of individuals being overweight and underweight. *J Strength Cond Res* 2013; **27**: 2542–2551.
32. Pasanisi F, Pace L, Fonti R, Marra M, Sgambati D, De Caprio C *et al.* Evidence of brown fat activity in constitutional leanness. *The Journal of Clinical Endocrinology & Metabolism* 2013; **98**: 1214–1218.
33. Santonicola A, Siniscalchi M, Capone P, Gallotta S, Ciacci C, Iovino P. Prevalence of functional dyspepsia and its subgroups in patients with eating disorders. *World J Gastroenterol* 2012; **18**: 4379–4385.
34. Galusca B, Verney J, Meugnier E, Ling Y, Edouard P, Féasson L *et al.* Reduced fibre size, capillary supply and mitochondrial activity in constitutional thinness' skeletal muscle. *Acta Physiol (Oxf)* 2018; **224**: e13097.
35. Germain N, Viltart O, Loyens A, Bruchet C, Nadin K, Wolowczuk I *et al.* Interleukin-7 plasma levels in human differentiate anorexia nervosa, constitutional thinness and healthy obesity. *PLoS ONE* 2016; **11**: e0161890.
36. Galusca B, Jeandel L, Germain N, Alexandre D, Leprince J, Anouar Y *et al.* Orexigenic neuropeptide 26RFa: new evidence for an adaptive profile of appetite regulation in anorexia nervosa. *The Journal of Clinical Endocrinology & Metabolism* 2012; **97**: 2012–2018.
37. Gunes A, Yildirim Bas F, Arslan B, Tok L, Tok Ö, Salman Z. Assessment of corneal parameters in patients with constitutional thinness using Scheimpflug imaging. *Semin Ophthalmol* 2016; **33**: 175–178.
38. Galusca B, Prévost G, Germain N, Dubuc I, Ling Y, Anouar Y *et al.* Neuropeptide Y and α -MSH circadian levels in two populations with low body weight: anorexia nervosa and constitutional thinness. *PLoS ONE* 2015; **10**: e0122040.
39. Ling Y, Carayol J, Galusca B, Canto C, Montaurier C, Matone A *et al.* Persistent low body weight in humans is associated with higher mitochondrial activity in white adipose tissue. *Am J Clin Nutr* 2019; **110**: 605–616.
40. Ling Y, Galusca B, Martin F-P, Bartova S, Carayol J, Moco S *et al.* Resistance to lean mass gain in constitutional thinness in free-living conditions is not overpassed by overfeeding. *J Cachexia Sarcopenia Muscle* 2020; **11**: 1187–1199.
41. Bailly M, Germain N, Féasson L, Costes F, Estour B, Hourdé C *et al.* Skeletal muscle of females and males with constitutional thinness: a low intramuscular lipid content and oxidative profile. *Appl Physiol Nutr Metab* 2020; **45**: 1287–1298.
42. Bailly M, Boscaro A, Thomas T, Féasson L, Costes F, Pereira B *et al.* New Insights on Bone Tissue and Structural Muscle-Bone Unit in Constitutional Thinness. *Front Physiol* 2022; **13**: 921351.
43. Gabriel T, Massoubre C, Hanachi M, Doré J, Lambert C, Germain N *et al.* Association of gut-specific non-inflammatory T lymphocytes with chronic anorexia nervosa and constitutional thinness. *Eur Eat Disord Rev* 2022. doi:10.1002/erv.2934.

