UK Total Diet Replacement (TDR) ad hoc working group

SCIENTIFIC OPINION

Scientific opinion on additional scientific evidence in relation to the compositional requirements of total diet replacement for weight control products defined by Regulation (EU) No 609/2013

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Requestor Nutrition Related Labelling, Composition and Standards (NLCS) Policy Group

UK Total Diet Replacement ad hoc working group members

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Declarations of interest

Read the total diet replacement ad hoc working group register of interests containing all declarations of interests made by members.

UK Nutrition and Health Claims Committee (UKNHCC) secretariat

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TDR ad hoc working group disclaimer

[1] The TDR ad hoc working group code of practice states that Official observers attend TDR ad hoc working group meetings to provide updates from their respective nations on science and policy matters of relevance whilst respecting TDR ad hoc working group independence.

The present opinion does not constitute, and cannot be construed as, an authorisation for the marketing of total diet replacement for weight control (TDR) products, a positive assessment of their safety, nor a decision on whether TDR products are, or are not, classified as a foodstuff. It should be noted that such an assessment is not foreseen.

Process undertaken by the TDR ad hoc working group:

- the mandate was given by the Nutrition Related Labelling, Composition and Standards (NLCS) policy group in March 2022
- the UKNHCC secretariat (Office for Health Improvement and Disparities (OHID) (Department of Health and Social Care (DHSC)) received the mandate from the NLCS policy group and proceeded to establish an ad hoc working group
- the scientific assessment process started in March 2022
- during its meeting on 25 April 2022, the TDR ad hoc working group evaluated the evidence informing the European Food Safety Authority (EFSA) statement (2021) on additional scientific evidence in relation to the essential composition of total diet replacement for weight control and considered evidence identified from additional literature searches between June and December 2020, to March 2022 since publication of the EFSA statement (EFSA, 2021)
- during its meeting on 9 June 2022, the TDR ad hoc working group further discussed methodological approaches adopted in the EFSA statement (EFSA, 2021), agreed its conclusions on the scientific assessment process and discussed the draft scientific opinion
- following the meeting, the final scientific opinion was agreed via email correspondence

Formation of the TDR ad hoc working group

An ad hoc working group was formed to carry out a UK assessment of the evidence that was used to inform proposed changes to the compositional requirements of total diet replacement for weight control (TDR) products, as outlined in the EFSA statement (EFSA, 2021). The ad hoc working group was comprised of experts from the Scientific Advisory Committee on Nutrition (SACN) and the NHS Low Calorie Diet Programme Advisory Group. The ad hoc working group adhered to the TDR ad hoc working group code of practice (which closely reflects the SACN code of practice) and the SACN Framework for Evaluation of Evidence that Relates Food and Nutrients to Health (SACN, 2012). The work of the ad hoc working group was supported by the UK Nutrition and Health Claims Committee (UKNHCC) secretariat.

Summary

From 27 October 2022 new legislation governing the specific compositional and information requirements for total diet replacement for weight control (TDR) products Commission Delegated Regulation (EU) 2017/1798 began to apply in the EU. Whilst the UK was an EU member state it was involved in the scientific assessment that informed Regulation (EU) 2017/1798. However, as it was not retained by GB on EU Exit day, unless or until GB lay new legislation, the 1997 legislation (as amended) (96/8/EC) will continue to apply across GB.

Since Regulation (EU) 2017/1798 was adopted in the EU, Total Diet and Meal Replacements (TDMR) Europe appealed to the European Commission to issue a mandate to the European Food Safety Authority (EFSA) to review the scientific evidence on the compositional requirements of TDR products. EFSA published a statement in 2021 in light of the evidence, post EU Exit when the UK was no longer an EU member state (EFSA, 2021)[2].

Following a request from the UK Nutrition Related Labelling, Composition and Standards (NLCS) policy group an ad hoc working group was set up to assess the compositional requirements of TDR products (defined by Regulation (EU) No 609/2013).

The ad hoc working group were asked to assess the compositional requirements of:

- the minimum value of linoleic acid (LA) in TDR products
- the minimum value of alpha-linolenic acid (ALA) in TDR products
- the maximum value of magnesium (Mg) in TDR products

The ad hoc working group reviewed the methods used to identify and evaluate evidence as reported in the EFSA statement (EFSA, 2021). Methods were compared with those developed by the UK Scientific Advisory Committee on Nutrition (SACN) for conducting evidence reviews (SACN Framework for Evaluation of Evidence that Relates Food and Nutrients to Health) (SACN, 2012).

The ad hoc working group reviewed the evidence included in the EFSA statement (2021) against the reported eligibility criteria for its appropriateness.

[2] Terms of reference as interpreted by EFSA (2021):

- A) the amount of LA and ALA that is released from adipose tissue (AT) of overweight or obese adults during weight loss
- B) to what extent the minimum content of LA and ALA in TDRs proposed by the Panel (EFSA NDA Panel, 2015b) could be reduced based on the outcome of the review of the scientific evidence related to point (A)
- C) to what extent the minimum fat content in TDRs proposed by the Panel in the 2015 scientific opinion (EFSA, 2015b), that was derived from the proposed minimum content of LA and ALA in TDRs, is to be revised together with the minimum energy content that was based on the sum of the energy provided by macronutrients
- D) whether a maximum magnesium (Mg) content in TDRs of 350 mg/day, as proposed by TDMR, would give rise to concerns with respect to an increased risk of diarrhoea. In this context, the Panel is not expected to revise the tolerable upper intake level (UL) of the Scientific Committee on Food (SCF) (2001) for Mg salts

The ad hoc working group was also asked to identify any new evidence published since the EFSA statement (2021) and whether it affected their conclusions.

The ad hoc working group assessed the totality of evidence considering methodological assumptions and limitations of this scientific risk assessment.

The ad hoc working group concluded that:

- the release of linoleic acid from adipose tissue during weight loss when consuming total diet replacement products should be sufficient to cover the adequate intake and therefore no linoleic acid needs to be supplied by total diet replacement products
- the release of alpha-linolenic acid from adipose tissue during weight loss when consuming total diet replacement products is not sufficient to cover the adequate intake and a minimum of 0.8g per day alpha-linolenic acid needs to be supplied by total diet replacement products in order to meet the adequate intake for alpha-linolenic acid
- the likelihood that magnesium-induced diarrhoea occurs at a severity that may be considered of concern for individuals with overweight or obesity consuming total diet replacement products is low when the total maximum magnesium content in total diet replacement products is 350mg per day

1. Background

1.1. New legislation governing the specific compositional and information requirements for total diet replacement for weight control (TDR) products Commission Delegated Regulation (EU) 2017/1798 began to apply in the EU from 27 October 2022. This delegated Regulation supplements Regulation (EU) No 609/2013, which repealed Commission Directive 96/8/EC.

1.2. As Regulation (EU) 2017/1798 did not apply until 27 October 2022 and was not retained by GB on EU Exit day (1 January 2021); unless or until GB lays new legislation, the 1997 legislation (as amended) (96/8/EC) will continue to apply across GB. The Protocol on Ireland/Northern Ireland (NIP) provides that EU legislation relating to nutrition, as detailed in Annex 2 of the NIP, continues to be directly applicable in Northern Ireland.

1.3. Whilst the UK was an EU member state it was involved in the scientific assessment (EFSA, 2015b) that informed Regulation (EU) 2017/1798. As such, Regulation (EU) 2017/1798 sets out all other compositional requirements that are not covered in the terms of reference of this scientific risk assessment, including a minimum value for magnesium (Mg) of 150mg per day.

1.4. Since Regulation (EU) 2017/1798 was adopted in the EU, Total Diet and Meal Replacements (TDMR) Europe appealed to the European Commission on 7 November 2019 to issue a mandate to the European Food and Safety Authority (EFSA) to review the scientific evidence on the composition of TDR products. EFSA published a statement in 2021 in light of the evidence, post EU Exit when the UK was no longer an EU member state[2].

1.5. In accordance with the UK-wide Nutrition Related Labelling, Composition and Standards (NLCS) Provisional Common Framework, it is the responsibility of UK authorities to conduct the appropriate risk assessment and risk management processes (including seeking scientific evaluation) to amend GB domestic legislation. The NLCS policy group which was established under the NLCS Provisional Common Framework, and compromises of officials from across the UK governments, requested a scientific risk assessment of the proposed changes to the compositional requirements of TDR products (defined by Regulation (EU) No 609/2013 as food specially formulated for use in energy restricted diets for weight reduction which, when used as instructed by the food business operator, replaces the whole daily diet). This does not consider the process to assess the safety of TDR products.

1.6. This scientific opinion should be read together with EFSA's scientific opinion (EFSA, 2015b) which provides conclusions drawn from the scientific assessment on compositional requirements of TDR products for all other nutrients.

2. Terms of reference as provided by the mandate requestor

2.1. In March 2022 the NLCS policy group requested a scientific assessment of the proposed changes to the compositional requirements of TDR products. An ad hoc working group was established to critically appraise the evidence used to inform the proposed changes to the compositional requirements of TDR products, as reported in the EFSA statement, published post EU Exit (EFSA, 2021). The ad hoc working group was also asked to identify and review any other relevant new scientific evidence available that met the same inclusion criteria as outlined in appendix D of the EFSA statement (EFSA, 2021).

2.2. The ad hoc working group was not asked to assess the full nutritional composition of TDR products as in the EFSA scientific opinion (EFSA, 2015b), as the UK was an EU member state and had previously contributed to discussions that informed the scientific opinion (2015b) and subsequent legislation, Regulation (EU) 2017/1798.

2.3. The proposed compositional changes of TDR products as outlined in the EFSA statement (EFSA, 2021)[3] which the ad hoc working group was asked to assess were:

- the minimum value of linoleic acid (LA) in TDR products
- the minimum value of alpha-linolenic acid (ALA) in TDR products
- the maximum value of Mg in TDR products

2.4. The ad hoc working group was comprised of experts from the Scientific Advisory Committee on Nutrition (SACN) and the NHS Low Calorie Diet Programme Advisory Group. The approach to the work of this ad hoc working group is set out in detail in this scientific opinion and adhered to the TDR ad hoc working group code of practice (which closely reflected the SACN code of practice) and SACN Framework for Evaluation of Evidence that Relates Food and Nutrients to Health (SACN, 2012). The work of the ad hoc working group was supported by the UK Nutrition and Health Claims Committee (UKNHCC) secretariat.

3. Interpretation of the terms of reference

[3] EFSA (2021) conclusions based on their terms of reference:

- there is no need to add LA to TDRs, as the amount released from AT during weight loss when consuming TDRs is sufficient to cover the AI for this FA
- the release of ALA from AT during weight loss when consuming TDRs is not sufficient to cover the AI and a minimum of 0.8 g/day ALA needs to be supplied by TDRs in order to meet the AI for ALA
- the minimum fat content of TDRs of 20 g/day as derived in the previous opinion is proposed to be maintained until the availability of further evidence, given the considerable uncertainty as to the amount of fat required for reducing the risk of gallstone formation
- the likelihood that Mg-induced diarrhoea occurs at a severity that may be considered of concern for overweight or obese individuals consuming TDRs is low when the total maximum Mg content in TDRs is 350 mg/day

3.1. The TDR ad hoc working group agreed to assess the compositional requirements of TDR products with respect to whether:
- the minimum value of LA in TDR products as recommended by EFSA (2021) is appropriate for a UK population
- the minimum value of ALA in TDR products as recommended by EFSA (2021) is appropriate for a UK population
- the maximum value of Mg in TDR products as recommended by EFSA (2021) is appropriate for a UK population, and
- further evidence identified in updated literature searches effects either of the above nutrient recommendations

3.2. The scientific assessment of the ad hoc working group was based on the following assumptions with respect to the terms of reference:
- it is mandated to assess the maximum content of Mg supplied by TDR products per day only but recognise there is a requirement for TDR products to contain a minimum Mg content of 150mg per day (EU, 2017)
- users of TDR diets have an adequate nutritional status prior to starting the diet
- TDR products are consumed for up to 8 weeks only
- compositional criteria based on adequate intakes (AI) for the 'reference male' are to be used as they are based on the upper end of nutrient and energy requirements. The reference male subject is defined as a 40-year-old male with a physical activity level of 1.6 (moderate activity) and an average requirement (AR) for energy of 10.7MJ per day (2,500kcal per day)

4. Methods

4.1. The ad hoc working group followed the protocol as reported in appendix D of the EFSA statement (2021). This scientific opinion is based on the methods adopted and data used to inform the EFSA statement (2021) and considers:
- the approach used by EFSA (EFSA, 2021)
- evidence identified by EFSA, as outlined in the EFSA statement (EFSA, 2021)
- evidence identified through updated literature searches

Approach used by EFSA

4.2. The ad hoc working group reviewed the methods used to identify and evaluate evidence as reported in the EFSA statement (EFSA, 2021). Methods were compared with those the developed by SACN for conducting evidence reviews, as reported in the SACN Framework for Evaluation of Evidence that Relates Food and Nutrients to Health (SACN, 2012). Methods reviewed included study

selection, eligibility criteria, literature searches, data synthesis, quality assessment and data analysis (Annex 1 (Table A1. 1)).

