From the Mediterranean diet to the microbiome

Caroline E. Childs

Faculty of Medicine, University of Southampton, Southampton General Hospital, Southampton SO16 6YD, UK. Email: [c.e.childs@soton.ac.uk](mailto:c.e.childs@soton.ac.uk) Tel: +44 (0)23 8120 6925

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Diet quality in nutrition research is frequently characterised by how closely the dietary pattern adheres to either a ‘Mediterranean’ or ‘Western’ pattern. The Mediterranean diet is characterised as one rich in olive oil, fruits and vegetables, legumes nuts and seafood, with moderate alcohol intake, and low intakes of red meats and saturated fats. This is in contrast to the ‘Western’ diet typified by consumption of sugar sweetened soft-drinks, processed meats and refined grains. While broadly understood to be ‘healthy’, the high oil content of the Mediterranean diet places it in a position of conflict with current public health dietary recommendations. Current UK guidelines advise that oils and spreads be used “in small amounts” (1). In the USA, while the 2015-2020 dietary guidelines includes a section on a “Healthy Mediterranean-Style Eating Pattern”, this document recommends consuming less than two tablespoons of oils per day (2). This is in contrast to the higher reported habitual intakes of monounsaturated and polyunsaturated oils among those in Mediterranean regions (3).

The Mediterranean diet is associated with a reduced risk of mortality, cardiovascular diseases, cancer, neurodegenerative diseases and diabetes (4). The increasing incidence of obesity and metabolic syndrome among Western populations places a significant burden upon both individual health and health care systems. There is therefore significant interest in identifying whether dietary interventions can be an effective tool in reducing non-communicable disease risk or optimising health status. As any specific bioactive nutrients or components within the Mediterranean diet are identified, there may be the potential to reduce mortality or disease risk through targeted dietary interventions or recommendations. It would be of particular value if the simple addition of target foods could confer benefits among those following an otherwise ‘Western’ diet, particularly within established at-risk groups such as those with features of metabolic syndrome.

As a result, studies of walnuts and walnut oil have been conducted to assess whether short or long term regular consumption might confer health benefits. Studies to date have reported beneficial effects with potential to mitigate the incidence of obesity and metabolic syndrome. Acute consumption of walnuts is demonstrated to significantly increase post-meal satiety (5), with evidence that these effects may be exerted through changes to post-prandial gut hormones (6) or adipokines (7). Longer-term dietary interventions have also altered markers of cardiovascular risk, such as favourable changes to blood lipid profiles (8,9), apolipoprotein B (10), and measures of endothelial function (11,12). However, it is clear that the design of such studies and the characteristics of the cohort assessed significantly influences the results observed, with null findings among studies providing lower daily nut intakes (13) or in interventions conducted on obese participants (14, 15).

Walnuts contain a number of nutrients and components which may underpin their observed health effects. Walnuts are a rich source of polyunsaturated and monounsaturated fatty acids, but are also a source of protein, phytochemicals, fibre and minerals. Each of these features may confer distinct outcomes, or there may be additive or synergistic health effects arising from the multiple components. For example, the indigestible fibres contained within walnuts may have a role in influencing the composition of the gut microbiota. Observational studies have identified that broader dietary patterns influence the composition of the gut microbiota, with clear differences between those following a Western diet typified by animal protein and saturated fats when compared with those following a mainly vegetarian dietary pattern richer in carbohydrates (16). Given that there are significant differences between the gut microbiota of individuals with obesity or metabolic syndrome and that of healthy controls (17), the question arises as to whether modifying the pattern of foods within an individual’s diet can induce changes to the microbiome and thereby confer health benefits. Nutrition intervention studies which aim to influence the microbiome have tended to focus on foods with a known direct effect upon the gut microbiota such as probiotics or prebiotics, typically provided as supplements or within fortified foods.