44. Cominetti O, Núñez Galindo A, Corthésy J, Carayol J, Germain N, Galusca B *et al.* Proteomics reveals unique plasma signatures in constitutional thinness. *Proteomics Clin Appl* 2022; : e2100114.
45. Germain N, Galusca B, Caron-Dorval D, Martin J-F, Pujos-Guillot E, Boirie Y *et al.* Specific appetite, energetic and metabolomics responses to fat overfeeding in resistant-to-bodyweight-gain constitutional thinness. *Nutrition & Diabetes* 2014; **4**: e126.
46. World Health Organization. Prevalence of underweight among adults. 2020. [\(https://www.who.int/data/gho/data/indicators/indicator-details/GHO/prevalence-of-underweight-among-adults-bmi-18-\(crude-estimate\)-\(-\)\)](https://www.who.int/data/gho/data/indicators/indicator-details/GHO/prevalence-of-underweight-among-adults-bmi-18-(crude-estimate)-(-)) (accessed 20 Mar2020).
47. Estour B, Galusca B, Germain N. Constitutional thinness and anorexia nervosa: a possible misdiagnosis? *Front Endocrinol (Lausanne)* 2014; **5**: 175.
48. Bailly M, Germain N, Galusca B, Courteix D, Thivel D, Verney J. Definition and diagnosis of constitutional thinness: a systematic review. *British Journal of Nutrition* 2020; **124**: 531–547.
49. Bailly M, Boscaro A, Pereira B, Féasson L, Boirie Y, Germain N *et al.* Is constitutional thinness really different from anorexia nervosa? A systematic review and meta-analysis. *Rev Endocr Metab Disord* 2021. doi:10.1007/s11154-021-09650-4.
50. Bailly M, Boscaro A, Pereira B, Courteix D, Germain N, Galusca B *et al.* Underweight but not underfat: is fat-free mass a key factor in constitutionally thin women? *Eur J Clin Nutr* 2021; **75**: 1764–1770.
51. Estour B, Galusca B, Germain N. [Constitutional thinness]. *Correspondances en Métabolismes Hormones Diabète et Nutrition* 2012; **XVI**: 109–114.
52. Estour B, Galusca B, Germain N. [Constitutional thinness]. *Cahiers de Nutrition et de Diététique* 2013; **48**: 26–32.
53. Estour B, Galusca B, Germain N. Thinness, weight loss and constitutional thinness. *Med Mal Metab* 2016; **10**: 10–15.
54. Galusca B, Germain N, Estour B. Thinness, bone and fracture risk. *Med Mal Metab* 2016; **10**: 16–21.
55. Germain N, Galusca B, Estour B. Thinness and resistance to weight gain: A proof of concept. *Med Mal Metab* 2016; **10**: 28–33.
56. Galusca B, Germain N, Estour B. Maigreur et hormones de régulation de l'appétit. *Médecine des Maladies Métaboliques* 2016; **10**: 22–27.
57. Decker ST, Matias AA, Bannon ST, Madden JP, Alexandrou-Majaj N, Layec G. Effects of cigarette smoke on in situ mitochondrial substrate oxidation of slow- and fast-twitch skeletal muscles. *Life Sci* 2023; **315**: 121376.
58. Blauw LL, Boon MR, Rosendaal FR, de Mutsert R, Gast KB, Willems van Dijk K *et al.* Smoking is associated with increased resting energy expenditure in the general population: The NEO study. *Metabolism* 2015; **64**: 1548–1555.
59. Hellerstein MK, Benowitz NL, Neese RA, Schwartz JM, Hoh R, Jacob P *et al.* Effects of cigarette smoking and its cessation on lipid metabolism and energy expenditure in heavy smokers. *J Clin Invest* 1994; **93**: 265–272.

60. Seoane-Collazo P, Romero-Picó A, Rial-Pensado E, Liñares-Pose L, Estévez-Salguero Á, Fernø J *et al.* κ -Opioid Signaling in the Lateral Hypothalamic Area Modulates Nicotine-Induced Negative Energy Balance. *Int J Mol Sci* 2021; **22**: 1515.