4.3. The ad hoc working group also considered dietary reference values (DRVs) used by EFSA (EFSA, 2019), the equivalent developed for the UK by the Committee on Medical Aspects of Food Policy (COMA, 1991) and methods taken to develop each set of DRVs (Annex 2 (Table A2. 1)).

Evidence identified by EFSA

4.4. The ad hoc working group reviewed articles against eligibility criteria included in appendix D of the EFSA statement (EFSA, 2021) also taking into account amendments to the protocol reported in section 2.3 (EFSA, 2021). Appropriateness of study design and methods, populations included in the studies, intervention and comparator treatments where relevant, outcomes reported, and relevance of study results that study authors reported were considered. The studies are listed in Annex 3.

Updated literature search

4.5. Data were retrieved through updated literature searches in Embase and PubMed, reflecting the searches reported in the EFSA statement (EFSA, 2021). Searches for literature that met the inclusion criteria and published after the EFSA searches were performed by the UK Health Security Agency (UKHSA) Knowledge and Library Services (KLS) between 21 to 24 March 2022 (Annex 4). Adjustments to the EFSA search strategies were both required and recommended by KLS (Table 1).

Table 1: Adjustments to the search strategies used in the updated literature reviews compared with the EFSA statement (EFSA, 2021)

Change made	Reason for change
Removal of animal search terms	Advice on including some animal species and not others was unusual and unlikely to dramatically increase the number of results.
Removal of human studies filter	Adding a human study filter can limit the number of results picked up in a search due to inaccurate or un-comprehensive tagging within the database itself.
Corrections for anomalies and incorrect syntax	Due to KLS using a different interface to EFSA to replicate the searches, each search line was checked for anomalies and incorrect syntax. Also, as database interfaces change over time some terms may have been amalgamated.

4.6. Limitations on publication date were applied, to restrict articles published from the date of the respective EFSA searches (from June to December 2020, date varying by question) to the date of the updated searches (March 2021). The searches were restricted to publications in English. Results from the searches were imported into bibliographic referencing software EndNote 20™ (Clarivate, Philadelphia, PA), one library for each search, and deduplicated.

4.7. To complete the updated literature review screening some adaptations were made to the methods (Table *2*) compared with those reported in the EFSA statement (EFSA, 2021).

Table 2: Methodological amendments used in the updated literature reviews compared with the EFSA statement (EFSA, 2021)

2022 literature review update	**EFSA statement (2021)**
≥10% duplicate title and abstract screen	Duplicate screen
100% single reviewer full text screen with 100% check by a second reviewer	100% single reviewer full text screen

4.8. Two reviewers independently screened a minimum of 10% of titles and abstracts retrieved from each of the literature searches in Microsoft Excel®. Agreement between reviewers was ≥99% for each screen. Any disagreements were discussed and resolved between the two reviewers. The remaining titles and abstracts were screened by one reviewer. Due to the limited inclusion of evidence, data extraction of studies identified in the updated literature review was not planned and data extraction forms were not developed.

4.9. Paragraphs 5.14 to 5.19 summarise the evidence retrieved from the updated literature searches. The search terms and the eligibility criteria in the protocol are reported in Annex 4 and Annex 5 respectively. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagrams detailing the study selection process for each literature search are included in Annex 6.

5. Assessment

Approach used by EFSA

5.1. Methods for evaluating evidence used by EFSA (2021) versus how the process would be approached in the UK were largely comparable (Annex 1 (Table A1. 1) and Annex 2 (Table A2. 1)).

5.2. The ad hoc working group discussed the approaches SACN and EFSA take to derive DRVs. Values used by SACN are based on those derived by COMA (COMA, 1991), whereas EFSA report updated values in their summary report (EFSA, 2019). COMA set a reference nutrient intake (RNI) and EFSA set a

population reference intake (PRI), both levels sufficient for the majority of the population, 97% and 97.5% for UK and Europe respectively. Both COMA and EFSA set average population nutrient requirements, COMA an estimated average requirement (EAR) (COMA, 1991) and EFSA an AR (EFSA, 2019). The UK EAR was defined as the amount of a nutrient which a specified group of people will, on average need, about half usually needing more than the EAR, and half less (COMA, 1991). The EU AR was defined as the level of (nutrient) intake that is adequate for half of the people in a population group, given a normal distribution of requirement (EFSA, 2019). Members agreed that assuming normal distribution, the separate approaches are approximately equivalent for a range of nutrients and derive broadly similar values.

5.3. Differences between EFSA and COMA methods for estimating DRVs for Mg were considered by the ad hoc working group. It was noted that UK DRVs were set by COMA in 1991 when an AR for Mg was set (COMA, 1991), whereas EFSA DRVs were considered more recently, in 2015 (EFSA, 2015a). EFSA Panel on Dietetic Products, Nutrition and Allergies noted that there was insufficient evidence to set an AR for Mg, but AI values were derived (350mg per day for men and 300mg per day for women) (EFSA, 2015a).

5.4. The ad hoc working group considered the values derived by EFSA (2021) for the 3 nutrients LA, ALA and Mg were sufficient for the context of this scientific assessment.

5.5. With regards to whether the fatty acid content of TDR products could result in a deficiency, the ad hoc working group discussed the use of TDR products from a clinical perspective and noted that TDR products are used for a short time, typically 8 to 12 weeks. The EFSA scientific opinion (2015b), states that none of the studies investigating adverse metabolic consequences of TDR products had a duration of longer than 3 months (EFSA, 2015b). Additionally, studies which investigated critical endpoints had not been conducted for longer than 8 weeks. Therefore, as outlined in Regulation (EU) 2017/1798 TDR products should be used for a single period of up to 8 weeks (EU, 2017). UK and EU DRV recommendations are generally for habitual lifelong diets, rather than those used in the short-term such as TDR products. The ad hoc working group concluded that the risk of fatty acid deficiency whilst using TDR products was low considering the short-term use.

5.6. The amount of fatty acids present in adipose tissue prior to following a TDR diet could have an effect on whether an individual becomes deficient. One aspect of determining the quantity of fatty acids to add to TDR products is to ascertain how much is lost from adipose tissue during weight loss. In considering this the ad hoc working group discussed the modelling exercise[4] conducted by EFSA (2021) and were content with the conservative approach used based on the information reported. The ad hoc working group discussed fatty acid release

[4] EFSA statement (2021), sections 3.1.1 and 3.1.4

from adipose tissue and its dependency on fatty acid composition of adipose tissue at the start of the diet with specific reference to limited amounts of ALA present in adipose tissue which may require more to be supplied through the diet.

5.7. The ad hoc working group also discussed the effect of a poor diet before TDR treatment and the possibility that it may compromise the availability of ALA from adipose tissue. The consideration of non-essential longer chain n3 polyunsaturated fatty acids (PUFAs) was also discussed. However, it was noted that these issues were out of scope of the current scientific assessment.

5.8. The ad hoc working group discussed the adequacy of washout periods in cross-over studies included to identify data on supplemental Mg intake and risk of developing diarrhoea. Members' consensus was that the washout periods in the cross-over studies were appropriate as the diarrhoeal effect of Mg wears off quickly once the dose of Mg is reduced or withdrawn. The requirement for a maximum level of Mg was also discussed given that Mg is stored in the body and TDR products are typically consumed for a short time period. It was noted that while there are significant Mg stores in the body, Mg is not easily mobilised and acute Mg deficiency can occur quickly (Ehrenpreis et al, 2022). It was also noted that prior to starting a TDR diet, a patient's diet may have been deficient in Mg.

5.9. In addition, the ad hoc working group noted 3 points regarding the approach used by EFSA:

- the inclusion criteria were limited to English language only. The ad hoc working group agreed there were no concerns and noted that SACN would also normally limit inclusion criteria to English only publications
- the inclusion criteria excluded grey literature. The ad hoc working group recognised that there was a small risk of relevant grey literature not being identified but were content with this
- a formal call for evidence was not reported. The ad hoc working group agreed there were no concerns and noted this aligned with the approach taken by SACN whereby a call for evidence may be issued as an additional step in order to identify relevant research in the field that had recently been published or was due to be published

Conclusions on the approach used by EFSA

5.10. After considering the above points, the ad hoc working group agreed that the methods adopted in the EFSA statement (2021) were applicable to the UK population.

Conclusions on compositional requirements of TDR products proposed by EFSA (2021)

5.11. The ad hoc working group considered the minimum content of 0.8g per day for ALA and removing the minimum content requirement for LA proposed by EFSA (2021) to be appropriate given that TDR products are typically given for no longer than 8 weeks and that derived values were based on the AI for healthy individuals considering a 40-year-old male reference subject.

5.12. The ad hoc working group considered the 40-year-old male reference subject with a physical activity level of 1.6 (moderate activity) and an AR for energy of 10.7MJ per day (2,500kcal per day) to be an appropriate proxy. Members noted that although the 'reference male' does not reflect the population in which TDR products are intended for use (adults living with overweight or obesity who wish to lose weight and replace the whole diet in the context of energy-restricted diets for weight reduction) (EFSA, 2015b), the reference male requirements are assumed to be on the upper end of individuals' requirements compared with a female and provides a conservative estimate.

5.13. The ad hoc working group considered the maximum content of 350mg per day of Mg for both males and females proposed by EFSA to be appropriate for TDR products, given the evidence from cross-over trials and doses of Mg investigated between 300 and 400mg per day, as described by EFSA (2021).

Updated literature searches

5.14. The updated literature searches did not identify any new studies that met the inclusion criteria for Q1, 2 or 4 (Annex 6). Hand searches carried out on relevant systematic reviews and meta-analyses identified in the title and abstract screening did not result in any studies that met the eligibility criteria.

5.15. The search conducted for Q3 (Annex 6) identified 2 intervention studies (Schutten, 2021; Schutten, 2022) that met the eligibility criteria. Both studies were conducted in the Netherlands and included patients living with overweight or obesity who were otherwise healthy. Both studies reported on self-reported adverse events (AE) following administration of two different interventions and in at least one group participants were given readily dissociable Mg salts.

5.16. Schutten et al (2021) reported a post hoc analysis of a previously performed 24-week randomised, double-blind, placebo-controlled, parallel group intervention trial (Joris et al, 2016) evaluating long term Mg supplementation on arterial stiffness. AEs were also reported. The trial included 52 participants allocated to receive either 350mg per day Mg-citrate (n=27 (26 completed)) or placebo (n=25 (25 completed)). Out of the 52 participants randomised in the trial, 49 participants (25 allocated to Mg; 24 allocated to placebo) were included in the post hoc analysis. After 24 weeks of intervention no serious AEs were reported

and only mild headache and mild gastrointestinal complaints were reported in one patient in the Mg group during week 11 of the study (Schutten et al, 2021).

5.17. Schutten et al (2022) reported a follow-up study to that reported by Schutten et al (2021). By design this study was also a 24-week randomised, double-blind, placebo-controlled, parallel group intervention trial. The trial aimed to demonstrate the effect of Mg-citrate supplementation, in a higher dose than in the 2021 study (Joris et al, 2016) on arterial stiffness. AEs were also reported. The trial included 164 participants allocated to receive either 450mg per day Mg-citrate (n=46), 450mg per day Mg-oxide (n=46), 450mg per day Mg-sulphate (n=46) or placebo (n=26). After 24 weeks of intervention mild diarrhoea was reported by 5 out of 46 participants (10.9%) in the Mg-citrate group, 1 out of 46 participants (2.2%) in the Mg-oxide group, 5 out of 46 participants (10.9%) in the Mg-sulphate group and 2 out of 26 participants (7.7%) in the placebo group.

5.18. The ad hoc working group considered both the fact that the diarrhoeal AEs were self-reported without any reported use of predefined diagnostic criteria and the increased risk of bias in parallel group studies compared with cross-over studies (where bowel habits are described in both periods by the same person and reports are subject to the same subjective interpretations).

5.19. The ad hoc working group noted the dose of Mg given to participants, 350mg per day (Schutten et al, 2021) and 450mg per day (Schutten et al, 2022), was not lower than the range of Mg (300 to 400mg per day) doses given in each of the cross-over studies included by EFSA (2021).