In the current issue of the journal, Holscher et al. have investigated the effect of walnut consumption upon both serum lipid profiles and the gut microbiota. In this study, participants were provided with 42g of walnut pieces per day over a 3 week period, and serum and faecal samples were collected before and after treatment. This intervention lead to significant changes in the abundance of bacterial genera, including *Feacalibacterium* and *Bifidobacteria* and associated reductions in LDL cholesterol. It is of particular interest that the healthy population studied in this USA cohort could be described as a profile of a pre-symptomatic ‘at risk’ Western population, with an average age of 53 and BMI of 29, but with blood pressure measurements and plasma lipid concentrations within normal ranges.

These observations are supported by available evidence that dietary interventions targeting the gut microbiota can alter blood lipid profiles, with several meta-analyses indicating that probiotics can induce significant reductions in LDL cholesterol (18, 19). One mechanism by which the gut microbiome may influence blood cholesterol concentrations is via the action of gut bacteria upon bile acids (20). The work by Holscher et al. has identified that walnut consumption resulted in lower levels of toxic secondary bile acids and that these changes were correlated to the changes observed in the gut microbiota. This therefore provides a plausible mechanism by which consumption of walnuts may provide benefits to blood lipid profiles beyond those which can be attributed to the increased consumption of unsaturated oils within the nut.

Integration of microbiome analysis within nutrition science research will be fundamental to ensuring our full understanding of the complex and synergistic effects that foods or dietary patterns can have upon human health. This work by Holscher et al. provides a fascinating example of study design which interrogates both the direct and indirect health effect arising from foods consumed. Further studies will be required for full exploration of the translational value of such findings in improving individual health or as a potential public health message which could mitigate the broader burden of non-communicable diseases such as cardiovascular disease and metabolic syndrome. Ultimately, ensuring that any review of dietary advice given in public health messaging around consumption of oils or foods rich in polyunsaturated oils is informed by the scientific evidence will depend upon the effective and timely communication of nutrition science to policy makers.

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References

1. Public Health England in association with the Welsh Government FSSatFSAiNI. The Eatwell Guide. Public Health England, 2016 Contract No.: 9 August 2016. Available at <https://www.gov.uk/government/publications/the-eatwell-guide>.
2. U.S. Department of Health and Human Services and U.S. Department of Agriculture. 2015 – 2020 Dietary Guidelines for Americans. 8th Edition. December 2015. Available at <https://health.gov/dietaryguidelines/2015/guidelines/>.
3. Serra-Majem L, Ngo de la Cruz J, Ribas L, Tur JA. Olive oil and the Mediterranean diet: beyond the rhetoric. Eur J Clin Nutr. 2003 Sep;57 Suppl 1:S2-7.
4. Dinu M, Pagliai G, Casini A, Sofi F. Mediterranean diet and multiple health outcomes: an umbrella review of meta-analyses of observational studies and randomised trials. Eur J Clin Nutr. 2018 Jan;72(1):30-43. doi: 10.1038/ejcn.2017.58.
5. Brennan Am, Sweeney LL, Liu X, Mantzoros CS. Walnut consumption increases satiation but has no effect on insulin resistance or the metabolic profile over a 4-day period. Obesity (Silver Spring). 2010 Jun;18(6):1176-82. doi: 10.1038/oby.2009.409.
6. Rock CL, Flatt SW, Barkai H-S, Pakiz B, Heath DD. A walnut-containing meal had similar effects on early satiety, CCK, and PYY, but attenuated the postprandial GLP-1 and insulin response compared to a nut-free control meal. Appetite. 2017 Oct 1;117:51-57. doi: 10.1016/j.appet.2017.06.008.
7. Lozano A, Perez-Martinez P, Marin C, Tinahones FJ, Delgado-Lista J, Cruz-Teno C, Gomez-Luna P, Rodriguez-Cantalejo F, Perez-Jimenez F, Lopez-Miranda J. An acute intake of a walnut-enriched meal improves postprandial adiponectin response in healthy young adults. Nutr Res. 2013 Dec;33(12):1012-8. doi: 10.1016/j.nutres.2013.08.010.
8. Zibaeenezhad MJ, Farhadi P, Attar A, Mosleh A, Amirmoezi F, Azimi A. Effects of walnut oil on lipid proﬁles in hyperlipidemic type 2 diabetic patients: a randomized, double-blind, placebo-controlled trial. Nutr Diabetes. 2017 Apr 10;7(4):e259. doi: 10.1038/nutd.2017.8.
9. Torabian S, Haddad E, Cordero-MacIntyre Z, Tanzman J, Fernandez ML, Sabate J. Long-term walnut supplementation without dietary advice induces favorable serum lipid changes in free-living individuals. Eur J Clin Nutr. 2010 Mar;64(3):274-9. doi: 10.1038/ejcn.2009.152.
10. Wu L, Piotrowski K, Rau T, Waldmann E, Broedl UC, Demmelmair H, Kolezko B, Stark RG, Nagel JM, Mantzoros CS et al. Walnut-enriched diet reduces fasting non-HDL-cholesterol and

