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# Multicomponent (bio)markers for obesity risk prediction: a scoping review protocol

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## ABSTRACT

**Introduction** Despite international efforts, the number of individuals struggling with obesity is still increasing. An important aspect of obesity prevention relates to identifying individuals at risk at early stage, allowing for timely risk stratification and initiation of countermeasures. However, obesity is complex and multifactorial by nature, and one isolated (bio)marker is unlikely to enable an optimal risk stratification and prognosis for the individual; rather, a combined set is required. Such a multicomponent interpretation would integrate biomarkers from various domains, such as classical markers (eg, anthropometrics, blood lipids), multiomics (eg, genetics, proteomics, metabolomics), lifestyle and behavioural attributes (eg, diet, physical activity, sleep patterns), psychological traits (mental health status such as depression) and additional host factors (eg, gut microbiota diversity), also by means of advanced interpretation tools such as machine learning. In this paper, we will present a protocol that will be employed for a scoping review that attempts to summarise and map the state-of-the-art in the area of multicomponent (bio) markers related to obesity, focusing on the usability and effectiveness of such biomarkers.

**Methods and analysis** PubMed, Scopus, CINAHL and Embase databases will be searched using predefined key terms to identify peer-reviewed articles published in English until January 2024. Once downloaded into EndNote for deduplication, CADIMA will be employed to review and select abstracts and full-text articles in a two-step procedure, by two independent reviewers. Data extraction will then be carried out by several independent reviewers. Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews and Peer Review of Electronic Search Strategies guidelines will be followed. Combinations employing at least two biomarkers from different domains will be mapped and discussed.

**Ethics and dissemination** Ethical approval is not required; data will rely on published articles. Findings will be published open access in an international peer-reviewed journal. This review will allow guiding future directions for research and public health strategies on obesity prevention, paving the way towards multicomponent interventions.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A strength of this review is the attempt to combine multiple markers of obesity to allow superior risk prediction.
⇒ Novel markers of obesity prediction such as microRNA and various omics techniques will be included.
⇒ The study consortium integrates 24 partners from complementary scientific domains that will be optimally situated to address this interdisciplinary topic.
⇒ The review will map novel integrative approaches combining modifiable risks such as diet as well as host factors including genetic background.
⇒ A limitation is that environmental aspects such as built environment or pollutants will not be included.

## INTRODUCTION

Obesity has reached epidemic proportions as a global health concern in recent decades.[1] According to the last (2022) WHO report on overweight and obesity, it is estimated that about 60% of the European population is considered as having overweight or obesity, that is, a body mass index (BMI) above 25 kg/m$^2$, with 23% of the population having obesity (BMI over 30 kg/m$^2$).[2] Obesity has been associated with numerous adverse health outcomes, including type 2 diabetes,[3 4] cardiovascular diseases,[5 6] certain cancers[7] and reduced overall quality of life[8] and total mortality.[9] Despite extensive research on the causes and consequences of obesity, its aetiology remains challenging to understand as it is complex and multifactorial.[10] While behavioural and lifestyle factors such as diet,[11] physical activity[12] and sleep quality[13]

Table 1 Summary of inclusion and exclusion criteria

| Aspect | Inclusion | Exclusion |
|---|---|---|
| (a) Literature | Original peer-reviewed research papers, systematic reviews, meta-analyses, reviews | Grey literature, abstracts, PhD theses, editorials, books, project reports, non-reviewed conference proceedings |
| (b) Main outcome/ health complication | Risk of overweight and obesity and management and all markers thereof: physical activity, diet, socioeconomic aspects, host factors such as genetics, epigenetics etc. | Studies not related to the risk of overweight and obesity |
| (c) Population | All populations, all ages, later mapping to target groups (elderly ≥65 years, children (5–12 years), young adults (18–25 years) | N/A |
| (d) Region | Whole world | N/A |
| (e) Studies, to be appraised for quality | Intervention, observational (case–control, prospective…), pooled data | Case reports, case series |
| (f) Time | All until January 2024 | |
| (g) Language | English (abstract and whole text) | Non-English (abstract and whole text) |
| (h) Species | Human studies (both genders) | Animal studies, cellular models and in vitro studies |

play critical roles in the development of obesity, there is also an important contribution of biological risk factors.[14] Biological factors involved in the development of obesity include host factors such as genetics, epigenetics, gut microbiota and specific diseases.[14–16] These factors do not operate in isolation but interact in a complex network, making it challenging to unravel the precise mechanisms underlying the development of obesity. The emerging field of multicomponent (bio)marker analysis,[17] offers a promising approach to understanding the intricate interplay between these biological and lifestyle factors and their role in obesity development.[18 19] Of note, the term multimodal is also used but there is some disparity on the terminology. The term multilevel analysis is also used though may rather refer to, for example, obesity prediction at various levels, such as individual, environmental and political.