Conclusions

Having reviewed the methods used to identify and evaluate evidence as reported in the EFSA statement (2021), the ad hoc working group reviewed the additional evidence identified in updated literature searches and on the basis that they were not aware of any other significant evidence, concluded that:

- the release of linoleic acid from adipose tissue during weight loss when consuming total diet replacement products should be sufficient to cover the adequate intake and therefore no linoleic acid needs to be supplied by total diet replacement products
- the release of alpha-linolenic acid from adipose tissue during weight loss when consuming total diet replacement products is not sufficient to cover the adequate intake and a minimum of 0.8g per day alpha-linolenic acid needs to be supplied by total diet replacement products to meet the adequate intake for alpha-linolenic acid
- the likelihood that magnesium-induced diarrhoea occurs at a severity that may be considered of concern for individuals with overweight or obesity consuming total diet replacement products is low when the total maximum magnesium content in total diet replacement products is 350mg per day

Though not part of the terms of reference, the ad hoc working group agreed with the conclusion on minimum fat content of 20g per day to be provided by TDR products as proposed by EFSA (2015b). Due to a lack of further evidence the conclusion on minimum fat content of 20g per day to be provided by TDR products was maintained in the EFSA statement (EFSA, 2021).

The ad hoc working group caveats the conclusions drawn with the following points:

- it assumes users of TDR diets have an adequate nutritional status prior to starting the diet
- it assumes that TDR products are only consumed for up to 8 weeks based on the observation that none of the studies included in the EFSA scientific opinion (EFSA, 2015b) investigating adverse metabolic consequences of TDR products had a duration of longer than 3 months, and, studies which investigated critical endpoints had not been conducted for longer than 8 weeks
- the compositional criteria for TDR products are based on adequate intakes for the ‘reference male’ (40-year-old male with a physical activity level of 1.6 (moderate activity) and an average requirement for energy of 10.7MJ per day (2,500kcal per day)) which is not the population intended for use of TDR products. The ad hoc working group identified this as a limitation and acknowledged that the value used based on the upper end of requirements and therefore represents a conservative estimate of adequate intakes
- it was mandated to assess the maximum value of magnesium only. The ad hoc working group recognised that there was a required minimum Mg content for TDR products of 150mg per day, which was not assessed as it was outside the terms of reference

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Annexes

Annex 1: Comparison of methods used in the EU and UK

Table A1. 1: Summary of EFSA statement (2021) methods compared to SACN Framework (2020)

Method	EFSA statement (2021) methods	Methods reported in SACN Framework (2020)[5]
Eligibility criteria	To address the terms of reference, a series of pre-defined questions and sub-questions were developed. Eligibility criteria to identify relevant evidence required to address the questions are reported in appendix D.	To address the terms of reference, eligibility criteria are defined and the rationale for the chosen review approach made clear and detailed under 'Scope of evaluation', 'Literature searches' and 'Publication type'.
Scope of evaluation	A pre specified protocol is reported. Population, intervention, comparator, outcomes and study design (PICOS) are not explicitly reported for each term of reference, however, relevant information can be extrapolated, as reported in appendix D.	Pre specified PICOs are agreed at the outset of an evidence review.
Literature searches	• Literature searches were conducted by EFSA's information specialist • Search strategies for each literature review including search terms and the databases searched are provided in appendix E • Search terms included relevant PICOS and limits on species, English language (due to translation constraints) and publication type were applied. No limitations on publication date were applied except for the search on gallstone formation • Two databases (PubMed and Embase) were searched	• Literature searches are conducted by specialist Knowledge and Library Services (KLS) (as reported in SACN report: lower carbohydrate diets for type 2 diabetes) • Search strategies are reported in annexes (as reported in SACN report: lower carbohydrate diets for type 2 diabetes) • Search terms include relevant PICOS. Limits on English language and publication date are agreed based on the requirements of each evidence review. Further limits may be applied to the eligibility criteria instead of search terms • Databases Medline and PubMed are searched as a minimum • Hand searches if undertaken are agreed at the outset of each evidence review

[5] Where methods are not presented in the SACN framework, methods adopted in SACN reports have been referenced

Method	EFSA statement (2021) methods	Methods reported in SACN Framework (2020)[5]
	• Hand searches on comprehensive reviews and meta-analyses excluded during the screening were undertaken	• Other sources of information may be considered detailed under 'Grey literature', 'Stakeholder contributions' and 'Call for evidence'
Publication type	Relevant publication types were defined in the eligibility criteria (appendix D).	For all SACN evidence reviews eligible publication types are defined in the inclusion and exclusion criteria at the outset.
Grey literature	Grey literature was not eligible for inclusion.	Grey literature is only considered if agreed a priori. Preference is given to data published in peer-reviewed journals but other sources, such as official or expert reports based on peer-reviewed literature and official statistics, may provide some valuable information. Where such data are used, the source is clearly specified.
Stakeholder contributions	Contributions from stakeholders and interested parties would be considered. Data that could be provided spontaneously by stakeholders and interested parties were reported to be screened for their eligibility. In addition, previously published scientific reports of officially recognised scientific bodies, and the studies reported, for example SCF (2001) and VKM (2016), regarding Mg were also reported to possibly be considered.	SACN to do not have a formal process for stakeholder contributions however if a formal call for evidence is issued, stakeholders would have the opportunity to submit evidence.
Call for evidence	A formal call for evidence was not reported.	Depending on the type of evidence review, in addition to the database searches, a call for evidence may be issued in order to identify relevant research in the field that may not have been identified (for example, if it has recently been published or is due to be published).
Consultation	No public consultation was found on EFSA relating to the EFSA statement (2021).	Draft SACN reports are issued for public consultation and comments arising are considered. Where appropriate,

Method	EFSA statement (2021) methods	Methods reported in SACN Framework (2020)[5]
		amendments are made before the final report is published. SACN's responses to comments made at consultation are published at the same time as the final report. The ad hoc working group will report the outcome of their scientific assessment directly to the NLCS policy group.
Study selection	Reviewer screening, software used and methods for dealing with conflicts are reported in appendix D.	Reviewer screening and methods for dealing with conflicts are reported as a minimum (as reported in SACN report: lower carbohydrate diets for type 2 diabetes).
Reporting the inclusion of evidence	PRISMA flow charts summarising the flow of articles identified through searches, study selection and inclusion for each literature search are provided in appendix A.	SACN includes flow charts detailing the identification, inclusion and exclusion of evidence at each stage of the risk assessment process.
Data synthesis	Methods were primarily semiquantitative. A qualitative approach was reported to be followed for specified sub-questions. A conservative approach was reported to be taken when assessing the evidence to cover the entire population that could potentially consume TDRs. Expert knowledge elicitation was reported to be sought in specified situations if needed. Data are reported narratively in the main text with main data presented in tables for terms of reference C and D.	The main results are tabulated indicating the author, date, country, sample size, duration of study, dietary assessment method, exposure, outcome, main results, adjustment for confounders and sources of funding and included in SACN reports as annexes. Results are described narratively in SACN reports.
Data analysis	Forrest plots (appendix B) and scatter plots (appendix C) are reported.	When deliberating whether data analysis can be conducted from information extracted from the studies reviewed, the following points are considered:

Method	EFSA statement (2021) methods	Methods reported in SACN Framework (2020)[5]
	No meta-analysis was conducted as this risk assessment was not a full systematic review.	• study duration, power and source of funding • potential for meta-analysis • When meta-analysis would be considered appropriate • the models to be used and rationale such as random versus fixed-effects models • consistency of meta-analysis results • how heterogeneity will be assessed, such as consideration of the I^2 statistic and associated criteria • investigation of publication bias Consideration is given to presenting results graphically, for example with forest plots.
Quality assessment	No quality assessment was conducted.	SACN considers the methodologies of included studies in order to assess their quality.
Protocol amendments	Protocol amendments were reported due to the limited evidence available.	No formal process for handling protocol amendments in the SACN framework but any change to scope would be noted within report methods as necessary.

Annex 2: Derivation of EU and UK DRVs

Table A2. 1: EU and UK DRVs for AL, ALA and Mg, and methods used to derive values

Nutrient	Unit of measure	AI/AR	Value on which EFSA statement (2021) was based	UK value	Reference (EU)	Reference (UK)	Methods for deriving EU DRVs	Methods for deriving UK DRVs
LA	% Energy	AI	4[6]	≥1	EFSA NDA Panel, 2010	SACN, 2019	LA was based on the lowest estimated mean intakes of the various population groups from a number of European countries, where overt deficiency symptoms are not present. Noted insufficient scientific data to derive an AR, Lower Threshold Intake (LTI) or PRI. Set by EFSA (2010).	DRVs for EFAs were derived only on the basis of prevention of EFA deficiency. DRVs initially set by COMA (1991). In 2019 SACN made the same recommendations in the SACN report on Saturated fats and health.
ALA	% Energy	AI	0.5[6]	≥0.2	EFSA NDA Panel, 2010	SACN, 2019	ALA was based on the lowest estimated mean intakes of the various population groups from a number of European countries, where overt	DRVs for EFAs were derived only on the basis of prevention of EFA deficiency.

[6] Based on lowest estimated mean intakes in EU where overt deficiency symptoms are not present

							deficiency symptoms are not present. Noted insufficient scientific data to derive an AR, Lower Threshold Intake (LTI) or PRI. Set by EFSA (2010).	DRVs initially set by COMA (1991). In 2019 SACN made the same recommendations in the SACN report on Saturated fats and health.
Mg	Mg per day	AR[7]	150 to 500	Males: 250; Females: 200	SCF, 1993	COMA, 1991	The SCF (1993) did not set a PRI for Mg, but concluded on an AR of intake of 150 to 500mg per day based on observed Mg intakes in the USA and the UK, as it considered that results from balance studies were difficult to interpret owing to methodological considerations.	Relied upon physiological data from balance studies, noting that it is difficult to define deficiency symptoms or toxic effects of Mg in humans as well as difficulty in interpreting data owing to the long periods of time to achieve equilibrium for Mg in balance studies. Requirements were established based on kilogram (kg) body weight, set by COMA (1991).

[7] The EFSA statement (2021) acknowledged TDMR Europe's suggestion to raise the maximum Mg content in TDRs to 350mg per day (AI set in EFSAs 2015 Scientific Opinion on Dietary Reference Values for magnesium), published after the EFSA 2015 Scientific Opinion on the essential composition TDRs for weight control. However, in the absence of data that allowed the Panel to conclude on an Mg content in TDRs below which diarrhoea is not expected to occur, the Panel did comment on the likelihood of occurrence of Mg-induced diarrhoea when TDRs contain a maximum Mg dose of 350mg per day, the AI set for adult males.

Annex 3: Evidence identified in the EFSA statement (2021)

Behary et al (2019) Combined GLP-1, Oxyntomodulin, and Peptide YY Improves Body Weight and Glycemia in Obesity and Prediabetes/Type 2 Diabetes: A Randomized, Single-Blinded, Placebo-Controlled Study. Diabetes Care. 42(8): 1446-1453

Broomfield et al (1988) Effects of ursodeoxycholic acid and aspirin on the formation of lithogenic bile and gallstones during loss of weight. New England Journal of Medicine. 319(24): 1567-72

Cappuccio et al (1985) Lack of effect of oral magnesium on high blood pressure: a double blind study. British Medical Journal (Clinical research edition). 291(6490): 235-8

Cosaro et al (2014) Effects of magnesium supplements on blood pressure, endothelial function and metabolic parameters in healthy young men with a family history of metabolic syndrome. Nutrition, Metabolism & Cardiovascular Diseases. 24(11): 1213-20

Davies et al (1989) Metabolic response to low- and very-low-calorie diets. American Journal of Clinical Nutrition. 49(5): 745-51

Dolberg et al (2017) Pharmacokinetic Profile of Oral Magnesium Hydroxide. Basic & Clinical Pharmacology & Toxicology. 120(3): 264-269

Festi et al (1998) Gallbladder motility and gallstone formation in obese patients following very low calorie diets. Use it (fat) to lose it (well). International Journal of Obesity and Related Metabolic Disorders. 22(6): 592-600

Gebhard et al (1996) The role of gallbladder emptying in gallstone formation during diet-induced rapid weight loss. Hepatology. 24(3): 544-8

Gils Contreras et al (2018) Effects of Two Preoperatory Weight Loss Diets on Hepatic Volume, Metabolic Parameters, and Surgical Complications in Morbid Obese Bariatric Surgery Candidates: a Randomized Clinical Trial. Obesity Surgery. 28(12): 3756-3768

Hill et al (1987) Effects of exercise and food restriction on body composition and metabolic rate in obese women. American Journal of Clinical Nutrition. 46(4): 622-30

Johansson et al (2014) Risk of symptomatic gallstones and cholecystectomy after a very-low-calorie diet or low-calorie diet in a commercial weight loss program: 1-year matched cohort study. International Journal of Obesity. 38(2): 297-84

Kato et al (2004) Changes in urinary parameters after oral administration of potassium-sodium citrate and magnesium oxide to prevent urolithiasis. Urology. 63(1): 7-11; discussion 11-2

Kishimoto et al (2010) Effects of magnesium on postprandial serum lipid responses in healthy human subjects. British Journal of Nutrition. 103(4): 469-72

Kunesová et al (2002) The responses of serum and adipose Fatty acids to a one-year weight reduction regimen in female obese monozygotic twins. Annals of the New York Academy of Sciences. 967: 311-23