Table

Table 1 – Rating scale to estimate the level of quality in the recruitments processes

Main clinical criteria	
Thinness	<p>0: not reported</p> <p><i>Consideration of the severity of thinness</i></p> <p>2: 3rd or 4th silhouettes on Stunkard FRS (declarative, respectively women/men)</p> <p>6: <90 % of ideal body weight</p> <p>7: stated 'severely underweight' or 'same BMI as in AN' – No further information</p> <p>8: BMI < 18.5 kg.m⁻²</p> <p>9: BMI < 17.5 kg.m⁻² or BMI < 15th percentile</p> <p>10: BMI < 16.5 kg.m⁻²</p>
Weight History	<p>0: not reported</p> <p><i>Consideration of personal weight history</i></p> <p>7: without clear period</p> <p>8: throughout the post pubertal period</p> <p>9: throughout the growth period</p> <p>10: from the birth to at least 18 years old</p>
Physiological menstruations	<p>0: not reported</p> <p><i>Presence of menstruations</i></p> <p>2: artificial (presence of oral contraception)</p> <p>8: potentially artificial (oral contraception: unspecified)</p> <p>10: physiological and regular (without oral contraception)</p>
Eating disorders	<p>0: not reported</p> <p><i>Consideration of the absence of eating disorders only stated</i></p> <p>1: as 'desire to gain weight' or 'good eaters'</p> <p>2: as 'no eating disorders'</p> <p><i>Consideration of the absence of eating disorders assessed using</i></p> <p>3: DSM-IV or V</p> <p>4: food behaviour questionnaires</p> <p>5: undernutrition markers</p>

	6: evaluations by health practitioner
	7: food behaviour questionnaires + undernutrition markers
	8: food behaviour questionnaires + evaluations by health practitioner
	9: undernutrition markers + evaluations by health practitioner
	10: food behaviour questionnaires + undernutrition marker + evaluations by health practitioner
Metabolic-related biasing criteria	
Pathologies	0: not reported 5: no disorders that could affect the outcomes 10: no chronic or congenital disorders
Medication	0: not reported 5: no drugs that could affect the outcomes 10: no drugs
Tobacco use	0: not reported 5: daily smokers or stated as 'light-to-moderate smokers' without further information 10: no smokers
Physical Activity	0: not reported <i>Consideration of over exercising only stated</i> 7: as an absence of excessive physical activity <i>Consideration of over exercising assessed using</i> 8: personal appreciation (< 3 sessions of exercise per week) 9: validated physical activity questionnaire 10: accelerometry

AN: Anorexia Nervosa; BMI: Body mass index; DSM: Diagnostic and statistical manual of mental disorders; FRS: Figure rating scale