Multicomponent (bio)markers for obesity risk prediction can encompass a range of biological measurements, including genetic markers, epigenetic modifications, transcriptomic markers (eg, RNA expression profiles and RNA modifications), metabolites, hormones and inflammatory markers,[20] which may be measured by multiomics approaches.[21] Such analyses can be combined with lifestyle characteristics such as dietary patterns, physical activity or sedentary behaviour,[22] as well as with psychological state,[23] thus covering risk factors from several domains. Examining multiple (bio)markers simultaneously through integrative research methodology such as machine learning,[24] allows to gain a more comprehensive understanding of the biological processes that contribute to obesity and its associated risks. However, and to the best of our knowledge, no systematic effort has been made to comprehensively review the existing literature on multicomponent (bio)markers and their association with obesity risk. Systematic reviews exist in selected settings such as workplace-related multicomponent interventions[25] and individual multicomponent interventions for children/adolescents with obesity[26 27] and adults,[28] but these lack focus on prevention, including early risk markers.

The concept of multicomponent biomarker has already been highlighted for other specific diseases such as psoriasis.[29] This scoping review will summarise and map existing evidence, providing a holistic understanding of obesity's complex nature influenced by various biological and non-biological factors. By identifying knowledge clusters and gaps in current literature, the scoping review will contribute to research prioritisation, guiding future directions for research on obesity prevention, especially regarding multicomponent interventions.[27] The findings hold potential clinical and public health implications, offering insights into novel approaches for obesity prevention and management, impacting personalised medicine, nutrition strategies and broader public health initiatives.

To address these aspects and to conduct high-quality research, a scoping review in this field is justified over other types of reviews as it is best suited to investigate multicomponent (bio)markers related to obesity risk due to its capacity to explore diverse and poorly defined literature. Its inclusive approach incorporates various evidence sources, making it valuable for synthesising insights in this multidisciplinary field. This scoping review will serve as a foundational step for subsequent systematic reviews, refining research questions and providing policy-makers with a comprehensive overview to inform interventions for obesity prevention and treatment.[30–35]

## Aims and objectives

The main purpose of this scoping review is to explore the literature on the topic of multicomponent (bio)markers related to obesity risk, to highlight the state-of-the-art and existing knowledge, as well as to identify gaps and ways forward. Thus, the main objective of this scoping review

Table 2 Example of search terms and their combinations targeted for PubMed search

| Number | Search |
|---|---|
| 1 | (overweight [mesh] OR overweigh* [tw] OR "excess weight" [tw] OR "excess fat" [tw] OR "excess mass" [tw] OR obesity [mesh] OR obes* [tw] OR adip* OR corpulent [tw]) |
| 2 | (biomarkers [mesh] OR biomarker* [tw] OR marker* [tw] OR indicator [tw] OR endpoint [tw]) |
| 3 | (multimodal [tw] OR multi-modal [tw] OR "multi modal" [tw] OR "multi level" OR multi-level [tw] OR "combined modality treatment" [mesh]" OR "multilevel analysis" [mesh] OR multicomponent [tw] OR multi-component [tw]) |
| 4 | (Diet* [mesh] OR diet* [tw] OR nutrition* [tw] OR food* [mesh] OR nutrients [mesh] OR nutrient* [tw]) |
| 5 | ("Physical activity" [tw] OR exercise [mesh] OR exercise* [tw] OR sports [mesh] OR sport [tw] OR inactivity [tw] OR "physical behaviour" [tw] OR "sedentary behaviour" [mesh] OR sedent* [tw] OR sleep [mesh] OR sleep* [tw]) |
| 6 | (omics* [tw] OR microbiota [mesh] OR microbiot*[tw] OR microbiome* [tw] OR multiomics [mesh] OR multiomic*[tw]) |
| 7 | (genetic* [tw] OR genetics [mesh] OR epigenetic* [tw] OR "genetic markers" [mesh] OR epigenomics [mesh] OR epigenomic*[tw]) |
| 8 | (mental [tw] OR "mental health" [mesh] OR emotion* [tw] OR emotions [mesh] OR psycholog* [tw] OR psychology [mesh] OR cognit* [tw] OR cognition[mesh]) |
| 9 | (Animal* [tw] OR animals [mesh] OR mice [mesh] OR mice [tw] OR "cell culture" [tw] OR "cell model" [tw] Or "cell culture techniques" [mesh] OR "case reports" [mesh] OR "in vitro" [tw]) |
| 10 | List of Boolean Operators of the above search terms:<br>1 and 2 and 3 AND; 1 and 2 AND 4 and 5 OR; 1 and 2 AND 4 and 6 OR; 1 and 2 AND 4 and 7 OR; 1 and 2 AND 4 and 8 OR; 1 and 2 AND 5 and 6 OR; 1 and 2 AND 5 and 7 OR; 1 and 2 AND 5 and 8 OR; 1 and 2 AND 6 and 7 OR; 1 and 2 AND 6 and 8 OR; 1 and 2 AND 7 and 8; NOT 9. |

