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# Development of the European Association for the Study of Obesity (EASO) Grade-Based Framework on the Pharmacological Treatment of Obesity: Design and Methodological Aspects

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**Keywords**
Obesity · Adiposity · Obesity management drugs and comorbidities

**Abstract**

***Introduction:*** The aim of this study was to describe the design and methodological aspects of the upcoming European Association for the Study of Obesity (EASO) Framework for the Pharmacological Treatment of Obesity utilizing currently available evidence, which is grounded in a rigorous and transparent approach to evidence synthesis and guideline development. ***Methods:*** An expert panel of 13 members, selected by EASO, has developed the framework using the GRADE methodology to ensure transparent, evidence-based guideline development. Clinical questions were formulated using the population, intervention, comparator, outcomes (PICO) framework, focusing on the effectiveness and safety of

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European Medicines Agency-approved obesity management medications, including orlistat, naltrexone/bupropion, liraglutide, semaglutide, and tirzepatide. A comprehensive literature search is being conducted using Medline and Embase, including randomized controlled trials with a minimum duration of 48 weeks. Meta-analyses and network meta-analyses are planned to compare treatment effectiveness and safety profiles across various patient subgroups. The guidelines will target adults with a body mass index (BMI) ≥27 kg/m$^2$ and at least one weight-related comorbidity or a BMI ≥30 kg/m$^2$. The primary endpoint will be total body weight loss. Secondary outcomes include changes in body composition (i.e., fat mass, fat-free mass), metabolic improvements (i.e., glucose levels, HbA1c, lipid profile), remission of obesity-related comorbidities (i.e., type 2 diabetes, obstructive sleep apnea syndrome, metabolic dysfunction-associated steatotic liver disease, cardiovascular disease, and knee osteoarthritis), and improvements in mental health and quality of life. The methodological framework ensures that recommendations are tailored, evidence-based, and applicable across clinical settings. ***Conclusions:*** The EASO framework provides a structured and individualized approach to optimize pharmacological treatment for obesity. Its methodological rigor, based on GRADE and PICO, enhances the reliability, reproducibility, and clinical relevance of the guidelines. By integrating clinical efficacy, safety outcomes, and patient-specific factors, this framework offers solid, actionable guidance to support healthcare professionals in delivering high-quality, personalized obesity care.



## Introduction

Obesity is an adiposity-based chronic disease (ABCD) [1] that significantly affects both physical and mental health [2–4]. Excessive and/or dysfunctional adipose tissue has detrimental effects on health, quality of life (QoL) and life expectancy [5]. Furthermore, significant complications associated with obesity include type 2 diabetes (T2D), ischemic heart disease, heart failure, metabolic dysfunction-associated steatotic liver disease, obstructive sleep apnoea syndrome (OSAS), knee osteoarthritis, mental disorders, and certain forms of cancer, among others [6].

Current methods of obesity treatment include lifestyle intervention, endoscopic, or surgical procedures and obesity management medications (OMMs) [1]. However, most of these tools are often characterized by limited long-term adherence and efficacy or few/no available data on their effectiveness and safety [7]. In Europe, there are several European Medicines Agency (EMA)-approved OMM such as orlistat, naltrexone/bupropion, liraglutide, semaglutide, and tirzepatide. Additionally, in some countries, phentermine-topiramate is approved. The OMM, especially the analogues of peptides stimulated by nutrients, act at several levels in both the brain and peripheral tissues [8]. Their primary effects include reducing appetite, enhancing energy metabolism – leading to weight loss, changes in body composition, and positively influencing obesity-related complications [8].

The 2024 European Association for the Study of Obesity (EASO) framework for the diagnosis, staging, and management of obesity in adults recommends that the treatment of obesity should aim at an individualized approach, reducing adiposity, improving adipose tissue function, managing obesity-related complications and, overall, improving the QoL of patients with obesity. The present manuscript describes the design and methodological aspects of the upcoming EASO Framework for the Pharmacological Treatment of Obesity.