Figures

	Type of recruitment	SAMPLE SIZE (CT subjects)	MAIN CLINICAL CRITERIA				METABOLIC-RELATED BIASING CRITERIA				GLOBAL QUALITY (%) (main clinical + metabolic-related biasing criteria)					
			Thinness	Weight History	Physiological menstruations	Eating disorders	Main clinical criteria score (%)	Pathologies	Medication	Tobacco use		Physical activity level	Metabolic-related biasing criteria score (%)			
Mazzeo et al., 2004	C	158	0	1	2	3	4	5	6	7	8	9	10	25%	0%	12.5%
Bosy-Westphal et al., 2004	N	12	1	2	3	4	5	6	7	8	9	10	10	27.5%	0%	13.75%
Bang et al., 2020	N	53	2	3	4	5	6	7	8	9	10	10	10	32.5%	0%	16.25%
Slof et al., 2003	C	80	3	4	5	6	7	8	9	10	10	10	10	32.5%	0%	16.25%
Diaz et al., 1992	N	7	4	5	6	7	8	9	10	10	10	10	10	10%	37.5%	23.75%
Miljic et al., 2006 & 2007	N	10	5	6	7	8	9	10	10	10	10	10	10	47.5%	0%	23.75%
Florent et al., 2019	N	10	6	7	8	9	10	10	10	10	10	10	10	52.5%	0%	26.25%
Fernández-García et al., 2009	F	22	7	8	9	10	10	10	10	10	10	10	10	55%	12.5%	33.75%
Margaritelis et al., 2019	N	12	8	9	10	10	10	10	10	10	10	10	10	25%	45%	35%
Schneider et al., 1979	C	53	9	10	10	10	10	10	10	10	10	10	10	45%	25%	35%
Van Binsbergen et al., 1990	N	10	10	10	10	10	10	10	10	10	10	10	10	45%	25%	35%
Marra et al., 2019	F	15	10	10	10	10	10	10	10	10	10	10	10	32.5%	42.5%	37.5%
Petretta et al., 1997	N	10	10	10	10	10	10	10	10	10	10	10	10	75%	0%	37.5%
Tagami et al., 2004	F	6	10	10	10	10	10	10	10	10	10	10	10	55%	25%	40%
Hasegawa et al., 2011	N	20	10	10	10	10	10	10	10	10	10	10	10	50%	37.5%	43.75%
Paschalis et al., 2013	N	8	10	10	10	10	10	10	10	10	10	10	10	42.5%	45%	43.75%
Pasanisi et al., 2013	F	7	10	10	10	10	10	10	10	10	10	10	10	65%	25%	45%
Hinney et al., 1997	C	112	10	10	10	10	10	10	10	10	10	10	10	55%	37.5%	46.25%
Tolle et al., 2003	N	7	10	10	10	10	10	10	10	10	10	10	10	42.5%	50%	46.25%
Riveros Mckay et al., 2019 (STILTS cohort)	C	1 622	10	10	10	10	10	10	10	10	10	10	10	55%	45%	50%
Santonicola et al., 2012	F	9	10	10	10	10	10	10	10	10	10	10	10	77.5%	25%	51.25%
Scalfi et al., 1992	N	7	10	10	10	10	10	10	10	10	10	10	10	60%	55%	57.5%
Galusca et al., 2018	N	10	10	10	10	10	10	10	10	10	10	10	10	55%	62.5%	58.75%
Orthofer et al., 2020	C	881	10	10	10	10	10	10	10	10	10	10	10	50%	67.5%	58.75%
Marra et al., 2007 & 2009	F	20	10	10	10	10	10	10	10	10	10	10	10	47.5%	80%	63.75%
Germain et al., 2007	F	10	10	10	10	10	10	10	10	10	10	10	10	85%	50%	67.5%
Estour et al., 2017	F	56	10	10	10	10	10	10	10	10	10	10	10	87.5%	50%	68.75%
Germain et al., 2009	F	10	10	10	10	10	10	10	10	10	10	10	10	87.5%	50%	68.75%
Germain et al., 2016	N	10	10	10	10	10	10	10	10	10	10	10	10	72.5%	75%	73.75%
Galusca et al., 2012	F	14	10	10	10	10	10	10	10	10	10	10	10	87.5%	67.5%	77.5%
Gunes et al., 2016	F	24	10	10	10	10	10	10	10	10	10	10	10	80%	80%	80%
Galusca et al., 2015	F	22	10	10	10	10	10	10	10	10	10	10	10	87.5%	72.5%	80%
Bossu et al., 2007	F	7	10	10	10	10	10	10	10	10	10	10	10	85%	80%	82.5%
Galusca et al., 2008	F	25	10	10	10	10	10	10	10	10	10	10	10	87.5%	80%	83.75%
Ling et al., 2019 & 2020*	F	30	10	10	10	10	10	10	10	10	10	10	10	95%	87.5%	91.25%
Germain et al., 2014	F	8	10	10	10	10	10	10	10	10	10	10	10	87.5%	97.5%	92.5%
Quality score per each individual criterion (%)			72%	52%	64%	46%	58.4%	72%	46%	22%	30%	42.6%	50.5%			

Figure 1

Heatmap of the evaluation of quality scores in the inclusion process of participants with constitutional thinness in clinical trials

CT: Constitutional thinness; C: Among an existing cohort or database without physical contact with patients; F: Medical files of already known patients or participants; N: New recruitment through advertising campaign; * Single recruitment process re-used for: Ling et al. (2019 & 2020), Bailly et al. (2020 & 2022), Cominetti et al. (2022), Gabriel et al. (2022)

The 'Main clinical criteria' and 'metabolic-related biasing criteria' scores are expressed in percentage (0%: lower quality, 100%: maximum quality score) after adding up the scores obtained for each criterion that respectively belongs to each of these two main categories. A 'Global Quality' score is expressed in percentage (0%: lower quality, 100%: maximum quality score) after adding up all the scores (from both 'main clinical' and 'metabolic-related biasing' criteria). A 'Quality score per each individual criterion' is also expressed in percentage (0%: lower quality, 100%: maximum quality score) after adding up all the scores of each individual recruitment process.