is to map available knowledge and findings and further emphasise the gaps to successfully employ multicomponent markers and their predictive power towards the risk of developing obesity. The main research question is, therefore, which studies and strategies, combining at least two markers from different fields (eg, nutrition, physical activity, multiomics), have been reported to predict the risk of developing overweight or obesity? A secondary objective is to obtain further insights on combinations that have been the most frequently employed and which approaches may be promising towards obesity risk prediction. Searches will be conducted for all segments of the population, although a particular emphasis will be put on key periods of transitions in life, that is, young schoolchildren (age 5–12 years), young adults (18–25 years) and the elderly (>64 years).

## METHODS AND ANALYSIS

The protocol for this scoping review has been submitted to the Open Science Framework (OSF) platform, where it has been registered and received the following DOI: https://doi.org/10.17605/OSF.IO/4WT9X .

### Framework and protocol design

This scoping review will follow the criteria as outlined in this protocol and also PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for Scoping Reviews, more specifically, the extension for scoping reviews (PRISMA-SCR and flow chart).[36] In addition, we adhered to the OSF guidelines in designing the methods for this study.[37] The approach was structured based on Arksey and O'Malley's scoping review methodology,[38] with methodological enhancements by Levac *et al*.[39] The framework comprises six key stages:

i. Defining the research question.
ii. Identifying pertinent studies.
iii. Selecting studies.
iv. Organising and extracting data.
v. Compiling, summarising and reporting results.
vi. Engaging with relevant stakeholders. We will also create a flow diagram to report on the information flow during different stages of this review, which will show the number of literature records found, included and excluded, as well as the rationale for exclusion.

### Eligibility criteria and rationale

Inclusion criteria for this scoping review encompass various literature types, including original research papers, systematic reviews and meta-analyses, aiming for a comprehensive exploration of multicomponent biomarkers related to overweight and obesity. Thus, the main outcome from a statistical point of view is the risk of developing overweight or obesity. It considers health complications, risk factors and management across diverse populations, ages, regions and study types (interventional, observational). The broad time frame (all published and retrievable studies until January 2024) and English language focus facilitate a global perspective. Exclusion criteria aim to maintain rigour by excluding grey literature and non-peer-reviewed materials such as abstracts, theses, editorials, books, project reports and conference proceedings. Case series, reports, studies in languages other than English and those involving animal or cellular models are excluded to allow for a more homogeneous data interpretation and also to assure higher evidence

