Consultation on draft scope – deadline for comments 11:59pm on 01/06/2025 **email: MASLD@nice.org.uk**

Checklist for submitting comments

- Use this comment form and submit it as a **Word document (not a PDF)**.
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Include **page and line number (not section number)** of the text each comment is about.
- Combine all comments from your organisation into 1 response. **We cannot accept more than 1 comments form from each organisation**.
- Do not paste other tables into this table – type directly into the table.
- Ensure each comment stands alone; do not cross-refer within one comment to another comment.
- **Clearly mark any confidential information or other material that you do not wish to be made public with underlining and highlighting. Also, ensure you state in your email to NICE that your submission includes confidential comments.**
- **Do not name or identify any person or include medical information about yourself or another person** from which you or the person could be identified as all such data will be deleted or redacted.
- Spell out any abbreviations you use
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- **We do not accept comments submitted after the deadline stated for close of consultation.**

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory Committees.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly or arrive after the deadline. In addition to your comments below, we would like to hear your views on these questions: 1. Are there any cost saving interventions or examples of innovative approaches that should be considered for inclusion in this guideline? 2. The current guideline (NG49) recommends that, in secondary and tertiary care settings, pharmacological treatment with pioglitazone or vitamin E may be considered for adults with NAFLD (MASLD) and advanced liver fibrosis. The use of pioglitazone and vitamin E in the current guideline recommendations is off label. To what extent are the pioglitazone and vitamin E currently used in clinical practice for adults with advanced liver fibrosis and why? Please share any information about local clinical pathways you are aware of. Developing NICE guidance: how to get involved has a list of possible areas for comment on the draft scope.
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please specify).	British Association for Nutrition and Lifestyle Medicine
Disclosure (please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry).	None
Name of person completing form	Dr Susan McGInty

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Comment number	Page number or **'general'** for comments on the whole document	Line number or **'general'** for comments on the whole document	**Comments** Insert each comment in a new row. Do not paste other tables into this table, as your comments could get lost – type directly into this table.
1	General	General	First paragraph of the draft scope refers to making new recommendation or updating existing recommendations on lifestyle modifications for MASLD. This is welcome as the aetiology and progression of MASLD is largely lifestyle driven. Reducing liver fat through dietary and lifestyle modification requires improvement in insulin sensitivity and glycaemic control. It is therefore both inconsistent and unsafe for the scope to exclude updating 1.2.12 to 1.2.14. NICE NG246 Obesity and Weight Management Guidance published in January 2025 is restrictive in scope: it does not include up to date reviews on evidence relating to non-nutritive sweeteners, high glycaemic diets and specific nutrients which contribute to insulin resistance and fatty liver deposits. Nor does it include markers for insulin sensitivity or inflammation. Therefore the recommendations in NG246 are suitable only for those who are overweight or obese but metabolically healthy. It is unsafe to refer to NG246 for improvements in metabolic health. Lean MASLD makes up to 20% of MASLD cases overall which reinforces that body mass is unreliable as a predictor for metabolic health. References: 1. Kenneally, S., Sier, J. H., & Moore, J. B. (2017). Efficacy of dietary and physical activity intervention in non-alcoholic fatty liver disease: A systematic review. *BMJ Open Gastroenterology, 4*(1), e000139. 2. Romero-Gómez, M., Zelber-Sagi, S., Martín, F., Bugianesi, E., & Soria, B. (2023). Nutrition could prevent or promote non-alcoholic fatty liver disease: An opportunity for intervention. *The BMJ, 383*, e075179. 3. Xia, Y., Wu, Q., Dai, H., Lv, J., Liu, Y., Sun, H., Jiang, Y., Chang, Q., Niu, K., & Zhao, Y. (2021). Associations of nutritional, lifestyle, and metabolic factors with non-alcoholic fatty liver disease: An umbrella review with more than 380,000 participants. *Frontiers in Nutrition, 8*, 642509. 4. Maier S, Wieland A, Cree-Green M, Nadeau K, Sullivan S, Lanaspa MA, Johnson RJ, Jensen T. Lean NAFLD: an underrecognized and challenging disorder in medicine. Rev Endocr Metab Disord. 2021 Jun;22(2):351-366. doi: 10.1007/s11154-020-09621-1. Epub 2021 Jan 3. PMID: 33389543; PMCID: PMC8893229.