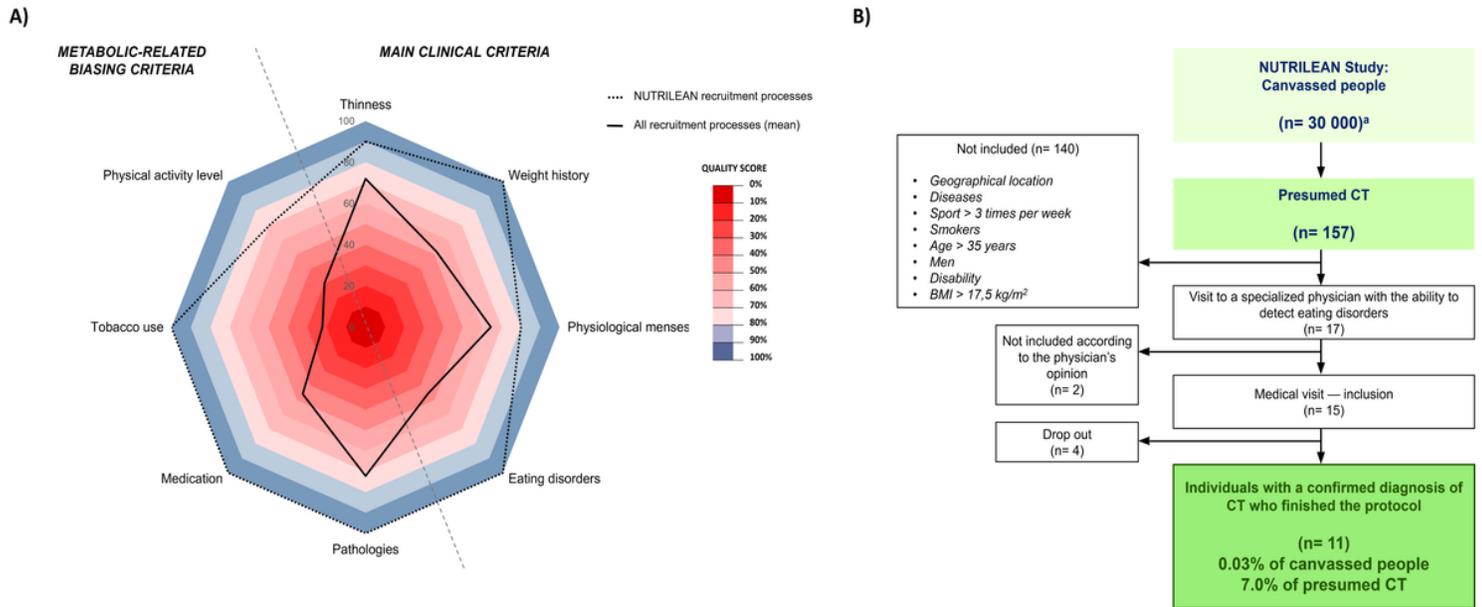


Figure 2

A real challenge to recruit participants with constitutional thinness: insights from the NUTRILEAN Study

A) Quality of the recruitment in the NUTRILEAN Study B) Flowchart of the recruitment process in the NUTRILEAN Study