## Methods

*Characteristics of the Panel of Experts*

Panel members ($n$ = 13) identified by the EASO (online suppl. Table S1; for all online suppl. material, see https://doi.org/10.1159/000546855), elected two coordinators according to EASO Guidelines (BG and AC, Co-chairs of the Obesity Management Working Group of EASO), and nominated the members of the Evidence Review Team (ERT). The ERT collected and analyzed all available evidence but did not participate in defining the clinical questions, selecting the outcomes, or formulating the recommendations. The complete list of the panel and ERT members, including their roles, is reported in online supplementary Table S1. Only individuals with the role of "Panelist" ($n$ = 9) were involved in voting and in the formulation of the recommendations. The complete list of all contributors, including panelists, ERT members, coordinators, methodologists, and management representatives, along with their specific roles, is reported in online supplementary Table S1. All members reported a declaration of potential conflicts of interest, which were collectively discussed to determine their relevance. The conflicts of interest s were considered not relevant for this work. The panel of experts agreed to use the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) as described below and to

formulate recommendations exclusively on results of meta-analyses of either placebo-controlled randomized clinical trials (RCTs) or head-to-head RCT. The decision to exclude non-RCTs was made due to methodological concerns with observational studies (i.e., selection bias, prescription bias, etc.) and to comply with the Cochrane Manual, which recommends avoiding the use of non-randomized studies in systematic reviews and meta-analyses, particularly when assessing pharmacological interventions (https://training.cochrane.org/handbook/current/chapter-24).

*GRADE Methodology for the Development of Guidelines*

The GRADE methodology is the most commonly adopted tool for transparently developing healthcare guidelines (https://training.cochrane.org/grade-approach). The formulations of any recommendation should be based on the best available evidence, which should be synthesized to achieve a reliable balance between benefits and harms, patient values, and preferences. Following GRADE methodology, the first step was to formulate clinical questions using the Population, Intervention, Comparator, Outcomes (PICO) framework (https://training.cochrane.org/grade-approach), as reported in Table 1. The panel identified several outcomes classified as critical, important, or less important after internal discussion. For critical outcomes, the ERT will perform formal meta-analyses, including all relevant trials fulfilling predefined search strategies and inclusion criteria, as reported in the results section.

A crucial component of the GRADE methodology consists of evaluating the quality of evidence. This assessment considers the impact of several possible biases on the overall quality of the included studies. The domains considered will include: (1) evaluation of the methodological quality of the studies; (2) inconsistency (i.e., assessing the variability in study results); (3) indirectness (i.e., applicability of the evidence to the clinical question); (4) imprecision (i.e., evaluation of the certainty of the evidence); (5) publication bias (i.e., checking for selective publication of studies) [9]. The quality of evidence will be rated as high, moderate, low, or very low. This rating will be the basis for deciding the strength of each recommendation [10] (i.e., strong or weak). Strong recommendations indicate high confidence in the benefits outweighing the risks; on the contrary, weak recommendations suggest that the benefits and risks are closely balanced or uncertain [10]. GRADE methodology will be used to assess the quality of the body of retrieved evidence. GRADEpro GDT software (GRADEpro Guideline Development Tool, McMaster University, 2015) will be used.

## Results

This guideline will apply to adult patients either with a body mass index (BMI) ≥27 kg/m$^2$ and at least one weight-related comorbid condition or with BMI ≥30 kg/m$^2$. In developing these guidelines, healthcare systems, infrastructures, and human and financial resources across European regions will be considered.

*Panel of Experts*

The present guidelines will be developed by a multidisciplinary team composed of specialists in endocrinology and nutrition, internal medicine, epidemiology, and basic and clinical scientists (online suppl. Table S1). The panel proposed eight clinical questions, which were approved without the need for further discussion (Table 1). The approved questions and their related approved critical outcomes are reported in Table 1. For critical PICO, formal systematic reviews and network meta-analyses (NMAs) will be performed to rank the effectiveness and safety of OMM considered in the present guidelines.