Kunešová et al (2012) Fatty acid composition of adipose tissue triglycerides after weight loss and weight maintenance: the DIOGENES study. Physiological Research. 61(6): 597-607

Lee et al (2010) Effects of dihydrocapsiate on adaptive and diet-induced thermogenesis with a high protein very low calorie diet: a randomized control trial. Nutrition & Metabolism. 7: 78

Liddle et al (1989) Gallstone formation during weight-reduction dieting. Archives of Internal Medicine. 149(8): 1750-3

Marken et al (1989) Effects of magnesium oxide on the lipid profile of healthy volunteers. Atherosclerosis. 77(1): 37-42

Navarrete-Cortes et al (2014) No effect of magnesium supplementation on metabolic control and insulin sensitivity in type 2 diabetic patients with normomagnesemia. Magnesium Research. 27(2): 48-56

Phinney et al (1988) Effects of aerobic exercise on energy expenditure and nitrogen balance during very low calorie dieting. Metabolism. 37(8): 758-65

Phinney et al (1990) Reduced adipose 18:3 omega 3 with weight loss by very low calorie dieting. Lipids. 25(12): 798-806

Purvis et al (1994) Effect of oral magnesium supplementation on selected cardiovascular risk factors in non-insulin-dependent diabetics. Archives of Family Medicine. 3(6): 503-8

Shechter et al (2012) Comparison of magnesium status using X-ray dispersion analysis following magnesium oxide and magnesium citrate treatment of healthy subjects. Magnesium Research. 25(1): 28-39

Shiffman et al (1995) Prophylaxis against gallstone formation with ursodeoxycholic acid in patients participating in a very-low-calorie diet program. Annals of Internal Medicine. 122(12): 899-905

Stanko et al (1992a) Body composition, energy utilization, and nitrogen metabolism with a severely restricted diet supplemented with dihydroxyacetone and pyruvate. American Journal of Clinical Nutrition. 55(4): 771-6

Stanko et al (1992b) Body composition, nitrogen metabolism, and energy utilization with feeding of mildly restricted (4.2 MJ/d) and severely restricted (2.1 MJ/d) isonitrogenous diets. American Journal of Clinical Nutrition. 56(4): 636-40

Stone et al (1992) Gallbladder emptying stimuli in obese and normal-weight subjects. Hepatology. 15(5): 795-8

Tang et al (1993) Preferential reduction in adipose tissue alpha-linolenic acid (18:3 omega 3) during very low calorie dieting despite supplementation with 18:3 omega 3. Lipids. 28(11): 987-93

Van Dale et al (1987) Does exercise give an additional effect in weight reduction regimens? International Journal of Obesity. 11(4): 367-75

Vazquez and Kazi (1994) Lipolysis and gluconeogenesis from glycerol during weight reduction with very-low-calorie diets. Metabolism. 43(10): 1293-9

Vezina et al (1998) Similarity in gallstone formation from 900 kcal/day diets containing 16 g vs 30 g of daily fat: evidence that fat restriction is not the main culprit of cholelithiasis during rapid weight reduction. Digestive Diseases and Sciences. 43(3): 554-61

Vu et al (2000) The osmotic laxative magnesium sulphate activates the ileal brake. Alimentary Pharmacology & Therapeutics. 14(5): 587-95

Widman et al (1993) The dose-dependent reduction in blood pressure through administration of magnesium. A double blind placebo controlled cross-over study. American Journal of Hypertension. 6(1): 41-5

Wing et al (1995) Cognitive effects of ketogenic weight-reducing diets. International Journal of Obesity and Related Metabolic Disorders. 19(11): 811-6

Yang et al (1981) Metabolic effects of substituting carbohydrate for protein in a low-calorie diet: a prolonged study in obese patients. International Journal of Obesity. 5(3): 231-6

Yang et al (1992) Risk factors for gallstone formation during rapid loss of weight. Digestive Diseases and Sciences. 37(6): 912-8

Annex 4: Search strategies

Q1: Linoleic acid and alpha-linolenic acid concentrations in adipose tissue and their release from adipose tissue

Embase: Search date 21 March 2022

Search line	Search term	Results
1	((ffa or ffas or efa or efas or pufa or pufas or ufa or ufas or "fatty acid" or "fatty acids" or "alpha linolenic acid" or "alpha linolenic acids" or "alphalinolenic acid" or "alphalinolenic acids" or "linoleic acid" or "linoleic acids" or linolate or linoleate or linolenate or "n 3 acid" or "n 3 acids" or "n 6 acid" or "n 6 acids" or "omega 3" or "omega 6" or omega3 or omega6 or X3 or x6 or "18 3x3" or "183omega3" or "18 3 omega3") adj5 (amount* or biops* or composition or concentration* or constituent* or content* or distribution* or level or levels or pattern* or percentage* or profile*)).ab,kw,ti.	80,213
2	(fatty acid/ or exp essential fatty acid/ or exp unsaturated fatty acid/ or (ffa or ffas or efa or efas or pufa or pufas or ufa or ufas).ab,kw,ti. or ((fatty or alphalinolenic or alphalinolenic or linolic or linoleic or "n 3" or "n 6") adj5 (acid or acids)).ab,kw,ti. or (linolate or linoleate or linolenate or "omega 3" or "omega 6" or omega3 or omega6 or x3 or x6 or "18 3x3" or "183omega3" or "18 3omega3").ab,kw,ti.) and exp lipid composition/	20,349
3	exp adipose tissue/ or exp adipose tissue cell/ or "adipocyte*".ab,kw,ti. or (((adipose or fat or fatty) adj3 (tissue* or body)) or (fat adj3 (abdominal or cell or cells or intraabdominal or pad or pads or subcutaneous or visceral))).ab,kw,ti.	302,114
4	1 or 2	87,926
5	3 and 4	10,429
6	limit 5 to (human and english language)	3,874
7	limit 6 to (editorial or letter)	16
8	6 not 7	3,858
9	limit 8 to dc=20200608-20220321	409

PubMed: Search date 21 March 2022

Search line	Search term	Results
22	#21 AND #13	760
21	#19 not #20	7,467
20	("editorial"[Publication Type]) OR ("letter"[Publication Type])	1,771,553

Search line	Search term	Results
19	#18 not #7	7,488
7	(rat[ti] OR rats[ti] OR mouse[ti] OR mice[ti] OR swine[ti] OR porcine[ti] OR murine[ti] OR sheep[ti] OR lambs[ti] OR pigs[ti] OR piglets[ti] OR rabbit[ti] OR rabbits[ti] OR cat[ti] OR cats[ti] OR dog[ti] OR dogs[ti] OR cattle[ti] OR bovine[ti] OR monkey[ti] OR monkeys[ti] OR trout[ti] OR marmoset*[ti])	2,106,148
18	#17 NOT #5	8,490
5	("Animals"[Mesh] NOT ("Animals"[Mesh] AND "Humans"[Mesh]))	4,975,149
17	#3 AND #15 AND #16	18,231
16	Adiposity"[Mesh] OR "Adipose Tissue"[Mesh] OR "Adipocytes"[Mesh] OR adipocyte*[tiab] OR Adipose tissue*[tiab] OR Adipose body[tiab] OR Abdominal fat[tiab] OR Body fat[tiab] OR Fat cell[tiab] OR Fat cells[tiab] OR Fat pad[tiab] OR Fat pads[tiab] OR Fat tissue*[tiab] OR Fatty tissue*[tiab] OR Intraabdominal fat[tiab] OR Subcutaneous fat[tiab] OR Visceral fat[tiab]	214,963
3	"Fatty Acids"[Mesh:NoExp] OR "Fatty Acids, Unsaturated"[Mesh] OR "Fatty Acids, Essential"[Mesh] OR Fatty acid[tiab] OR fatty acids[tiab] OR FFA[tiab] OR FFAs[tiab] OR EFA[tiab] OR EFAs[tiab] OR PUFA[tiab] OR PUFAs[tiab] OR UFA[tiab] OR UFAs[tiab] OR Alpha linolenic acid[tiab] OR Alpha linolenic acids[tiab] OR Alphalinolenic acid[tiab] OR Alphalinolenic acids[tiab] OR Linoleic acid[tiab] OR Linoleic acids[tiab] OR Linolic acid [tiab] OR Linolic acids[tiab] OR linolate[tiab] OR linoleate[tiab] OR Linolenate[tiab] OR "omega 3"[tiab] OR "omega 6"[tiab] OR omega3[tiab] OR omega6[tiab] OR (("n 3"[tiab] OR "n 6"[tiab]) AND (acid[tiab] OR acids[tiab])) OR "183x3"[tiab] OR "18 3x3"[tiab] OR "183omega3"[tiab] OR "18 3omega3"[tiab] OR x3[tiab] OR x6[tiab]	474,227
15	Amount[tiab] OR biops*[tiab] OR composition[tiab] OR concentration*[tiab] OR constituent[tiab] OR content*[tiab] OR distribution*[tiab] OR level[tiab] OR levels[tiab] OR pattern*[tiab] OR percentage*[tiab] OR profile[tiab]	9,388,959
14	#12 AND #13	243
13	"english"[Language] AND 2020/06/08:2022/03/21[dp]	2,780,209
12	#6 AND #11	1,820
9	"clinical trial"[pt] OR "Random Allocation"[Mesh] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR ("group 1"[tiab] AND "group 2"[tiab]) OR "Clinical Trials as Topic"[Mesh] OR "Double Blind Method"[Mesh] OR "Single-Blind Method"[Mesh] OR ((singl*[tiab] OR doubl*[tiab] OR trebl*[tiab] OR tripl*[tiab]) AND (mask*[tiab] OR blind*[tiab] OR dumm*[tiab])) OR "Cross-Over Studies"[Mesh] OR ((crossover[tiab] OR "cross	3,900,024

Search line	Search term	Results
	over"[tiab]) AND (study[tiab] OR studies[tiab] OR design*[tiab] OR method*[tiab] OR procedure[tiab] OR comparison [tiab]))	
11	#9 OR #10	4,241,387
10	systematic[sb] OR meta-analysis[pt] OR meta-analysis as topic[Mesh] OR metaanalysis[Mesh] OR meta analy*[tw] OR metanaly*[tw] OR metaanaly*[tw] OR met analy*[tw] OR integrative research[tiab] OR integrative review*[tiab] OR integrative overview*[tiab] OR research integration*[tiab] OR research overview*[tiab] OR collaborative review*[tiab] OR collaborative overview*[tiab] OR systematic review*[tiab] OR comparative efficacy[tiab] OR comparative effectiveness[tiab] OR outcomes research [tiab] OR indirect comparison*[tiab] OR Embase*[tiab] OR Cinahl*[tiab] OR systematic overview*[tiab] OR methodological overview*[tiab] OR methodologic overview*[tiab] OR methodological review*[tiab] OR methodologic review*[tiab] OR quantitative review* [tiab] OR quantitative overview*[tiab] OR quantitative synthes*[tiab] OR pooled analy* [tiab] OR Cochrane[tiab] OR Medline[tiab] OR Pubmed[tiab] OR Medlars[tiab] OR handsearch*[tiab] OR hand search*[tiab] OR meta-regression*[tiab] OR metaregression* [tiab] OR data synthes*[tiab] OR data extraction[tiab] OR data abstraction*[tiab] OR mantel haenszel[tiab] OR peto[tiab] OR der-simonian[tiab] OR dersimonian[tiab] OR fixed effect*[tiab] OR "Cochrane Database Syst Rev"[Journal:__jrid21711]	536,052
1	"Adiposity"[Mesh] OR "Adipose Tissue"[Mesh] OR "Adipocytes"[Mesh] OR adipocyte*[tiab] OR Adipose tissue*[tiab] OR Adipose body[tiab] OR Abdominal fat[tiab] OR Body fat[tiab] OR Fat cell[tiab] OR Fat cells[tiab] OR Fat pad[tiab] OR Fat pads[tiab] OR Fat tissue*[tiab] OR Fatty tissue*[tiab] OR Intraabdominal fat[tiab] OR Subcutaneous fat[tiab] OR Visceral fat[tiab] OR Intraabdominal fats[tiab] OR Subcutaneous fats[tiab] OR Visceral fats[tiab]	215,005
8	#6 NOT #7	5,245
6	#4 NOT #5	6,147
4	#1 AND #2 AND #3	14,131
2	body weight changes[MeSH Terms] OR (("adipose tissue"[tiab] OR fat[tiab] OR weight[tiab]) AND (decreas*[tiab] OR chang*[tiab] OR loss[tiab] OR losing[tiab] OR reduc*[tiab])) OR "body weight"[tiab] OR "body weights"[tiab]	718,045

Q2: Range of weight loss when consuming total diet replacements for weight control

Embase: Search date 21 March 2022

Search line	Search term	Results
1	exp low calorie diet/	1,561
2	exp very low calorie diet/	397
3	exp elimination diet/	816
4	exp liquid diet/	1,090
5	(low adj3 calori*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	7,953
6	(low adj3 energy adj5 diet*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	1,953
7	(low adj3 elimination adj5 diet*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	13
8	vlcd.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	848
9	vled.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	208
10	lcd.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	3,244
11	(ketogenic adj5 diet*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	7,635
12	(replacement adj5 diet*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	1,630
13	(substitute adj5 diet*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	340