apolipoprotein B in healthy Caucasian subjects: A randomized controlled cross-over clinical trial. Metabolism 2014 Mar;63(3):382-91. doi: 10.1016/j.metabol.2013.11.005.

1. Ros E, Núñez I, Pérez-Heras A, Serra M, Gilabert R, Casals E, Deulofeu R. A walnut diet improves endothelial function in hypercholesterolemic subjects: a randomized crossover trial. Circulation. 2004 Apr 6;109(13):1609-14.
2. Ma Y, Njike VY, Millet J, Dutta S, Doughty K, Treu JA, Katz DL. Effects of walnut consumption on endothelial function in type 2 diabetic subjects: a randomized controlled crossover trial. Diabetes Care. 2010 Feb;33(2):227-32.
3. Din JN, Aftab SM, Jubb AW, Carnegy FH, Lyall K, Sarma J, Newby DE, Flapan AD. Effect of moderate walnut consumption on lipid profile, arterial stiffness and platelet activation in humans. Eur J Clin Nutr. 2011 Feb;65(2):234-9. doi: 10.1038/ejcn.2010.233.
4. Davis L, Stonehouse W, Loots du T, Mukuddem-Petersen J, van der Westhuizen FH, Hanekom SM, Jerling JC. The effects of high walnut and cashew nut diets on the antioxidant status of subjects with metabolic syndrome. Eur J Nutr. 2007 Apr;46(3):155-64.
5. Mukuddem-Petersen J, Stonehouse Oosthuizen W, Jerling JC, Hanekom SM, White Z. Effects of a high walnut and high cashew nut diet on selected markers of the metabolic syndrome: a controlled feeding trial. Br J Nutr. 2007 Jun;97(6):1144-53.
6. Wu GD, Chen J, Hoffmann C, Bittinger K, Chen YY, Keilbaugh SA, Bewtra M, Knights D, Walters WA, Knight R, et al. Linking long-term dietary patterns with gut microbial enterotypes. Science. 2011 Oct 7;334(6052):105-8. doi:10.1126/science.1208344.
7. Sanders ME, Guarner F, Guerrant R, Holt PR, Quigley EM, Sartor RB, Sherman PM, Mayer EA. An update on the use and investigation of probiotics in health and disease. Gut. 2013 May;62(5):787-96. doi: 10.1136/gutjnl-2012-302504.
8. Wu Y, Zhang Q, Ren Y, Ruan Z. Effect of probiotic Lactobacillus on lipid profile: A systematic review and meta-analysis of randomized, controlled trials. PLoS One. 2017 Jun 8;12(6):e0178868. doi: 10.1371/journal.pone.0178868.
9. Cho YA, Kim J. Effect of Probiotics on Blood Lipid Concentrations: A Meta-Analysis of Randomized Controlled Trials. Medicine (Baltimore). 2015 Oct;94(43):e1714. doi: 10.1097/MD.0000000000001714.
10. Ridlon JM, Kang DJ, Hylemon PB, Bajaj JS. Bile acids and the gut microbiome. Curr Opin Gastroenterol. 2014 May;30(3):332-8. doi: 10.1097/MOG.0000000000000057.