2	General	General	Review of evidence for 1.2.15 and 1.2.16 should include a much wider field of lifestyle intervention than just exercise and alcohol.
3	5	1.1.1	Should stipulate that while MASLD is often associated with obesity and overweight, about 20% of cases are classified as Lean MASLD. Reference: Maier S, Wieland A, Cree-Green M, Nadeau K, Sullivan S, Lanaspa MA, Johnson RJ, Jensen T. Lean NAFLD: an underrecognized and challenging disorder in medicine. Rev Endocr Metab Disord. 2021 Jun;22(2):351-366. doi: 10.1007/s11154-020-09621-1. Epub 2021 Jan 3. PMID: 33389543; PMCID: PMC8893229.
4	7	1.2.5	Propose expanding to: Refer adults and young people diagnosed with advanced liver fibrosis to a relevant specialist in hepatology and a dietitian or registered nutritionist for assessment of homocysteine status and nutritional interventions. Rationale: Homocysteine plays a significant role in hepatic fibrosis. by promoting hepatic stellate cell (HSC) activation, increasing oxidative stress, and stimulating extracellular matrix deposition. Higher plasma homocysteine concentrations correlate with more severe liver fibrosis. References: 1. Zou, CG., Gao, SY., Zhao, YS. *et al.* Homocysteine enhances cell proliferation in hepatic myofibroblastic stellate cells. *J Mol Med* **87**, 75–84 (2009). https://doi.org/10.1007/s00109-008-0407-2 2. Suzuki A, Henao R, Reed MC, Nijhout HF, Tripathi M, Singh BK, Yen PM, Diehl AM, Abdelmalek MF. Lower hepatic *CBS* and *PEMT* expression in advanced NAFLD: inferencing strategies to lower homocysteine with a mathematical model. *Metab Target Organ Damage*. 2024;4:21. http://dx.doi.org/10.20517/mtod.2024.16

4	8	1.2.12	Evidence for review on dietary advice to include low glycaemic and lower carbohydrate diets (than those recommended in the Eatwell Guide), which include mediterranean and ketogenic diets, to improve insulin sensitivity and reduce hepatic fat accumulation. The Eatwell Guide provides general dietary recommendations for a balanced diet, but there are several arguments against using it as a clinical model for individualised patient care for MASLD: 1. Lack of Personalisation – The Eatwell Guide is designed for population-wide health rather than individualised medical needs. MASLD patients often require tailored dietary interventions based on their metabolic profile, insulin resistance, and liver function. 2. Carbohydrate emphasis – The guide promotes starchy carbohydrates (e.g., bread, rice, pasta, potatoes), which may not be ideal for MASLD patients who benefit from lower carbohydrate intake to reduce liver fat accumulation. 3. Limited focus on specific nutrients – MASLD management often requires targeted nutrient modifications, such as higher omega-3 intake, lower fructose consumption, and specific micronutrient adjustments (e.g., vitamin D, choline). The Eatwell Guide does not emphasize these aspects. 4. Fats recommendations – The guide suggests reducing fat intake, but NMASLD patients may benefit from healthy fats (e.g., monounsaturated and polyunsaturated fats) to improve liver health. A Mediterranean-style diet is often recommended instead. 5. Insufficient guidance on highly processed foods – While the Eatwell Guide advises limiting high-fat, high-sugar foods, it does not provide specific restrictions on ultra-processed foods, which are linked to worsening MASLD outcomes. It gives no advice on what constitutes minimally processed whole grains.