*Search Strategy*

A Medline and Embase search will be performed without establishing a starting date, up to 31st January 2025, using the following keywords: obesity AND (orlistat OR naltrexone OR bupropion OR topiramate OR phentermine OR liraglutide OR semaglutide OR tirzepatide). The name of the OMM is placed in chronological order, which means according to when these drugs were available in the market. We will include only RCTs enrolling patients either with BMI ≥27 kg/m$^2$ and at least one weight-related comorbid condition or obesity (BMI ≥30 kg/m$^2$) and comparing different OMM either versus placebo/no therapy (add-on to lifestyle intervention) or active comparators, with a duration of at least 48 weeks.

*Interventions Included for Guideline Development*

The interventions that were considered to develop the guideline included OMM (i.e., orlistat 360 mg/day, naltrexone SR/bupropion 32–360 mg/day, topiramate/phentermine 15–92 mg/day, liraglutide 3.0 mg/day, semaglutide 2.4 mg/week, tirzepatide 10–15 mg/week versus placebo/none), lifestyle interventions, or active comparators.

*Endpoints*

The principal endpoint will be total body weight loss (TBWL%) at the study endpoint in clinical studies designed primarily to investigate the effects of OMM on patients for whom the major issue is body weight reduction and not the control of other obesity-associated

**Table 1.** Population, intervention, comparator, outcomes (PICO) definitions and related outcomes

| *N* | PICO |
|---|---|
| 1 | In patients with a BMI ≥27 kg/m$^2$ and at least one obesity-related comorbid condition, or BMI ≥30 kg/m$^2$, which OMM is preferable to placebo for treating overweight/obesity? |
| *Outcomes* (efficacy) | |
| 1.1 | Body weight reduction (TBWL [%], change in waist circumference and BMI, and proportion of subjects achieving at least a reduction of 5, 10, 15, 20, and 25% or more of baseline body weight; changes in body composition) |
| 1.2 | Improvement of glycometabolic control (HbA1c, fasting plasma glucose, lipid and blood pressure profile, and renal function) |
| 1.3 | Comorbid conditions remission[a] (T2D, hypertension, dyslipidemia, OSAS, KOA, MASLD, hospital admission for heart failure) or improvement (KCCQ scores, liver fibrosis, pulmonary indexes) |
| 1.4 | All-cause mortality reduction |
| 1.5 | MACE reduction |
| 1.6 | Improvement of QoL |
| *Outcomes* (safety) | |
| 1.7 | SAEs |
| 1.8 | Change in mental health/emotional status parameters |
| 2 | In patients with a BMI ≥27 kg/m$^2$ and T2D, which OMM is preferable to placebo for treating overweight/obesity? |
| *Outcomes* (efficacy) | |
| 2.1 | Body weight reduction (TBWL [%], change in waist circumference and BMI, and proportion of subjects achieving at least a reduction of 5, 10, 15, 20, and 25% or more of baseline body weight; changes in body composition) |
| 2.2 | Improvement of glycometabolic control (HbA1c, fasting plasma glucose, lipid and blood pressure profile, and renal function) |
| 2.3 | T2D remission[a] and other comorbid conditions remission[a] (hypertension, dyslipidemia, OSAS, KOA, MASLD, hospital admission for heart failure) or improvement (KCCQ scores, liver fibrosis, pulmonary indexes) |
| 2.4 | All-cause mortality reduction |
| 2.5 | MACE reduction |
| 2.6 | Improvement of QoL |
| *Outcomes* (safety) | |
| 2.7 | SAEs |
| 2.8 | Change in mental health/emotional status parameters |
| 3 | In patients with a BMI ≥27 kg/m$^2$ and OSAS, which OMM is preferable to placebo for treating overweight/obesity? |
| *Outcomes* (efficacy) | |
| 3.1 | Body weight reduction (TBWL [%], change in waist circumference and BMI, and proportion of subjects achieving at least a reduction of 5, 10, 15, 20, and 25% or more of baseline body weight; changes in body composition) |
| 3.2 | OSAS remission and improvement of parameters evaluating apnea[a] |
| 3.3 | Other comorbid conditions remission[a] (T2D, hypertension, dyslipidemia, KOA, MASLD, hospital admission for heart failure) or improvement (KCCQ scores, liver fibrosis) |
| 3.4 | All-cause mortality reduction |
| 3.5 | MACE reduction |
| 3.6 | Improvement of QoL |
| *Outcomes* (safety) | |
| 3.7 | SAEs |
| 3.8 | Change in mental health/emotional status parameters |