Search line	Search term	Results
14	(liquid adj5 diet*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	9,104
15	'reducing diet*'.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	1,186
16	(calori* adj3 reduc* adj5 diet*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	764
17	(calori* adj3 restrict* adj5 diet*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	3,160
18	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17	35,634
19	exp body weight loss/	62,363
20	(weight adj3 decreas*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	33,018
21	(weight adj3 los*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	201,434
22	(weight adj3 reduc*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	184,917
23	(fat adj3 decreas*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	11,620
24	(fat adj3 reduc*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	16,539
25	(fat adj3 los*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade	6,582

Search line	Search term	Results
	name, keyword heading word, floating subheading word, candidate term word]	
26	('adipose tissue' adj3 reduc*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	2,686
27	('adipose tissue' adj3 decreas*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	2,067
28	('adipose tissue' adj3 los*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	1,044
29	(weight adj3 management).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	13,531
30	(weight adj3 chang*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	46,804
31	(chang* adj3 'adipose tissue').mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	1,747
32	(chang* adj3 'fat mass').mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	1,242
33	(chang* adj3 'fat tissue').mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	87
34	(chang* adj3 weight).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	46,804
35	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34	375,465

Search line	Search term	Results
36	18 and 35	8,623
37	exp clinical trial/	1,680,630
38	exp randomization/	93,630
39	(randomised or randomized or placebo or randomly or trial or groups or 'clinical trial').mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	5,602,325
40	exp double blind procedure/	193,251
41	exp single blind procedure/	45,524
42	exp triple blind procedure/	323
43	(((single or double or treble) adj10 mask) or dumm* or blind).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	381,024
44	exp crossover procedure/	69,709
45	((("cross over" or crossover) adj10 study) or studies or design* or method* or procedure or comparison).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	17,434,772
46	exp meta analysis/	241,582
47	exp "systematic review"/	337,473
48	exp biomedical technology assessment/	15,635
49	((systematic* adj3 review*) or overview*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	675,054
50	((methodologic* adj3 review*) or overview*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	239,691
51	((quantitative adj3 review*) or overview* or synthes*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	1,961,198
52	((research adj3 integrati*) or overview*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer,	239,352

Search line	Search term	Results
	drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	
53	((integrative adj3 review*) or overview*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	240,424
54	((collaborative adj3 review*) or overview*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	236,017
55	(pool* adj3 analy*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	41,504
56	((data adj1 synthes*) or extraction* or abstraction*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	566,436
57	(handsearch* or "hand search" or "hand searches" or "hand searching'" or "mantel haenszel" or peto or "der simonian" or dersimonian or "fixed effect" or "fixed effects" or "latin square" or "latin squares" or "meta analysis" or "meta analyses" or "met analysis" or "met analyses" or metaanaly* or metanaly* or "meta regression" or "meta regressions" or metaregression* or medline or cochrane or pubmed or medlars or embase or cinahl or Cochrane or "evidence report").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	616,231
58	((comparative adj3 efficacy) or effectiveness).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	985,084
59	("outcomes research" or "relative effectiveness").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	86,724
60	((indirect or "indirect treatment" or "mixed treatment") adj3 comparison).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade	4,314

Search line	Search term	Results
	name, keyword heading word, floating subheading word, candidate term word]	
61	37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60	20,355,911
62	36 and 61	6,834
63	limit 62 to dd=20200603-20220321	367
64	limit 63 to english language	365

PubMed: Search date 21 March 2022

Search line	Search term	Results
1	(("Systematic"[Filter] OR "meta-analysis"[Publication Type] OR "meta analysis as topic"[MeSH Terms] OR "meta analysis as topic"[MeSH Terms] OR "meta analy*"[Text Word] OR "metanaly*"[Text Word] OR "metaanaly*"[Text Word] OR "met analy*"[Text Word] OR "integrative research"[Title/Abstract] OR "integrative review*"[Title/Abstract] OR "integrative overview*"[Title/Abstract] OR "research integration*"[Title/Abstract] OR "research overview*"[Title/Abstract] OR "collaborative review*"[Title/Abstract] OR "collaborative overview*"[Title/Abstract] OR "systematic review*"[Title/Abstract] OR "comparative efficacy"[Title/Abstract] OR "comparative effectiveness"[Title/Abstract] OR "outcomes research"[Title/Abstract] OR "indirect comparison*"[Title/Abstract] OR "embase*"[Title/Abstract] OR "cinahl*"[Title/Abstract] OR "systematic overview*"[Title/Abstract] OR "methodological overview*"[Title/Abstract] OR "methodologic overview*"[Title/Abstract] OR "methodological review*"[Title/Abstract] OR "methodologic review*"[Title/Abstract] OR "quantitative review*"[Title/Abstract] OR "quantitative overview*"[Title/Abstract] OR "quantitative synthes*"[Title/Abstract] OR "pooled analy*"[Title/Abstract] OR "Cochrane"[Title/Abstract] OR "Medline"[Title/Abstract] OR "Pubmed"[Title/Abstract] OR "Medlars"[Title/Abstract] OR "handsearch*"[Title/Abstract] OR "hand search*"[Title/Abstract] OR "meta regression*"[Title/Abstract] OR "metaregression*"[Title/Abstract] OR "data synthes*"[Title/Abstract] OR "data extraction"[Title/Abstract] OR "data abstraction*"[Title/Abstract] OR "mantel haenszel"[Title/Abstract] OR "peto"[Title/Abstract] OR "der-simonian"[Title/Abstract] OR "dersimonian"[Title/Abstract] OR "fixed effect*"[Title/Abstract] OR "Cochrane Database Syst Rev"[All Fields]) AND (("clinical trial"[Publication Type] OR "meta-analysis"[Publication Type] OR "randomized controlled trial"[Publication Type] OR "systematic review"[Filter]) AND	113

Search line	Search term	Results
	2020/06/02:2022/03/15[Date - Publication] AND "english"[Language]) AND ((("body weight changes"[MeSH Terms] OR ("body"[All Fields] AND "weight"[All Fields] AND "changes"[All Fields]) OR "body weight changes"[All Fields] OR "weight loss"[MeSH Terms] OR "adipose tissue"[Title/Abstract] OR "fat"[Title/Abstract] OR "weight"[Title/Abstract]) AND "decrease*"[Title/Abstract]) OR "chang*"[Title/Abstract] OR "Loss"[Title/Abstract] OR "losing"[Title/Abstract] OR "reduc*"[Title/Abstract]) AND (("clinical trial"[Publication Type] OR "meta-analysis"[Publication Type] OR "randomized controlled trial"[Publication Type] OR "systematic review"[Filter]) AND 2020/06/02:2022/03/15[Date - Publication] AND "english"[Language]) AND (("Caloric Restriction"[MeSH Terms] OR "diet, ketogenic"[MeSH Terms] OR (("caloric reduction"[Title/Abstract] OR "calorie reduction"[Title/Abstract] OR "Caloric Restriction"[Title/Abstract] OR "calorie restriction"[Title/Abstract] OR "calories restriction"[Title/Abstract] OR "energy reduction"[Title/Abstract] OR "energy restriction"[Title/Abstract] OR "low caloric"[Title/Abstract] OR "low calorie"[Title/Abstract] OR "low calories"[Title/Abstract] OR "low energy"[Title/Abstract] OR "meal replacement"[Title/Abstract] OR "meal substitute"[Title/Abstract] OR "total replacement"[Title/Abstract]) AND ("diet"[Title/Abstract] OR "diets"[Title/Abstract])) OR "diet replacement"[Title/Abstract] OR "ketogenic diet"[Title/Abstract] OR "ketogenic diets"[Title/Abstract] OR "liquid diet"[Title/Abstract] OR "liquid diets"[Title/Abstract] OR "reducing diet"[Title/Abstract] OR "reducing diets"[Title/Abstract] OR ("total diet"[Title/Abstract] AND "replacement"[Title/Abstract]) OR "VLED"[Title/Abstract] OR "VLCD"[Title/Abstract] OR "LCD"[Title/Abstract]) AND 2020/06/02:2022/03/21[Date - Publication] AND "english"[Language]))	

Q3: Supplemental magnesium intake and risk of developing diarrhoea

Embase: Search date 22 March 2022

Search line	Search term	Results
1	exp magnesium/ or exp magnesium intake/ or exp magnesium salt/ or magnesium.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	170,061
2	exp tolerability/ or exp diarrhea/ or diarrhe*.mp. or diarrhoe*.mp. or disenter*.mp. or exp feces/ or feces.mp. or faec*.mp. or fecal.mp. or laxative.mp. or stool*.mp. or tolerab*.mp. or (osmotic adj3 effect*).mp.	794,548

Search line	Search term	Results
	[mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	
3	1 and 2	7,374
4	exp *magnesium/ or exp *magnesium salt/ or exp *magnesium intake/ or magnesium.ti.	40,091
5	(toxic* or intox* or overdose* or (risk* adj5 (assessment* or factor*)) or contra?indication* or safe$).mp. or adverse event/ or exp adverse drug reaction/ or intoxication/ or exp drug intoxication/ or exp drug overdose/ or exp toxicity/ or exp contraindication/ or risk*/ or exp risk factor/ or exp risk assessment/ or safety/ or exp patient safety/ or exp food safety/ or exp drug safety/ or adverse.mp. or ((undesirable or harm* or serious or negative or side or unwanted or untoward) adj5 (effect* or reaction* or event* or interaction* or outcome* or response* or sequala* or sequela*)).mp.	6,955,043
6	4 and 5	7,550
7	exp magnesium/ae or exp magnesium salt/ae	635
8	6 or 7	7,899
9	((exp Magnesium/ or exp magnesium salt/ or magnesium.mp.) and (exp dietary supplement/ or exp fortified food/ or diet*/)) or (magnesium adj3 (intak* or supplement* or therap* or diet*)).mp. or mg supplement*.mp. or mg fortified.mp. or exp magnesium intake/ or *magnesium,dt,fs/ or *magnesium salt,dt/	7,172
10	3 or 6 or 8 or 9	19,904
11	exp clinical trial/ or exp randomization/ or random*.ti,ab. or placebo.ti,ab. or trial.ti,ab. or group*.ti,ab. or (group1 and group 2).ti,ab.	7,708,463
12	exp *clinical trial/ or exp double blind procedure/ or exp single blind procedure/ or exp triple blind procedure/	287,992
13	((singl* or doubl* or trebl* or tripl*) adj10 (mask* or blind* or dumm*)).ti,ab.	268,735
14	exp crossover procedure/ or (cross?over adj10 (stud* or design* or method* or procedure* or comparison*)).ti,ab.	89,475
15	exp meta analysis/ or exp meta analysis/ or exp systematic review/ or exp *systematic review/ or exp biomedical technology assessment/	465,916
16	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*)) or (quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab. or (integrati* adj3 (review* or overview*)).ab,ti. or (collaborative adj3 (review* or overview*)).ti,ab. or (pool* adj3 analy*).ti,ab.	365,972

Search line	Search term	Results
17	((data adj1 (synthes* or extraction* or abstraction*)) or hand?search* or mantel Haenszel or peto or der?simonian or fixed effect* or latin square* or meta?analysis or meta?analyses or metaanaly* or metanaly* or meta?regression* or medline or Cochrane or pubmed or medlars or embase or cinahl).ti,ab. or Cochrane.jn. or evidence report.jn. or ((comparative adj3 (efficacy or effectiveness)) or outcomes research or relative effectiveness or ((indirect or indirect treatment or mixed treatment) adj3 comparison)).ti,ab.	440,299
18	11 or 12 or 13 or 14 or 15 or 16 or 17	8,122,938
19	10 and 18	8,586
20	19 and 2020:2022.(sa_year).	1,140