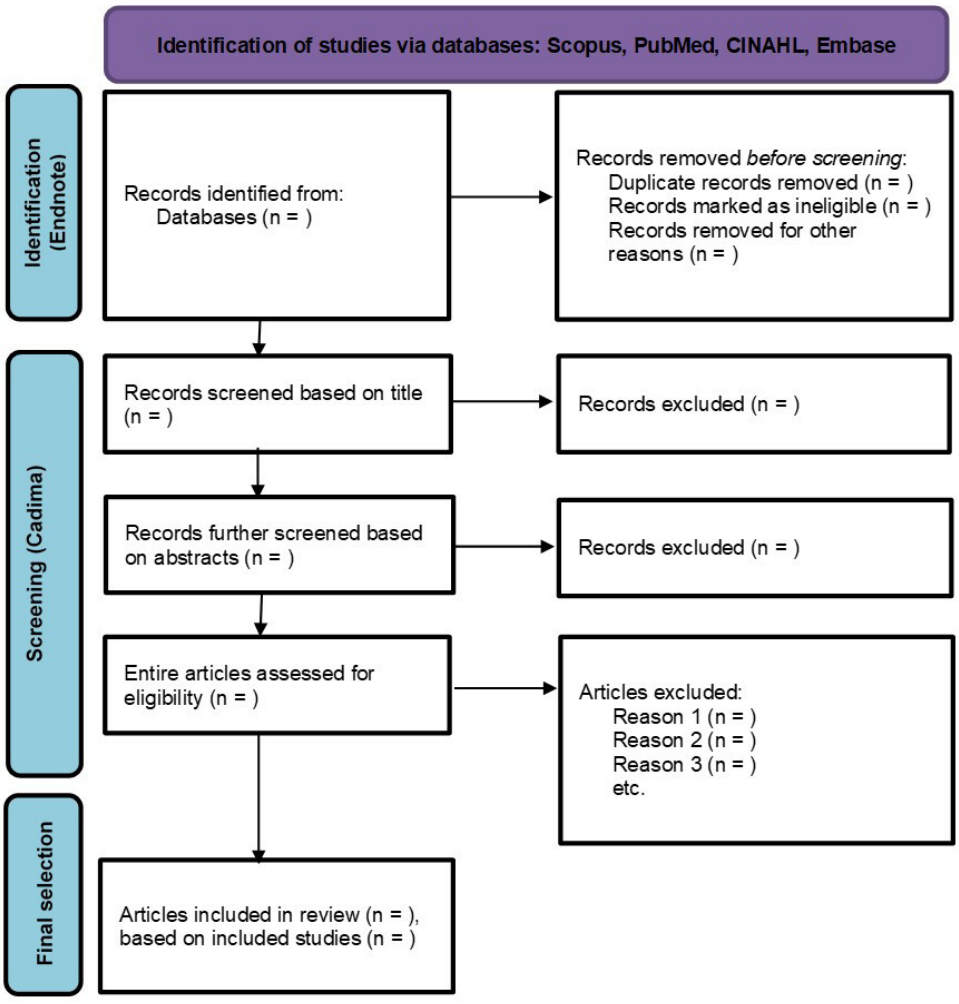


**Figure 1** PRISMA-ScR flow diagram example. PRISMA-ScR, Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews.

quality, that is, based on quality human studies.[40] The review excludes studies published after submission of this article (January 2024), ensuring a manageable dataset for analysis while maintaining a comprehensive approach. The inclusion and exclusion criteria are summarised in table 1.

### Information sources and search strategy

The four databases PubMed, Embase, Scopus and CINAHL will be used for our search. The search strategy for PubMed is shown in table 2. The electronic search strategy was developed with feedback from all authors based on their specific expertise in collaboration with an experienced librarian. The search will be carried out with an initial set of search terms. Our research librarian has been involved in the following aspects of the search syntax development: (1) translating research questions into search terms; (2) appropriate use of adjacency proximity operators; (3) text word and mesh-term searching done by inspecting the truncation and inclusion of British and American spellings and (4) spelling and any syntax errors done by reading the syntax strategy line by line and inspecting the use of Boolean operators and brackets.

Two members of the team will carry out the search and the extraction of the articles from the databases. The articles will be exported to EndNote, which will also be used to deduplicate findings from the various databases. Following this step, articles will be transferred to the free, web-based CADIMA tool for further study screening and selection. The procedure adheres to the Peer Review of Electronic Search Strategies guideline.

### Study selection/screening

Initially, titles and abstracts of potential studies or sources (based on search strategy and terms on databases including PubMed, Embase, CINAHL and Scopus) will be screened for relevance. A pilot screening phase will be conducted to ensure consistency and alignment among the screening team members. At least two reviewers will perform screening independently. Any discrepancies or disagreements in the screening process will be addressed through discussion and consensus among the reviewers and the other authors if needed. The obtained articles will be reviewed regarding their thematic fit (the relevance of the articles to the main focus or theme of

Table 3 Data items to be collected

| Category | Data |
|---|---|
| Bibliographic Information: | Author(s) |
| | Title of the study |
| | Year of publication |
| | Journal or source name |
| | Digital object identifier (DOI) or International standard book number (ISBN) (if applicable) |
| Study characteristics: | Study design |
| | Study type |
| | Setting (location) |
| | Sample size and population studied |
| Participant information: | Demographics |
| | Inclusion/exclusion criteria |
| | Patient/subject characteristics (if applicable) |
| Interventions or exposures: | Description of interventions or exposures |
| | Exposure duration and timing |
| | Duration of the intervention |
| Outcomes: | Primary outcomes of interest |
| | Secondary outcomes |
| | Measurement tools or instruments used |
| | Outcome results |
| Key findings and results: | Summary of main findings |
| | Associations, relationships, or effects observed |
| Discussion and conclusions: | Authors' interpretations and conclusions |
| | Implications for practice, policy or further research |
| | Limitations of the study/approach as mentioned by authors |
| | Criteria used for quality assessment |
| Ambiguities or limitations: | Any uncertainties or limitations identified in the study or source |
| Data sources: | Database or source from which the study was retrieved |
| | Search strategies used (if relevant) |
| Additional information: | Any additional data items specific to the research question or objectives |

the study). If the information in titles and abstracts is unclear, additional context or full-text examination may be used to make an informed decision. CADIMA will be used to manage and document the title and abstract screening process. Following title and abstract screening, full texts of selected studies will be thoroughly examined in the next step to assess their eligibility. The results of the search will be presented in a PRISMA-ScR flow diagram (figure 1).