**Table 1** (continued)

| *N* | PICO |
|---|---|
| 4 | In patients with a BMI ≥27 kg/m$^2$ and MASLD, which OMM is preferable to placebo for treating overweight/obesity? |
| *Outcomes* (efficacy) | |
| 4.1 | Body weight reduction (TBWL [%], change in waist circumference and BMI, and proportion of subjects achieving at least a reduction of 5, 10, 15, 20, and 25% or more of baseline body weight; changes in body composition) |
| 4.2 | MASH remission[a] and improvement of fibrosis and liver content indexes |
| 4.3 | Other comorbid conditions remission[a] (T2D, hypertension, dyslipidemia, KOA, OSAS, hospital admission for heart failure) or improvement (KCCQ scores, and pulmonary indexes) |
| 4.4 | All-cause mortality reduction |
| 4.5 | MACE reduction |
| 4.6 | Improvement of QoL |
| *Outcomes* (safety) | |
| 4.7 | SAEs |
| 4.8 | Change in mental health/emotional status parameters |
| 5 | In patients with a BMI ≥27 kg/m$^2$ and previous heart failure, which OMM is preferable to placebo for treating overweight/obesity? |
| *Outcomes* (efficacy) | |
| 5.1 | Body weight reduction (TBWL [%], change in waist circumference and BMI, and proportion of subjects achieving at least a reduction of 5, 10, 15, 20, and 25% or more of baseline body weight; changes in body composition) |
| 5.2 | Reduction of hospital admission for heart failure[a], incidence of MACE[a], improvement of Kansas City Cardiomyopathy Questionnaire clinical summary score, change in 6-min walking test distance |
| 5.3 | Other comorbid conditions remission[a] (T2D, hypertension, dyslipidemia, KOA, MASLD, and OSAS) or improvement (liver fibrosis and pulmonary indexes) |
| 5.4 | All-cause mortality reduction |
| 5.5 | Improvement of QoL |
| *Outcomes* (safety) | |
| 5.6 | SAEs |
| 5.7 | Change in mental health/emotional status parameters |
| 6 | In patients with a BMI ≥27 kg/m$^2$ and cardiovascular disease, which OMM is preferable to placebo for treating overweight/obesity? |
| *Outcomes* (efficacy) | |
| 6.1 | Body weight reduction (TBWL [%], change in waist circumference and BMI, and proportion of subjects achieving at least a reduction of 5, 10, 15, 20, and 25% or more of baseline body weight; changes in body composition) |
| 6.2 | Incidence of MACE[a] |
| 6.3 | Other comorbid conditions remission[a] (diabetes, hypertension, dyslipidemia, KOA, MASLD, and OSAS) or improvement (liver fibrosis and pulmonary indexes, and KCCQ scores). Reduction of hospital admission for heart failure[a] |
| 6.4 | All-cause mortality reduction |
| 6.5 | Improvement of QoL |
| *Outcomes* (safety) | |
| 6.6 | SAEs |
| 6.7 | Change in mental health/emotional status parameters |