BMI: Body mass index; CT: Constitutional Thinness

a: crude estimation

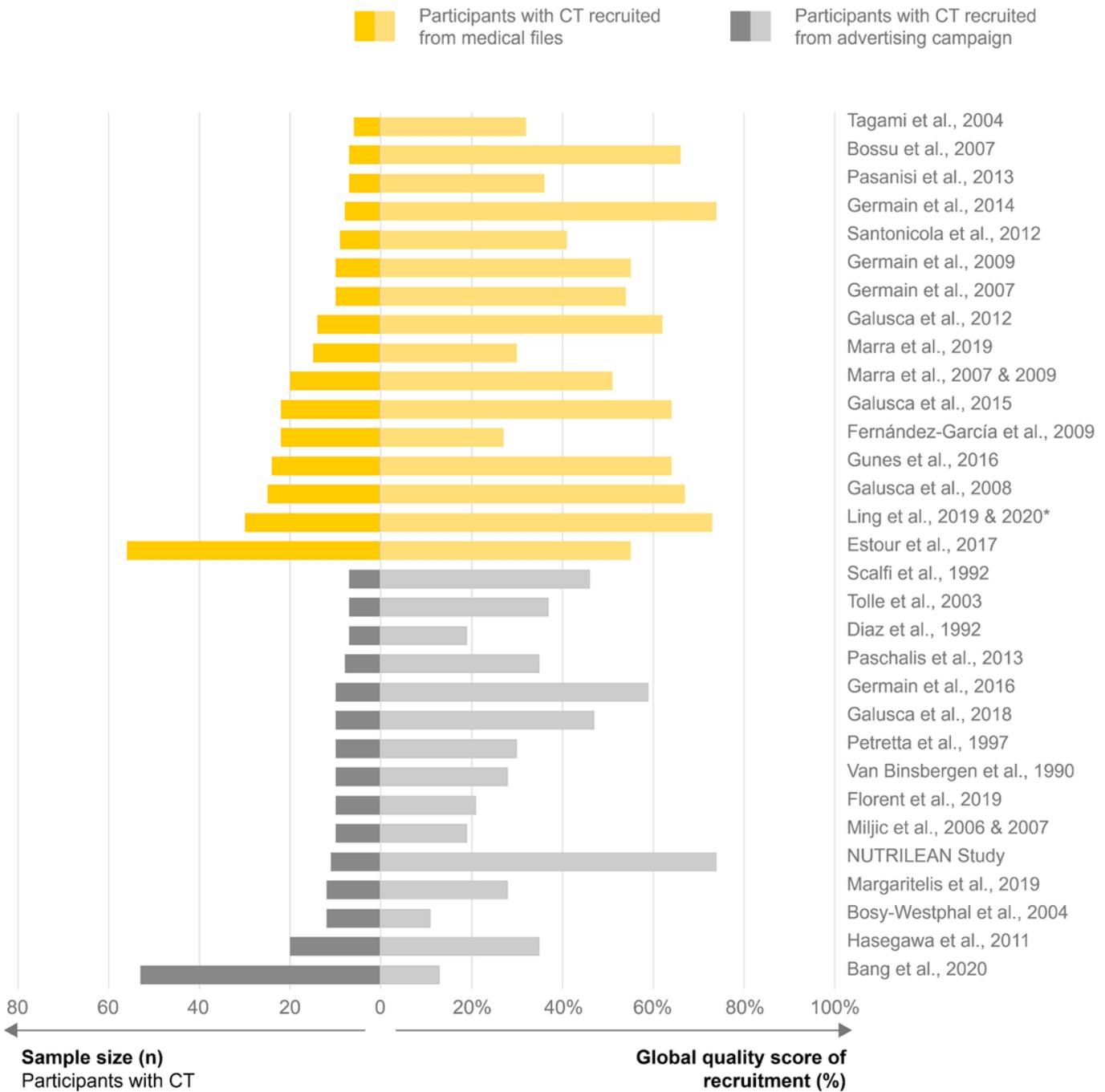


Figure 3

Differentiating between two types of recruitment processes in studies on constitutional thinness: effect on the number of enrolled participants and the recruitment quality

CT: Constitutional Thinness, * Single recruitment process re-used for: Ling et al. (2019 & 2020), Bailly et al. (2020 & 2022), Cominetti et al. (2022), Gabriel et al. (2022)