PubMed: Search date 22 March 2022

Search line	Search term	Results
1	Magnesium[Mesh] OR magnesium[tiab]	107,028
2	Diarrhea[Mesh] OR diarrhe*[tiab] OR diarrho*[tiab] OR dysenter*[tiab]OR "Feces"[Mesh] OR feces[tiab] OR fecal[tiab] OR faec*[tiab] OR laxative[tiab] OR stool* [tiab] OR osmotic effect*[tiab] OR tolerab*[tiab]	411,758
3	("Magnesium"[Mesh] OR magnesium[tiab]) AND ("Diarrhea"[Mesh] OR diarrhe* [tiab] OR diarrho*[tiab] OR dysenter*[tiab]OR "Feces"[Mesh] OR feces[tiab] OR fecal [tiab] OR faec*[tiab] OR laxative[tiab] OR stool*[tiab] OR osmotic effect*[tiab] OR tolerab*[tiab])	2,103
4	Magnesium[Majr] OR magnesium[ti]	36,201
5	Drug-Related Side Effects and Adverse Reactions[Mesh] OR Poisoning[Mesh] OR "Drug Hypersensitivity"[Mesh] OR "Drug Overdose"[Mesh] OR "Contraindications"[Mesh] OR "Risk"[Mesh] OR "Risk Factors"[Mesh] OR "Risk Assessment"[Mesh:noexp] OR "Safety"[Mesh:noexp]] OR "Patient Safety"[Mesh] OR "Food Safety"[Mesh] OR adverse[tiab] OR contraindication*[tiab] OR "contra indication*"[tiab] OR safe[tiab] OR safety[tiab] OR risk assessment*[tiab] OR risk factor* [tiab] OR ((undesirable[tiab] OR harm*[tiab] OR serious[tiab] OR negative[tiab] OR side [tiab] OR unwanted[tiab] OR untoward[tiab]) AND (effect*[tiab] OR reaction*[tiab] OR event*[tiab] OR interaction*[tiab] OR outcome*[tiab] OR response*[tiab] OR sequala* [tiab] OR sequela*[tiab]))	4,292,578
6	("Magnesium"[Majr] OR magnesium[ti]) AND ("Drug-Related Side Effects and Adverse Reactions"[Mesh] OR "Poisoning"[Mesh] OR "Drug Hypersensitivity"[Mesh] OR "Drug Overdose"[Mesh] OR	3,918

Search line	Search term	Results
	"Contraindications"[Mesh] OR "Risk"[Mesh] OR "Risk Factors"[Mesh] OR "Risk Assessment"[Mesh:NoExp] OR "Safety"[Mesh:NoExp] OR "Patient Safety"[Mesh] OR "Food Safety"[Mesh] OR adverse[tiab] OR contraindication* [tiab] OR "contra indication*"[tiab] OR safe[tiab] OR safety[tiab] OR risk assessment* [tiab] OR risk factor*[tiab] OR ((undesirable[tiab] OR harm*[tiab] OR serious[tiab] OR negative[tiab] OR side[tiab] OR unwanted[tiab] OR untoward[tiab]) AND (effect*[tiab] OR reaction*[tiab] OR event*[tiab] OR interaction*[tiab] OR outcome*[tiab] OR response*[tiab] OR sequala*[tiab] OR sequela*[tiab])))	
7	"magnesium/adverse effects"[MeSH Terms] OR "magnesium/poisoning"[MeSH Terms] OR "magnesium/toxicity"[MeSH Terms]	612
8	(("Magnesium"[Majr] OR magnesium[ti]) AND ("Drug-Related Side Effects and Adverse Reactions"[Mesh] OR "Poisoning"[Mesh] OR "Drug Hypersensitivity"[Mesh] OR "Drug Overdose"[Mesh] OR "Contraindications"[Mesh] OR "Risk"[Mesh] OR "Risk Factors"[Mesh] OR "Risk Assessment"[Mesh:NoExp] OR "Safety"[Mesh:NoExp] OR "Patient Safety"[Mesh] OR "Food Safety"[Mesh] OR adverse[tiab] OR contraindication* [tiab] OR "contra indication*"[tiab] OR safe[tiab] OR safety[tiab] OR risk assessment* [tiab] OR risk factor*[tiab] OR ((undesirable[tiab] OR harm*[tiab] OR serious[tiab] OR negative[tiab] OR side[tiab] OR unwanted[tiab] OR untoward[tiab]) AND (effect*[tiab] OR reaction*[tiab] OR event*[tiab] OR interaction*[tiab] OR outcome*[tiab] OR response*[tiab] OR sequala*[tiab] OR sequela*[tiab])))) OR ("magnesium/adverse effects"[MeSH Terms] OR "magnesium/poisoning"[MeSH Terms] OR "magnesium/toxicity"[MeSH Terms])	901
9	(("Magnesium"[Mesh] OR Magnesium[tiab]) AND ("Dietary Supplements"[Mesh:noexp] OR "Food, Fortified"[Mesh] OR "Diet"[Mesh:NoExp] OR diet* [tiab] OR intak*[tiab] OR supplement*[tiab] OR therap*[tiab])) OR "Mg supplement*"[tiab] OR "Mg fortified"[tiab] OR "Magnesium/therapeutic use"[Mesh]	20,611
10	#3 OR #8 OR #9	23,857
11	”clinical trial”[pt] OR “Random Allocation”[Mesh] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR (group 1[tiab] AND group 2[tiab]) OR “Clinical Trials as Topic”[Mesh] OR “Double-Blind Method”[Mesh] OR “Single-Blind Method”[Mesh] OR ((singl*[tiab] OR doubl*[tiab] OR trebl*[tiab] OR tripl*[tiab]) AND (mask*[tiab] OR blind*[tiab] OR dumm*[tiab])) OR “Cross-Over Studies”[Mesh] OR ((crossover[tiab] OR “cross	

Search line	Search term	Results
	over"[tiab]) AND (study[tiab] OR studies[tiab] OR design*[tiab] OR method*[tiab] OR procedure[tiab] OR comparison [tiab]))	
12	systematic[sb] OR meta-analysis[pt] OR meta-analysis as topic[Mesh] OR metaanalysis[Mesh] OR meta analy*[tw] OR metanaly*[tw] OR metaanaly*[tw] OR met analy*[tw] OR integrative research[tiab] OR integrative review*[tiab] OR integrative overview*[tiab] OR research integration*[tiab] OR research overview*[tiab] OR collaborative review*[tiab] OR collaborative overview*[tiab] OR systematic review*[tiab] OR comparative efficacy[tiab] OR comparative effectiveness[tiab] OR outcomes research [tiab] OR indirect comparison*[tiab] OR Embase*[tiab] OR Cinahl*[tiab] OR systematic overview*[tiab] OR methodological overview*[tiab] OR methodologic overview*[tiab] OR methodological review*[tiab] OR methodologic review*[tiab] OR quantitative review* [tiab] OR quantitative overview*[tiab] OR quantitative synthes*[tiab] OR pooled analy* [tiab] OR Cochrane[tiab] OR Medline[tiab] OR Pubmed[tiab] OR Medlars[tiab] OR handsearch*[tiab] OR hand search*[tiab] OR meta-regression*[tiab] OR metaregression* [tiab] OR data synthes*[tiab] OR data extraction[tiab] OR data abstraction*[tiab] OR mantel haenszel[tiab] OR peto[tiab] OR der-simonian[tiab] OR dersimonian[tiab] OR fixed effect*[tiab] OR "Cochrane Database Syst Rev"[Journal:__jrid21711]	536,217
13	#11 OR #12	5,444,830
14	#10 AND #13	8,359
15	(#14) AND (English[Language])	6,919
16	#15 AND (human* OR humans [Mesh])	4,833
17	(#16) AND (("2020/06/22"[Date - Create] : "3000"[Date - Create]))	390

Q4: Fat content of energy-restricted diets and risk of gallstone formation

Embase: Search date 24 March 2022

Search line	Search term	Results
1	(exp *low calorie diet/ or exp *very low calorie diet/ or exp *elimination diet/ or exp liquid diet/ or (low adj3 (calori* or energy or elimination) adj5 diet*).mp. or vlcd.mp. or vled.mp. or lcd.mp. or ((ketogenic or replacement or meal substitute or liquid) adj5 diet*).mp. or reducing diet*.mp. or ((calori* or energ*) adj3 (reduc* or restrict*)).mp.) adj5 diet*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name,	33,090

Search line	Search term	Results
	keyword heading word, floating subheading word, candidate term word]	
2	exp biliary sludge/ or exp cholelithiasis/ or exp gallbladder/ or exp gallbladder function/ or ((bile or biliary) adj3 (calculus or calculi or sludge*)).mp. or cholelith*.mp. or cholecystolithias*.mp. or gall?bladder*.mp. or gall?sludge*.mp. or gall?stone*.mp. or vesica biliaris.mp. or vesica fellea.mp.	111,132
3	1 and 2	207
4	3 and 2020:2022.(sa_year).	30

PubMed: Search date 24 March 2022

Search line	Search term	Results
1	"Caloric Restriction"[Mesh] OR "Diet, Ketogenic"[Mesh] OR (("caloric reduction"[tiab] OR calorie* reduction[tiab] "caloric restriction"[tiab] OR calorie* restriction[tiab] OR "energy reduction"[tiab] OR "energy restriction"[tiab] OR "low caloric"[tiab] OR "low calorie*"[tiab] OR "low energy"[tiab] OR "meal replacement"[tiab] OR "meal substitute"[tiab] OR "total replacement"[tiab]) AND diet*[tiab]) OR "diet replacement"[tiab] OR "ketogenic diet*"[tiab] OR "liquid diet*"[tiab] OR "reducing diet*"[tiab] OR ("total diet"[tiab] AND replacement[tiab]) OR VLED[tiab] OR VLCD[tiab] OR LCD[tiab]	25,022
2	"Cholecystolithiasis"[Mesh] OR "Gallbladder"[Mesh] OR "Gallbladder Emptying"[Mesh] OR "Gallstones"[Mesh] OR "bile duct calcul*"[tiab] OR "bile duct sludge*"[tiab] OR "bile calcul*"[tiab] OR "bile sludge*"[tiab] OR "biliary calcul*"[tiab] OR "biliary sludge"[tiab] OR "biliary system calcul*"[tiab] OR "biliary system sludge*"[tiab] OR cholelith*[tiab] OR cholecystolithias*[tiab] OR gallbladder*[tiab] OR "gall bladder*"[tiab] OR gallsludge[tiab] OR "gall sludge*"[tiab] OR gallstone*[tiab] OR "gall stone*"[tiab] OR "vesica biliaris"[tiab] OR "vesica fellea"[tiab]	71,746
3	#1 AND #2	84
4	#3 AND Human*	69
5	#4 AND (("2020/06/22"[Date - Create] : "3000"[Date - Create]))	2
6	#3 AND #5	2

Annex 5: Eligibility criteria

Q1: Linoleic acid and alpha-linolenic acid concentrations in adipose tissue and their release from adipose tissue

Category	Included	Excluded	EFSA statement (2021) protocol amendments
Population	• study populations living in Europe or US • adults not on an intentionally modified diet (irrespective of weight status) AND • healthy subjects or overweight or obese individuals with hypertension, hyperlipidaemia or type 2 diabetes mellitus (T2DM), but no other disease Medication use should be restricted to medicines related to these diseases.	• study populations living outside Europe or US • infants, children and adolescents, pregnant and lactating women • studies on patients except for diseases included (as they may have an effect on the outcome of interest)	Protocol amendment (2): A hand search in the pertinent references was also performed from which relevant studies conducted in the US were taken into account, given the limited references found in humans in Europe.
Intervention/ Exposure	None	None	None
Outcomes	• studies on fatty acid (FA) composition of subcutaneous (SC) adipose tissue (AT) in which samples were taken by biopsies or from visceral (VC) AT taken during surgery or autopsy (including	• studies on dietary FA or FA intake only • studies on FA concentration not measured in AT, for example, in liver, muscle, brain, bone marrow • studies on plasma free FA only	None

Category	Included	Excluded	EFSA statement (2021) protocol amendments
	subsequent gas chromatography or other methods of sample analysis) • studies on FA composition of SC AT before and after weight loss • studies on FA release during weight loss or in the fasting state via microdialysis of the tissue of interest or using isotopes to study the fate of the FA in metabolism		
Study type and design	• human intervention (clinical trials) • observational studies (prospective, retrospective, cross sectional, case report, case series, case control)	• systematic reviews[8] • meta-analyses[8] • narrative reviews • animal studies • *in vitro* studies • studies on cells	None
Literature type	• peer-reviewed papers published in scientific or medical journals (except contributions from stakeholders and interested parties)	• protocols (as no results are reported) • commentaries • editorials • letters to the editor • grey literature (PhD theses, extended abstracts, conference proceedings), or other publications not peer-reviewed (except contributions from stakeholders and interested parties)	None

[8] Relevant systematic reviews and meta-analyses were included for hand searching then excluded

Category	Included	Excluded	EFSA statement (2021) protocol amendments
Date	• 8 June 2020 to present	• published 7 June 2020 or earlier	None
Language	• English	• languages other than English	None

Full text screening

To be finally included:

- quantitative data on LA (18:2 (n-6)) and/or ALA (18:3 (n-3)) concentration of AT
- preferably full-text papers should report on the study population characteristics (including age, sex), diet, weight and health status to be included. For large observational studies, this information may be provided in other publications on the same studies

Additional reasons for exclusion:

- studies not reporting on LA and/or ALA quantitatively in SC AT or VC AT
- inappropriate method of measurement

Q2: Range of weight loss when consuming total diet replacements for weight control