**Table 1** (continued)

| *N* | PICO |
|---|---|
| 7 | In patients with a BMI ≥27 kg/m$^2$ and prediabetes, which OMM is preferable to placebo for treating overweight/obesity? |
| *Outcomes* (efficacy) | |
| 7.1 | Body weight reduction (TBWL [%], change in waist circumference and BMI, and proportion of subjects achieving at least a reduction of 5, 10, 15, 20, and 25% or more of baseline body weight; changes in body composition) |
| 7.2 | Improvement of glycometabolic control (HbA1c, fasting plasma glucose, lipid and blood pressure profile, and renal function) |
| 7.3 | Reduction of incident diabetes[a] |
| 7.4 | Comorbid conditions remission[a] (hypertension, dyslipidemia, OSAS, KOA, hospital admission for heart failure) or improvement (KCCQ scores, liver fibrosis, pulmonary indexes) |
| 7.5 | All-cause mortality reduction |
| 7.6 | MACE reduction |
| 7.7 | Improvement of QoL |
| *Outcomes* (safety) | |
| 7.8 | SAEs |
| 7.9 | Change in mental health/emotional status parameters |
| 8 | In patients with a BMI ≥27 kg/m$^2$ and knee osteoarthritis (KOA), which OMM is preferable to placebo for treating overweight/obesity? |
| *Outcomes* (efficacy) | |
| 8.1 | Body weight reduction (TBWL [%], change in waist circumference and BMI, and proportion of subjects achieving at least a reduction of 5, 10, 15, 20, and 25% or more of baseline body weight; changes in body composition) |
| 8.2 | KOA resolution or improvement of scales evaluating osteoarthritis outcome scores (e.g., pain) |
| 8.3 | Comorbid conditions remission[a] (hypertension, dyslipidemia, OSAS, hospital admission for heart failure) or improvement (KCCQ scores, liver fibrosis, pulmonary indexes) |
| 8.4 | All-cause mortality reduction |
| 8.5 | MACE reduction |
| 8.6 | Improvement of QoL |
| *Outcomes* (safety) | |
| 8.7 | SAEs |
| 8.8 | Change in mental health/emotional status parameters |

BMI, body mass index; HbA1c, hemoglobin A1c; KCCQ, Kansas City Cardiomyopathy Questionnaire; KOA, knee osteoarthritis; MACE, major adverse cardiovascular events; MASLD, metabolic dysfunction-associated steatotic liver disease; OMM, obesity management medications; OSAS, obstructive sleep apnea syndrome; PICO, population, intervention, comparison, outcome; T2D, type 2 diabetes. [a]Only adjudicated events will be considered.

medical conditions. For patients included in the other subgroups (e.g., T2D, prediabetes, previous heart failure, etc.), the primary endpoint is reported in online supplementary Table S2.

Secondary endpoints (for all subgroups) will include the following (placebo-subtracted absolute differences from baseline, if not otherwise specified):

- TBWL% at 52 weeks, 53–104 weeks, and ≥105 weeks.
- Change in endpoint BMI and waist circumference.
- Change in fat mass (FM), subcutaneous fat, and visceral fat measured only by dual-energy X-ray absorptiometry or abdomen computed tomography.
- Change in fat-free mass (FFM) measured only by dual-energy X-ray absorptiometry or abdomen computed tomography.

- Proportion of subjects achieving at least 5, 10, 15, 20, and 25% of body weight reduction (odds ratio [OR]).
- Proportion of subjects undergoing remission of the following obesity-associated medical conditions: T2D (defined as the achievement of glycated hemoglobin [HbA1c] <6.5%), hypertension (defined as the cessation of antihypertensive drugs), dyslipidemia (defined as the normalization of lipid profile without the need for lipid-lowering medications), Metabolic dysfunction-associated steatohepatitis (MASH, defined as no steatotic liver disease or simple steatosis without steatohepatitis), reduction of at least one stage of liver fibrosis, OSAS remission (defined as apnea-hypopnea index <5 or apnea-hypopnea index of 5–14), and reduction of hospital admission for heart failure (OR).
- Serious adverse events (SAEs), all-cause mortality, or major adverse cardiovascular events (MACEs) (OR).
- Changes in fasting plasma glucose, HbA1c, lipid profile, blood pressure, eGFR, creatinine, and albuminuria.
- Improvement of Kansas City Cardiomyopathy Questionnaire scores, liver fibrosis and fat content, and pulmonary indexes.
- Change in mental health parameters measured by questionnaires. We will also obtain psychiatric serious adverse events when reported.
- Improvement of QoL measured by questionnaires.