5	8	1.2.12	Fructose and digestible maltodextrins should be highlighted for particular review and advice: - Excessive fructose intake contributes to hepatic lipid accumulation and worsens insulin resistance, particularly in paediatric fatty liver disease. - Digestible maltodextrins, as high-GI carbohydrates, trigger blood glucose spikes, increase insulin secretion, and may lead to insulin resistance through lipogenesis, inflammation, and gut microbiota disruption. References: 1. Hrncir T, Trckova E, Hrncirova L. Synergistic Effects of Fructose and Food Preservatives on Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD): From Gut Microbiome Alterations to Hepatic Gene Expression. Nutrients. 2024 Oct 30;16(21):3722. doi: 10.3390/nu16213722. PMID: 39519554; PMCID: PMC11547954. 2. Jensen T, Abdelmalek MF, Sullivan S, Nadeau KJ, Green M, Roncal C, Nakagawa T, Kuwabara M, Sato Y, Kang DH, Tolan DR, Sanchez-Lozada LG, Rosen HR, Lanaspa MA, Diehl AM, Johnson RJ. Fructose and sugar: A major mediator of non-alcoholic fatty liver disease. J Hepatol. 2018 May;68(5):1063-1075. doi: 10.1016/j.jhep.2018.01.019. Epub 2018 Feb 2. PMID: 29408694; PMCID: PMC5893377. 3. Page KA, Chan O, Arora J, Belfort-Deaguiar R, Dzuira J, Roehmholdt B, Cline GW, Naik S, Sinha R, Constable RT, Sherwin RS. Effects of fructose vs glucose on regional cerebral blood flow in brain regions involved with appetite and reward pathways. JAMA. 2013 Jan 2;309(1):63-70. doi: 10.1001/jama.2012.116975. Erratum in: JAMA. 2013 May 1;309(17):1773. PMID: 23280226; PMCID: PMC4076145. 4. Schwarz JM, Noworolski SM, Erkin-Cakmak A, Korn NJ, Wen MJ, Tai VW, Jones GM, Palii SP, Velasco-Alin M, Pan K, Patterson BW, Gugliucci A, Lustig RH, Mulligan K. Effects of Dietary Fructose Restriction on Liver Fat, De Novo Lipogenesis, and Insulin Kinetics in Children With Obesity. Gastroenterology. 2017 Sep;153(3):743-752. doi: 10.1053/j.gastro.2017.05.043. Epub 2017 Jun 1. PMID: 28579536; PMCID: PMC5813289.

6	8	1.2.12	Intermittent Fasting and Time-Restricted Eating - Intermittent fasting can improve insulin sensitivity, reduce hepatic fat, and enhance metabolic function. - Long-term effects are still under investigation, but time-restricted eating may help optimize glucose regulation. References: 1. Marjot T, Tomlinson JW, Hodson L*, et al.* Timing of energy intake and the therapeutic potential of intermittent fasting and time-restricted eating in NAFLD. *Gut* 2023;**72:**1607-1619. 2. Yin C, Li Z, Xiang Y, Peng H, Yang P, Yuan S, Zhang X, Wu Y, Huang M, Li J. Effect of Intermittent Fasting on Non-Alcoholic Fatty Liver Disease: Systematic Review and Meta-Analysis. Front Nutr. 2021 Jul 12;8:709683. doi: 10.3389/fnut.2021.709683. PMID: 34322514; PMCID: PMC8310935.
7	8	1.2.12	Non-Nutritive Sweeteners. Some evidence suggests that artificial sweeteners may not be inert but have metabolic effects influencing liver fat accumulation and insulin sensitivity and markers of liver dysfunction. . There is evidence that NNS can act via various routes, including: - Altering gut microbiota, which can influence liver fat accumulation. - Affect insulin sensitivity, potentially contributing to insulin resistance - Directly Modulating hepatic lipid metabolism and promoting fat deposition Some animal studies have shown that chronic consumption of NNS can lead to hepatic steatosis (fatty liver), even in the absence of excess caloric intake. Reference: Liauchonak I, Qorri B, Dawoud F, Riat Y, Szewczuk MR. Non-Nutritive Sweeteners and Their Implications on the Development of Metabolic Syndrome. Nutrients. 2019 Mar 16;11(3):644. doi: 10.3390/nu11030644. PMID: 30884834; PMCID: PMC6471792.

8	8	1.2.12	Gut Microbiota and Inflammation. Dietary choices that support a healthy gut microbiome, including fibre-rich fruit and vegetables and low-GI foods, reduce inflammation associated with insulin resistance and fatty liver. References: 1. Benedé-Ubieto R, Cubero FJ, Nevzorova YA. Breaking the barriers: the role of gut homeostasis in Metabolic-Associated Steatotic Liver Disease (MASLD). Gut Microbes. 2024 Jan-Dec;16(1):2331460. doi: 10.1080/19490976.2024.2331460. Epub 2024 Mar 21. PMID: 38512763; PMCID: PMC10962615. 2. Hamamah S, Iatcu OC, Covasa M. Dietary Influences on Gut Microbiota and Their Role in Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD). Nutrients. 2024 Dec 31;17(1):143. doi: 10.3390/nu17010143. PMID: 39796579; PMCID: PMC11722922.
9	8	1.2.12	Counterweight diet model vs. Eatwell Guide. Structured weight management programmes (e.g., Counterweight) may offer superior benefits over general dietary recommendations like the Eatwell Guide, particularly for targeted weight loss and metabolic health. Counterweight diet was used by the DiRECT study, funded by the NHS, and recommends moderate starch as compared to the high starch Eatwell Guide. References: 1. The Counterweight Project Team. A new evidence-based model for weight management in primary care: the Counterweight Programme. J Hum Nutr Diet 2004; 17: 191-208. 2. Counterweight Project Team. Empowering Primary Care to tackle the obesity epidemic: The Counterweight Programme. European Journal of Clinical Nutrition 2005; 59: Supplement 1, S93-101. 3. Counterweight Project Team. Evaluation of the Counterweight Programme for obesity management in primary care: a starting point for continuous improvement. Br J Gen Pract 2008; 58: 548-54. 4. Counterweight Project Team. The implementation of the Counterweight Programme in Scotland, UK. Family Practice 2012; 29:i139- i144. 5. Lean et al. Feasibility and indicative results from a 12-month low-energy liquid diet treatment and maintenance programme for severe obesity. Br J Gen Pract 2013; e115-124.