### Data collection and extraction

In preparation for the data extraction process, we will begin with a pilot phase aimed at refining our approach and achieving consistency. During this phase, a selected subset of studies or sources will be used for practice and feedback. The data extraction itself will involve several independent reviewers, each working on their assigned set of studies. Data will be extracted by several team members, but not in parallel and independently, due to the expected high workload. Instead, extracted data will be critically reviewed by additional team members at the end of this step. Inconsistent terminology will be harmonised, and incomplete data in the articles will be strived to be retrieved by additional published sources or by contacting the authors if required. It will be attempted to standardise formats and data units, duplicate reporting will be removed, and missing data or outliers will be highlighted by conducting validation checks. Data will be collected in commonly available spreadsheet software, including Excel, Word and SPSS (version 25). To tackle any potential discrepancies, we follow a multipronged approach, including regular team meetings for discussion and resolution, the involvement of an arbitrator or lead reviewer when consensus is elusive and detailed guidelines within our codebook to minimise discrepancies. When confronted with unclear or missing information in the selected studies, we plan to reach out to authors for clarification and meticulously documenting any remaining uncertainty. To enhance the efficiency and reliability of the process, CADIMA, a web tool designed for data entry, tracking and management, will be used.

In case of encountering 'friend studies' (ie, studies including an author of the present scoping review), we will commit to systematic and transparent procedures. We will document the sources of these studies, applying the same inclusion criteria and quality assessment as other studies, ensuring an independent review process.

### Specified data items to be collected

The data items to be collected are detailed in table 3.

### Synthesis and presentation of extracted information

To achieve a comprehensive and clear overview of the findings, we will follow a systematic approach, beginning with the selection of appropriate data synthesis methods, such as narrative synthesis and thematic analysis, tailored to the nature of the studies or sources. We will then aggregate, categorise and organise relevant data to identify common themes, patterns and key findings. Subgroup analyses will be conducted for the various combinations of markers from different

domains if research objectives warrant it. Additionally, relevant results may be presented in supplementary materials in the published final review.

To further facilitate understanding, we will integrate visual aids, including tables, charts, graphs and diagrams, into our presentation. Data presentation will thus include the following:

a. Summary tables of studies retained and interpreted.
b. Figures on studies with combinations of at least two markers from the various domains (eg, nutrition and physical activity).
c. Figures portraying approach versus risk prediction possibility, that is, quantitative prediction success.
d. Tables summarising approaches together with pitfalls and challenges.

Complementing visual aids, we will craft a narrative summary to provide context, explanations and interpretations of the synthesised data, guiding readers through the findings and their implications.

Finally, the synthesised results will be used to generate practical implications and recommendations for policy, practice or further research where relevant.

### Patient and public involvement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

## ETHICS AND DISSEMINATION

Ethical approval will not be required for this paper, as it will rely on already published articles.

The findings will be published as a scoping review in an international, high-ranked, peer-reviewed open-access journal. In addition, the results will be presented at selected international conferences, such as the International Congress of Nutrition organized by the International Union of Nutritional Sciences (IUNS-ICN) in Paris (https://www.icn2025.org/).

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**Contributors** TB, FV and YD proposed the type and structure of the proposed scoping review and were involved in the planning and conception of the protocol. FV and TB were the main authors of the written protocol. CD aided in the planned search and data extraction strategy. SF gave additional guidance on the structure of the manuscript. JAT, CB, LM, MM-M, AS, MSD, JT, EL, MP-J, GR-H, RA, RN, MFF, MGO, GGB and TDM have contributed in writing sections of the articles and all other authors provided further input on the structure of the article and will be involved in the extraction of data, interpretation of findings and writing of the scoping review. YO critically reviewed the final version of the article. All authors critically have read and approved and reviewed the final version of the article.

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**Competing interests** MSD works as a consultant and an advisory board member at Theralution, Germany. Otherwise, the authors declare no conflict of interest.

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