Category	Included	Excluded
Population	• studies including populations from Europe and US • overweight or obese adults without apparent co-morbidity, or with hypertension, hyperlipidaemia, T2DM, but no other disease Medication use should be restricted to medicines related to these diseases.	• study populations living outside Europe or US • infants, children and adolescents, pregnant and lactating women • normal weight and/or lean subjects (BMI below 25) • studies on subjects with catabolic diseases (such as cancer) should be excluded, as these diseases may have an effect on the outcome of interest) • studies undertaken after bariatric surgery
Intervention/ Exposure	• TDRs with an energy content between 600 and 1,200 kcal (2,510 to 5,020kJ per day) and that report on weight loss As the terms 'total diet replacement' are rarely present in the abstracts, studies on 'total meal replacement', 'very low calorie diet' or 'low calorie diet' will be included at title and abstract screening if the diet investigated is in the energy range as specified in the Regulation. TDRs may have been consumed with or without added/supplemental vitamins and/or minerals (considering vitamins and/or minerals will not have an effect on weight loss). TDRs could have been consumed before bariatric surgery.	• studies on weight loss following diets not based on specifically designed foods, for example Atkins, DASH, Paleolithic, Mediterranean, 'low carb', 'low fat', vegetarian, ketogenic (if not with specially designed foods), low glycaemic diet (if not with specially designed foods/TDR) or 'low calorie'/'low energy'/'hypocaloric'/'energy-restricted' diets using usual foods for example almonds, dairy, liquorice • studies on intermittent fasting • studies in which TDR/energy-restricted diets was consumed in combination with a medication for weight loss in all groups or with training/physical activity/exercise, or counselling/group sessions or with other foods (even if in limited amounts) in all groups (no arm with TDR/energy-restricted diet and without co-intervention) • studies on meal replacements (also called 'partial meal replacement'), as these are not covered by the Regulation

Category	Included	Excluded
		• studies not using a specifically formulated product (TDRs) or products with an energy content outside the range as specified in the Regulation
Outcomes	• change in body weight loss or fat mass - measured by investigators and reported for any time point up to 8 weeks • compliance - how it was and how many individuals were compliant Hydrostatic underwater weighing was considered an appropriate method (EFSA, 2021).	None Bioelectrical impedance analysis was not considered an appropriate method (EFSA, 2021).
Study type and design	• human intervention studies (clinical trials, including single arm trials)	• systematic reviews[8] • meta-analyses[8] • narrative reviews • animal studies • *in vitro* studies • observational studies for example surveys, case reports, case-series, prospective cohort, case-control, retrospective
Literature type	• peer-reviewed papers published in scientific or medical journals (except contributions from stakeholders and interested parties)	• protocols (as no results are reported) • commentaries • editorials • letters to the editor • grey literature (PhD theses, extended abstracts, conference proceedings), or other publication types not peer-reviewed (except contributions from stakeholders and interested parties)

Category	Included	Excluded
Date	• 2 June 2020 to present	• published 1 June 2020 or earlier
Language	• English	• languages other than English

Screening

- As abstracts sometimes do not provide information in a harmonised and/or detailed way, the following criteria will be applied:
  - the maximal duration of the studies included at title and abstract level should be less than 6 months (no minimal duration expected)
  - abstracts of studies only mentioning the daily energy restriction/deficit (compared to the initial diet) will be included for full-text screening if this deficit is of at least -800kcal per day (-3,347kJ per day), is expressed in absolute amount, or at least -40% energy per day if expressed as a percentage
  - if the abstracts report the energy intake per kg body weight, the 'rule of thumb' to decide if the inclusion or exclusion at the next step is to multiply by 60kg to calculate the calories per day

Full text screening

- For full-text screening, additional criteria are:
  - studies in which body weight (or fat mass) is measured by investigators (in other words, no self-reported body weight) using validated and standardised methods, before and immediately after energy restriction
  - studies that report on the amount of weight loss, the caloric content of the TDR administered and the duration of the energy restriction
  - studies that report on weight loss up to and including 2 months
  - studies that report on compliance and how compliance was assessed

- Preferably, full-text papers should report on the study population characteristics (including age, sex), diet, weight and health status

Q3: Supplemental magnesium intake and risk of developing diarrhoea

Category	Included	Excluded	EFSA statement (2021) protocol amendments
Population	• studies including populations from Europe and US • healthy or defined as overweight/obese subjects presenting with hypertension, hyperlipidaemia or T2DM • non-overweight/non-obese subjects with mild hypertension and not on medication	• study populations living outside Europe or US • infants, children and adolescents, pregnant and lactating women • studies on patients except for diseases included (as they may have an effect on the outcome of interest)	Protocol amendment (4): In addition, the Panel also considered studies conducted in non-overweight/non-obese individuals with mild to moderate hypertension treated with diet only that would have not met the original inclusion criteria of healthy non-overweight/non-obese individuals.
Intervention/ Exposure	• different levels of supplemental or Mg intentionally added to food (possibly including a placebo) administered orally • trials in which only the amount of Mg consumed between groups differ For example Mg versus placebo, Mg versus Mg (different doses and/or quantities).	• studies comparing similar doses of different forms of Mg • studies that investigate the effect of Mg in combination with other substances • Mg naturally present in food (as the UL for Mg set by SCF only applies to readily dissociable Mg salts) • non oral administration of Mg (such as injection, perfusion, infusion, nebulisation, intra-muscular, intrathecal, intravenous or intraperitoneal administration, transdermal administration, bioresorbable devices, placental	None

Category	Included	Excluded	EFSA statement (2021) protocol amendments
		transfer), including those with an initial parenteral Mg administration • studies not on the subject of interest, for example on Mg content of foods or breast milk, on Mg deficiency/insufficiency/ hypomagnesaemia, or on Mg status/ biomarkers/adequacy	
Outcomes	• adverse effects associated with Mg administration	None	None
Study type and design	• human intervention studies (clinical trials) with at least two arms • cross-over studies	• single arm studies • systematic reviews[8] • meta-analyses[8] • narrative reviews • animal studies • *in vitro* studies • studies on cells • observational studies	Protocol amendment (3): Cross-over studies were included as no studies were identified reporting on the criteria for diagnosis of diarrhoea and applying the WHO criteria.
Literature type	• peer-reviewed papers published in scientific or medical journals (except contributions from stakeholders and interested parties	• protocols (as no results are reported) • commentaries • editorials • letters to the editor	None

Category	Included	Excluded	EFSA statement (2021) protocol amendments
		• grey literature (PhD theses, extended abstracts, conference proceedings), or other publications not peer-reviewed (except contributions from stakeholders and interested parties)	
Date	• 22 June 2020 to present	• published 21 June 2020 or earlier	None
Language	• English	• languages other than English	None

Screening

- studies included at title and abstract level may report on adverse effects only at full-text level

Full text screening

To be finally included:

- studies for which the full texts report on various adverse effects but not diarrhoea will be also considered as relevant for inclusion
- studies that report on the definition of diarrhoea (applying the World Health Organization (WHO) criteria). For the full-text screening, trials reporting on Mg administration and (the severity of) diarrhoea should preferably report on the frequency and consistency of the stools using validated assessment methods and documenting diarrhoea by the frequency of ≥3 loose or watery stools per day. Hence, a ranking of the final included studies may be made, distinguishing those with a reliable outcome assessment from those with an unreliable outcome assessment or improper reporting
- after full-text screening, included studies should specify (among other parameters) the Mg dose and duration of administration in all groups
- preferably, full-text papers should report on the study population characteristics (including age, sex), diet, weight and health status to be included

Additional reasons for exclusion:

- publications not reporting on the Mg dose and duration of consumption
- publications not reporting on adverse events

Q4: Fat content of energy-restricted diets and risk of gallstone formation

Category	Included	Excluded	EFSA statement (2021) protocol amendments
Population	• studies including populations from Europe and US • adults	• study populations living outside Europe or US • infants, children and adolescents, pregnant and lactating women. • studies on patients except for diseases included	None
Intervention/ Exposure	• at least two different fat contents of energy-restricted diets, or • at least two test meals with varying fat content (on gallbladder emptying)	None	None
Outcomes	• risk of gallstone formation • risk of biliary sludge formation • gallbladder emptying	None	None
Study type and design	• human intervention studies (clinical trials) with at least two arms • single arm intervention studies (supportive evidence only) • observational studies (supportive evidence only)	• single arm studies • systematic reviews[8] • meta-analyses[8] • narrative reviews • animal studies • *in vitro* studies • studies on cells • observational studies	Protocol amendment (5): Observational and interventional studies either single arm or with only one arm consuming a TDR without co-intervention were considered as supportive evidence in relation to gallstone formation, biliary sludge formation and/or gallbladder emptying.

Category	Included	Excluded	EFSA statement (2021) protocol amendments
Literature type	• peer-reviewed papers published in scientific or medical journals (except contributions from stakeholders and interested parties)	• protocols (as no results are reported) • commentaries • editorials • letters to the editor • grey literature (PhD theses, extended abstracts, conference proceedings), or other publications not peer-reviewed (except contributions from stakeholders and interested parties)	None
Date	• 9 December 2020 to present	• published 8 December 2020 or earlier	None
Language	• English	• languages other than English	None

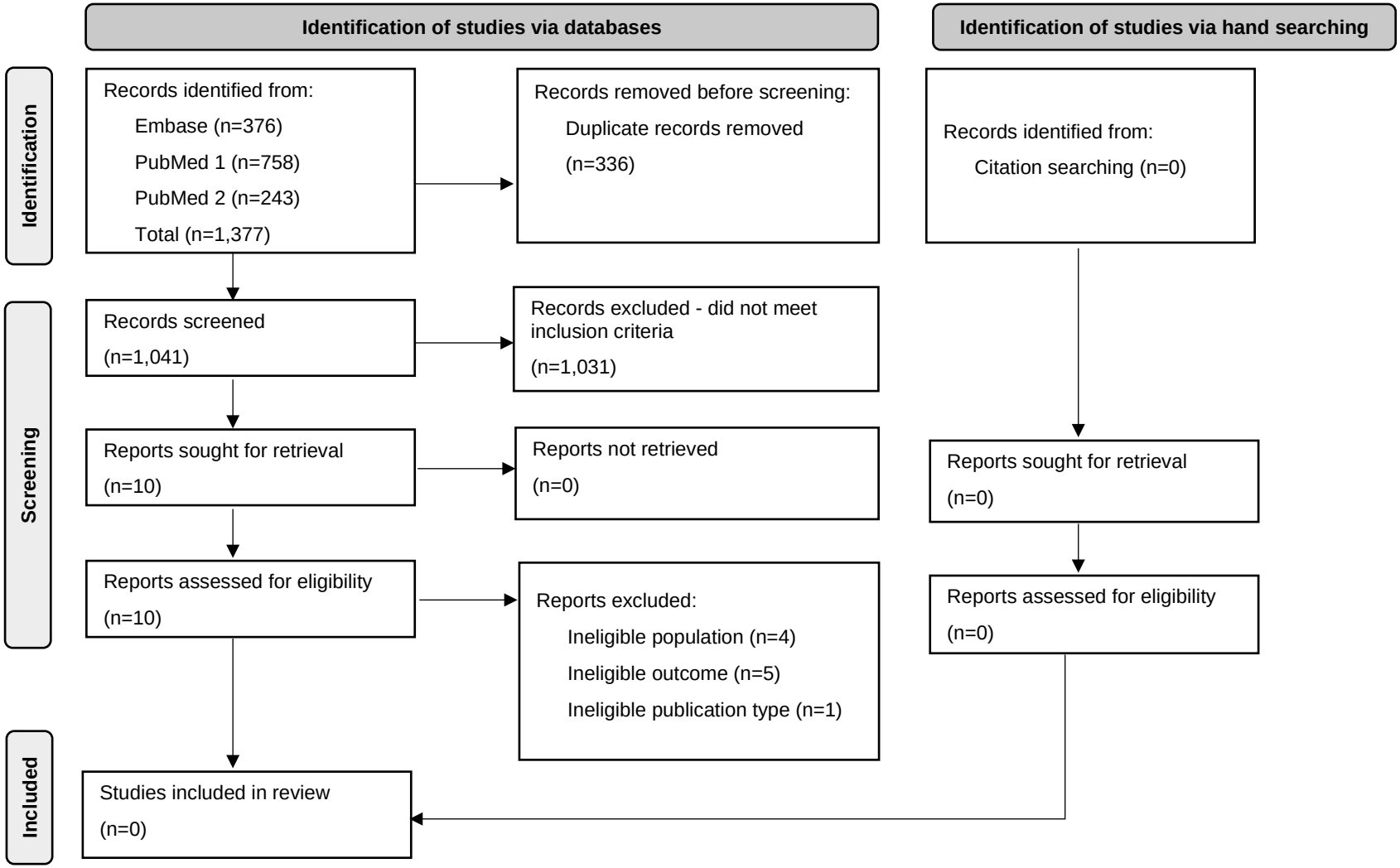
Full text screening

To be finally included:

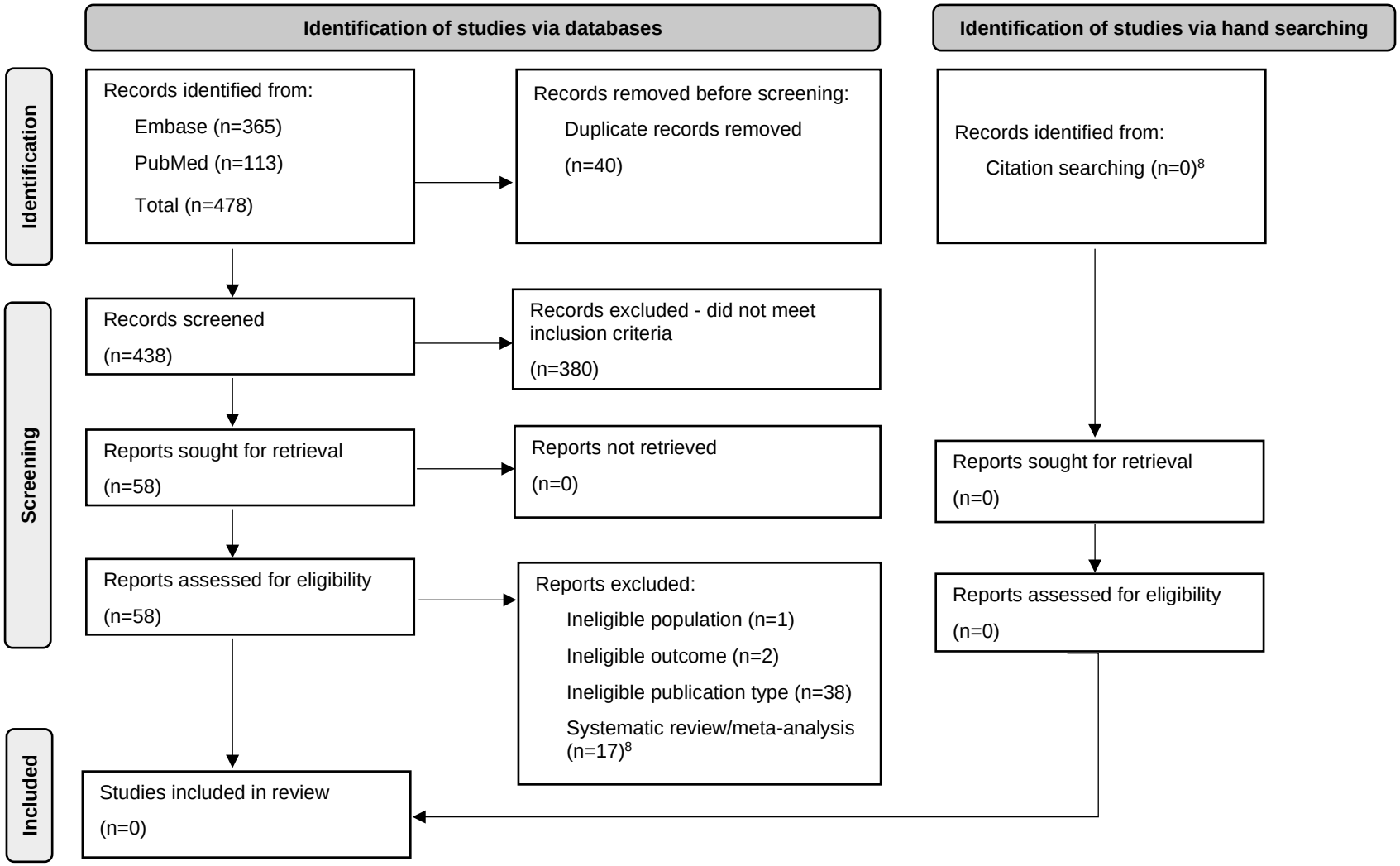
- studies that report on the fat and caloric content of the diet per day and the duration of the dietary intake
- preferably, full-text papers should report on the study population characteristics (including age, sex), diet, weight and health status to be included

Annex 6: PRISMA flow diagrams

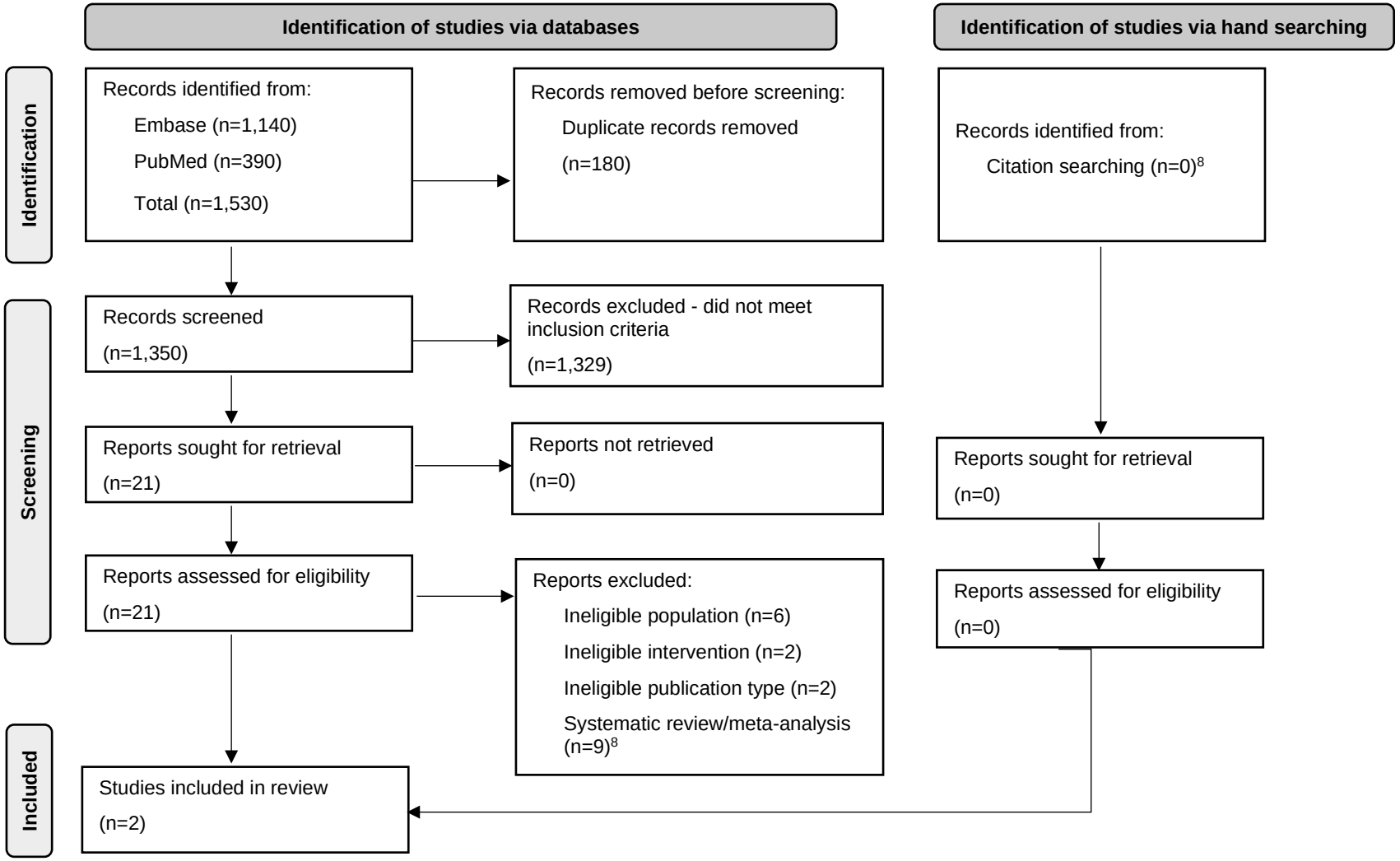
Q1: Linoleic acid and alpha-linolenic acid concentrations in adipose tissue and their release from adipose tissue



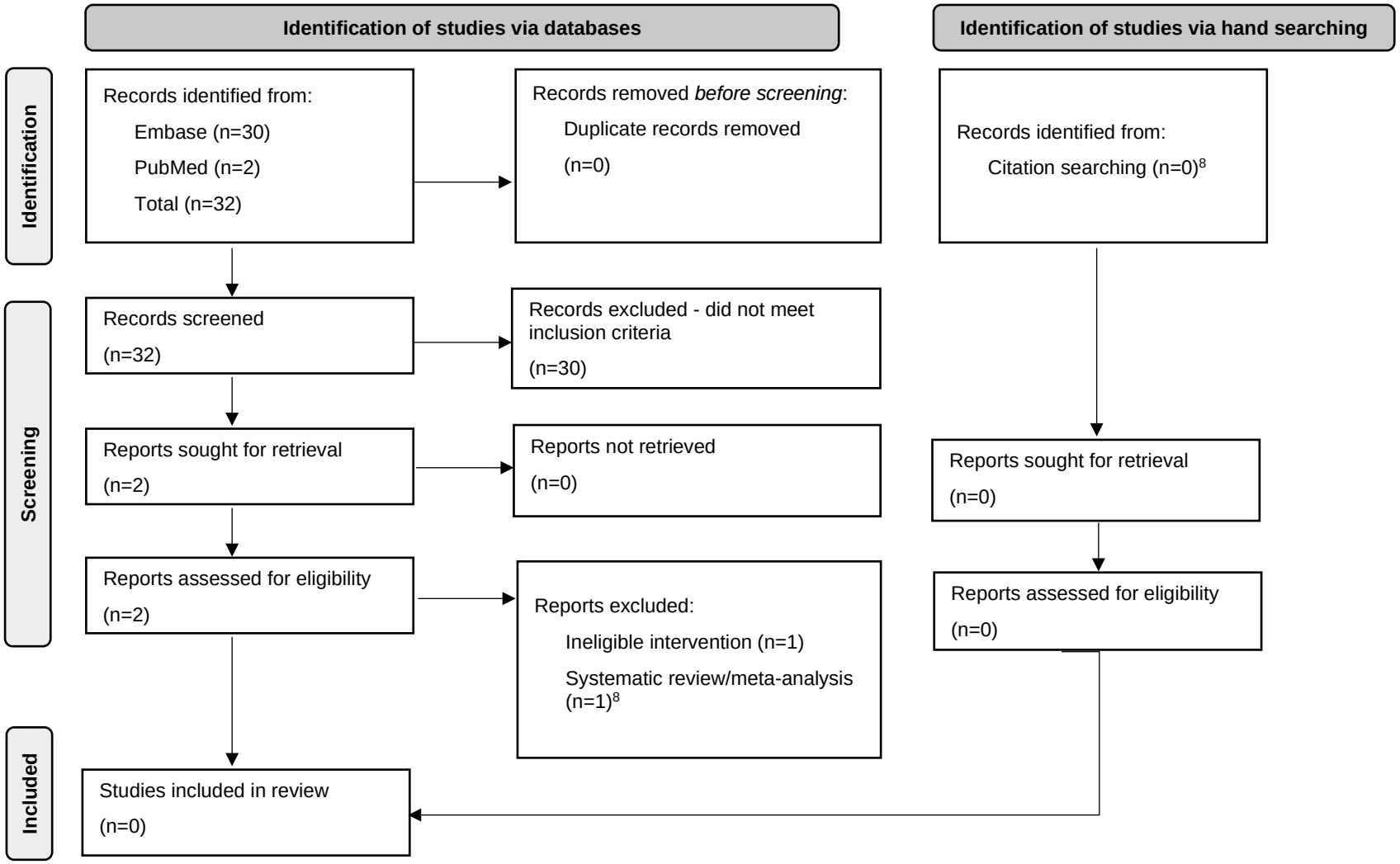
Q2: Range of weight loss when consuming total diet replacements for weight control



Q3: Supplemental magnesium intake and risk of developing diarrhoea



Q4: Fat content of energy-restricted diets and risk of gallstone formation



Abbreviations

AE	Adverse event
AI	Adequate intake
ALA	Alpha-linolenic acid
AR	Average requirement
COMA	Committee on Medical Aspects of Food Policy
DHSC	Department of Health and Social Care
DRV	Dietary reference value
EAR	Estimated Average Requirement
EFA	Essential fatty acid
EFSA	European Food Safety Authority
KLS	Knowledge and Library Services
LA	Linoleic acid
LRNI	Lower reference nutrient intake
Mg	Magnesium
NIP	Ireland/Northern Ireland Protocol
NLCS	Nutrition Related Labelling, Composition and Standards
OHID	Office for Health Improvement and Disparities
PICOS	Population, Intervention, Comparator, Outcome, Study Design
PRI	Population reference intake
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PUFA	Polyunsaturated fatty acids
RNI	Reference nutrient intake
SACN	Scientific Advisory Committee on Nutrition
T2DM	Type 2 diabetes mellitus
TDMR	Total Diet and Meal Replacements
TDR	Total Diet Replacement
UKHSA	UK Health Security Agency
UKNHCC	UK Nutrition and Health Claims Committee