10	8	1.2.14	Sleep. Poor sleep quality and short sleep duration negatively affect glucose metabolism and may contribute to NAFLD progression. Optimizing sleep patterns supports overall metabolic function. References: 1. Mir HM, Stepanova M, Afendy H, Cable R, Younossi ZM. Association of Sleep Disorders with Nonalcoholic Fatty Liver Disease (NAFLD): A Population-based Study. J Clin Exp Hepatol. 2013 Sep;3(3):181-5. doi: 10.1016/j.jceh.2013.06.004. Epub 2013 Jul 2. PMID: 25755498; PMCID: PMC3940103. 2. Okamura T, Hashimoto Y, Hamaguchi M, Obora A, Kojima T, Fukui M. Short sleep duration is a risk of incident nonalcoholic fatty liver disease: a population-based longitudinal study. J Gastrointestin Liver Dis. 2019 Mar;28(1):73-81. doi: 10.15403/jgld.2014.1121.281.alc. PMID: 30851175. 3. Chung GE, Cho EJ, Yoo JJ, Chang Y, Cho Y, Park SH, Shin DW, Han K, Yu SJ. Nonalcoholic fatty liver disease is associated with the development of obstructive sleep apnea. Sci Rep. 2021 Jun 29;11(1):13473. doi: 10.1038/s41598-021-92703-0. PMID: 34188101; PMCID: PMC8241839.

111	8	1.2.15	Supplements for consideration include: - folate, vitamin B6, B12, and betaine lower homocysteine levels and reduce fibrosis risk - riboflavin (vitamin B2) is a fundamental cofactor for folate metabolism, including function of MTHFR (methylenetetrahydrofolate reductase) enzyme. Variants such as C677T reduce MTHFR efficiency and influence fibrosis progression. Optimising riboflavin status mitigates fibrosis risk, particularly in individuals with MTHFR polymorphisms - choline is necessary for lipid transport. Insufficient choline intake can lead to impaired very low-density lipoprotein (VLDL) secretion, contributing to liver dysfunction. In the United States choline is considered an essential nutrient and has a reference daily intake of between 425-550 gm daily References: 1. Cai Liu, Hui Yao, Fang Wang, Effect of Nutritional Supplements for Reducing Homocysteine Levels in Healthy Adults: A Systematic Review and Network Meta-Analysis of Randomized Trials, *Nutrition Reviews*, 2025;, nuae191, https://doi.org/10.1093/nutrit/nuae191 2. Chen W, Xu M, Xu M, Wang Y, Zou Q, Xie S, Wang L. Effects of betaine on non-alcoholic liver disease. Nutr Res Rev. 2022 Jun;35(1):28-38. doi: 10.1017/S0954422421000056. Epub 2021 Apr 5. PMID: 33818349. 3. García-Minguillán, C.J., Fernandez-Ballart, J.D., Ceruelo, S. *et al.* Riboflavin status modifies the effects of methylenetetrahydrofolate reductase (MTHFR) and methionine synthase reductase (MTRR) polymorphisms on homocysteine. *Genes Nutr* **9**, 435 (2014). https://doi.org/10.1007/s12263-014-0435-1 4. Piras IS, Raju A, Don J, Schork NJ, Gerhard GS, DiStefano JK. Hepatic PEMT Expression Decreases with Increasing NAFLD Severity. Int J Mol Sci. 2022 Aug 18;23(16):9296. doi: 10.3390/ijms23169296. PMID: 36012560; PMCID: PMC9409182.

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