*Statistical Analyses*

To compare and rank the efficacy and safety of OMMs, depending on the data available, we will perform NMA, pairwise meta-analyses, or subgroup meta-analyses. Preplanned analyses will be performed based on the following patient baseline characteristics as specified in Table 1. The endpoints considered critical (primary and secondary) for each subpopulation of patients are specified in online supplementary Table S2.

Treatment effects will be reported as weighted mean differences (WMDs) with 95% confidence intervals (CIs) for continuous outcomes and ORs with 95% CI for categorical outcomes. Placebo will serve as the reference category for ranking treatments. In all analyses, between-study heterogeneity will be quantified using $I^2$ statistics. If substantial heterogeneity is detected ($I^2$ >50%), we will explore potential sources through subgroup analyses whenever possible.

We decided to use NMA as the principal methodology, due to its capability of allowing indirect comparisons when direct head-to-head trials are unavailable and because it combines direct and indirect evidence to provide a comprehensive estimate of treatment effects. We will use a random-effects model within a generalized pairwise modeling (GPM) framework. Before beginning the NMA, we will evaluate transitivity by examining key effect modifiers across treatment comparisons [11]. Studies with significant differences in effect modifiers will be considered in sensitivity analyses. These analyses will be performed in MetaXL (www.epigear.com).

If a NMA is not feasible due to less than 10 trials, disconnected networks, or clinical heterogeneity, we will conduct pairwise meta-analyses where direct comparisons are available. We will additionally assess statistical heterogeneity using Cochran's $Q$ test ($p < 0.10$ indicating heterogeneity). If heterogeneity is high, we will explore sources using subgroup and sensitivity analyses.

If pairwise meta-analyses are not feasible due to due to a lack of direct evidence or high heterogeneity, we will perform separate meta-analyses for predefined subgroups (e.g., OMM vs. placebo, OMM vs. LSI). These analyses will use random-effects models and be performed in RevMan, Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

If statistical pooling is not possible, we will provide a qualitative synthesis of the findings. We will use the risk of bias assessment tool to judge the reliability of the study. We will provide descriptive comparisons of treatment effects across studies based on the study population, OMM, comparison group, and outcome similarities. We will assess small-study effects and publication bias using funnel plots (for outcomes with ≥10 studies), Egger's test (for continuous outcomes), and Harbord's test (for binary outcomes).

## Discussion

While the history of obesity pharmacotherapy has been fraught with setbacks, safe and effective OMMs are currently available. However, so far, no specific recommendations have been developed. Thus, the areas covered by the clinical questions proposed by the expert panel include indications for the appropriate use of OMM in different subgroups of patients. Several OMM have been assessed in people living with obesity and obesity-related medical conditions [12, 13], such as metabolic dysfunction-associated steatotic liver disease, OSAS, heart failure, MACE, and T2D. These upcoming guidelines proposed by EASO will provide an algorithm to tailor the use of OMM by analyzing available evidence for several categories of individuals.

The decision to adopt a certain pharmacological treatment will be determined in some cases by its intrinsic efficacy to induce TBWL, and in other cases, it will be driven by the effect of the OMM to improve specific complications related to obesity, aligning the OMM recommendations with the EASO framework for the diagnosis, staging, and management of obesity as an ABCD [1, 14]. Based on the definition of obesity as an ABCD, some patients may be living with fat-mass disease, for example, patients with obesity and OSAS, where the goal would be to induce TBWL. Others may be affected by "sick-fat disease," and their goal would be the management and improvement of obesity-related medical conditions, in addition to TBWL. Moreover, the choice of a specific therapeutic option should be based on an accurate assessment of the risk-benefit ratio. Therefore, safety outcomes have been included for all proposed PICO, concurring with the development of recommendations.

Transparency in developing a GRADE-based guideline is one of the major determinants of its quality [15]. The GRADE manual recommends the publication of clinical questions, relevant outcomes, and summaries of evidence for each outcome [16]. The panel of experts involved in the present project decided to go beyond these requirements, preemptively publishing in extenso the entire process leading to clinical questions and definition of critical outcomes. In addition, the search strategy and inclusion criteria for the systematic review and meta-analysis for each outcome have been reported in the present study, allowing a transparent reproducibility of the whole process. Notably, the panel decided to extensively publish in peer-reviewed journals all systematic reviews and meta-analyses needed for formulating these guidelines. However, an important limitation of this analysis is that the durability of treatment effects and the potential for weight regain following discontinuation of OMM were not evaluated. These aspects are highly relevant in the long-term management of obesity and should be addressed in future studies.

What distinguishes the present design and methodological approach is its unprecedented level of transparency, depth, and rigor in guideline development. By preemptively publishing the clinical questions, outcome definitions, and systematic review protocols, this initiative sets a new benchmark for methodological clarity and reproducibility. Unlike traditional guideline efforts, this framework integrates a multidimensional view of obesity as a chronic, heterogeneous disease, tailoring pharmacological recommendations based on both weight-related and metabolic outcomes. This comprehensive and patient-centered strategy ensures that the upcoming guidelines are not only evidence-based, but also uniquely suited to real-world clinical complexity.

## Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines.

## Conflict of Interest Statement

Barbara McGowan has received speaker and/or advisory fees from Novo Nordisk, Eli Lilly, Astra Zeneca, Janssen, Pfizer, MSD and a research grant from Novo Nordisk. B.M. is a shareholder of Reset Health. Andreea Ciudin has received speaking fees from Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Sanofi, Menarini and research grants from Eli Lilly, Novo Nordisk and Menarini, member of the DMC of Boehringer Ingelheim. Jennifer L. Baker has received a consulting fee and is an advisory board member for Novo Nordisk A/S with fees paid to her institution. Luca Busetto has received payment of honoraria from Eli Lilly, Novo Nordisk, Boehringer Ingelheim, Pfizer, Bruno Farmaceutici, Regeneron, Rhythm Pharmaceuticals and Pronokal as speaker and/or member of advisory boards. Dror Dicker has received speaker and advisory board fees from Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Astra Zeneca, and research grants from Eli Lilly, Novo Nordisk, and Boehringer Ingelheim. Gema Frühbeck has received payment of honoraria from Eli Lilly, Novo Nordisk, Regeneron, and Astra Zeneca as speaker and/or member of advisory boards, and payment of honoraria as member of the OPEN Spain Initiative. Gijs H. Goossens has no relevant conflicts of interest to declare related to this article. Matteo Monami has received speaking fees from Astra Zeneca, Bristol Myers Squibb, Boehringer Ingelheim, Eli Lilly, Merck, Novo Nordisk, Sanofi, and Novartis and research grants from Bristol Myers Squibb. Benedetta Ragghianti and Euan Woodward have no conflicts of interest to declare. Paolo Sbraccia received payment of honoraria and consulting fees from Boehringer Ingelheim, Chiesi, Novo Nordisk, Eli Lilly, Pfizer, and Roche as a member of advisory boards. Borja Martinez-Tellez has received grants from the EASO New Clinical Investigator Award 2024 and the EFSD Rising Star 2024, both supported by the Novo Nordisk Foundation. Volkan Yumuk was engaged in advisory boards and lectures with: Novo Nordisk, Eli Lilly, Rhythm, and Regeneron. Volkan Yumuk, Gema Frühbeck, and Jennifer L. Baker were members of the journal's Editorial Board at the time of submission.

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## Author Contributions

All the authors approved the final version of this manuscript. Dr. Barbara McGowan and Andreea Ciudin are the persons who take full responsibility for the work as a whole, including the study design, and the decision to submit and publish the manuscript. Authors

involvement in each of the following points: (1) design: B.M., A.C., J.L.B., L.B., D.D., G.F., G.H.G., M.M., P.S., E.W., and V.Y.; (2) data collection: M.M., B.R., B.M.-T.; (3) analysis: M.M. and B.R.; (4) writing the manuscript: B.M., A.C., J.L.B., D.D., G.H.G., M.M., P.S., and B.M.-T.; and (5) review of final draft: all the authors.

## Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

## References


1 Perdomo CM, Avilés-Olmos I, Dicker D, Frühbeck G. Towards an adiposity-related disease framework for the diagnosis and management of obesities. Rev Endocr Metab Disord. 2023;24(5):795–807 (In eng). https://doi.org/10.1007/s11154-023-09797-2

2 Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration BMI Mediated Effects; Lu Y, Hajifathalian K, Ezzati M, Woodward M, Rimm EB, et al. Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1·8 million participants. Lancet. 2014;383(9921):970–83 (In eng). https://doi.org/10.1016/S0140-6736(13)61836-X

3 Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K, et al. Body fatness and cancer:-viewpoint of the IARC Working Group. N Engl J Med. 2016;375(8):794–8 (In eng). https://doi.org/10.1056/NEJMsr1606602

4 Jaacks LM, Vandevijvere S, Pan A, McGowan CJ, Wallace C, Imamura F, et al. The obesity transition: stages of the global epidemic. Lancet Diabetes Endocrinol. 2019;7(3):231–40 (In eng). https://doi.org/10.1016/S2213-8587(19)30026-9

5 Blüher M. Adipose tissue dysfunction in obesity. Exp Clin Endocrinol Diabetes. 2009;117(6):241–50 (In eng). https://doi.org/10.1055/s-0029-1192044

6 Swinburn BA, Kraak VI, Allender S, Atkins VJ, Baker PI, Bogard JR, et al. The global syndemic of obesity, undernutrition, and climate change: the lancet commission report. Lancet. 2019;393(10173):791–846 (In eng). https://doi.org/10.1016/S0140-6736(18)32822-8

7 Wadden TA, Tronieri JS, Butryn ML. Lifestyle modification approaches for the treatment of obesity in adults. Am Psychol. 2020;75(2):235–51 (In eng). https://doi.org/10.1037/amp0000517

8 Müller TD, Finan B, Bloom SR, D'Alessio D, Drucker DJ, Flatt PR, et al. Glucagon-like peptide 1 (GLP-1). Mol Metab. 2019;30:72–130 (In eng). https://doi.org/10.1016/j.molmet.2019.09.010

9 Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928 (In eng). https://doi.org/10.1136/bmj.d5928

10 Guyatt GH, Oxman AD, Santesso N, Helfand M, Vist G, Kunz R, et al. GRADE guidelines: 12. Preparing summary of findings tables-binary outcomes. J Clin Epidemiol. 2013;66(2):158–72 (In eng). https://doi.org/10.1016/j.jclinepi.2012.01.012

11 Higgins JP, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. Res Synth Methods. 2012;3(2):98–110 (In eng). https://doi.org/10.1002/jrsm.1044

12 Mantovani A, Petracca G, Beatrice G, Csermely A, Lonardo A, Targher G. Glucagon-like peptide-1 receptor agonists for treatment of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: an updated meta-analysis of randomized controlled trials. Metabolites. 2021;11(2):73 (In eng). https://doi.org/10.3390/metabo11020073

13 Malhotra A, Grunstein RR, Fietze I, Weaver TE, Redline S, Azarbarzin A, et al. Tirzepatide for the treatment of obstructive sleep apnea and obesity. N Engl J Med. 2024;391(13):1193–205 (In eng). https://doi.org/10.1056/NEJMoa2404881

14 Busetto L, Dicker D, Frühbeck G, Halford JCG, Sbraccia P, Yumuk V, et al. A new framework for the diagnosis, staging and management of obesity in adults. Nat Med. 2024;30(9):2395–9. https://doi.org/10.1038/s41591-024-03095-3

15 Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. Agree II: advancing guideline development, reporting and evaluation in health care. J Clin Epidemiol. 2010;63(12):1308–11. (In eng).https://doi.org/10.1016/j.jclinepi.2010.07.001

16 Brozek JL, Akl EA, Alonso-Coello P, Lang D, Jaeschke R, Williams JW, et al. Grading quality of evidence and strength of recommendations in clinical practice guidelines. Part 1 of 3. An overview of the GRADE approach and grading quality of evidence about interventions. Allergy. 2009;64(5):669–77 (In eng). https://doi.org/10.1111/j.1398-9995.2009.01973.x