Dietary factors and low grade inflammation in relation to overweight and obesity revisited

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In 2011 the *British Journal of Nutrition* published the output of the work of an expert group assembled by the European Branch of the International Life Sciences Institute (ILSI Europe) with the aim of exploring the role of low grade inflammation in overweight and obesity and identifying the potential of dietary exposures to modify that process [1]. The abstract of that publication is shown in Figure 1. According to Web of Science, the paper has now been cited 561 times, being the second most cited paper published in the *British Journal of Nutrition* in 2011 and the 21st most cited of all papers ever published in the journal. Citations of the paper have been sustained over time, being between 43 and 64 per year over the period 2013 to 2019. Remarkably the highest number of citations was received in 2020 and 2021 with 68 and 84 citations, respectively. The pattern of citations suggests a continued relevance of the paper and the higher number in the last two years undoubtedly reflects the recognition of both inflammation and overweight and obesity to poor outcome from coronavirus disease discovered in 2019 (COVID-19). This paper built on the activity of an earlier ILSI Europe expert group that considered biomarkers of inflammatory processes in different physiological and pathological states [2] and related to later expert group activities that gave a deeper consideration to biomarkers of inflammation that might be used in the substantiation of health clams [3] and to the role of low grade inflammation in ageing and the potential of dietary exposures to modify that process [4]. Those papers are also fairly well cited with 204, 196 and 180 Web of Science citations, respectively, reflecting the enduring interest in

inflammation as it relates to diet and nutrition and to different states and stages of human physiology.

Inflammation is a component of the innate immune responses and, as such, is a normal mechanism involved in host defence against pathogenic organisms and other insults. Physiologically, inflammatory responses are self-regulating. Loss of such self regulation is linked with many pathological states, where the on-going unregulated inflammatory responses cause damage to host tissues. The diseases that result involve activated inflammatory cells and excessive inflammatory mediator production at the site of tissue damage with elevated concentrations of markers of inflammation in the systemic circulation. The latter includes acute phase proteins, such as C-reactive protein (CRP), and cytokines such as tumour necrosis factor (TNF) and interleukin-6 (IL-6). Examples of such diseases include rheumatoid arthritis and the inflammatory bowel diseases. The impacts of these diseases are controlled, with varying degrees of success, with anti-inflammatory pharmaceutical agents. In the 1990s it was discovered that adipose tissue can produce inflammatory cytokines [5,6] and in the first decade of the 2000s there were many reports that the circulating concentrations of inflammatory markers, including CRP, TNF and IL-6, are higher in individuals living with obesity than in age-and sex-matched healthy weight controls (e.g. [7,8,9]). This state of enhanced inflammation could link obesity with its co-morbidities like type-2 diabetes, metabolic fatty liver disease and coronary heart disease, in part because the inflammatory mediators could have secondary effects at other sites (e.g. the liver or the blood vessel wall) and in part because inflammation induces insulin resistance. The concentrations of inflammatory markers observed in those with obesity, though higher than in controls, were much lower than observed in individuals with frank inflammatory diseases. Hence obesity came to be recognised as a state of low grade inflammation, a term that has only been widely used in the last two decades (the oldest paper identified in a PubMed search using “Adipose tissue AND Low grade inflammation” was published in 1999 [10] and this is the third oldest paper identified in a search using “Obesity AND Low grade inflammation”). Therefore, at the time of the work of the ILSI Europe expert group that was published in 2011, the broad recognition that obesity and inflammation are somehow linked was fairly new. In parallel with research on inflammation in obesity, was research on the influence of many foods and nutrients on inflammatory processes, with some foods and nutrients apparently increasing inflammation and others dampening it. It had also been discovered that the gut microbiota appears to be altered in obesity [11]. Given that diet is a

major determinant of the gut microbiota [12] and that the gut microbiota may have a role in regulating inflammation [13], there seem to be multiple axes of interaction between nutrition, the gut microbiota, adipose tissue and inflammation.

The ILSI Europe expert group set out to collate and review the evidence around obesity being a state of low grade inflammation and the evidence for various diets and dietary components being modulators of inflammation. The paper begins with a discussion of the concept of low grade inflammation and provides copious evidence from human research that obesity is a state of low grade inflammation, based mainly on measurements made in blood. It goes on to describe adipose tissue as a source of inflammatory mediators, explains how both adipocytes and infiltrating inflammatory cells from blood (especially monocyte-derived macrophages) are sources of these, and that the inflammatory milieu of the adipose tissue influences macrophages differentiation into phenotypes that are more or less inflammatory in nature. The evidence that visceral adipose tissue is "more inflammatory" than subcutaneous is described and then the role of inflammation in modulation insulin signalling and insulin sensitivity is reviewed. Next the paper moves on to nutritional aspects. The phenomenon of post-prandial inflammation is described: both high simple sugar and high fat meals induce a state of elevated inflammation in the hours following their consumption and there is a view that this is part of the link between poor quality diets and increased risk of non-communicable diseases [14]. Inclusion of fibre, some plant polyphenolic compounds, or omega-3 fatty acids, amongst others, in the meal can partly mitigate its effects on inflammation. The paper goes on to review the effects of different eating patterns, whole foods and beverages, glycated end products, fatty acids, carbohydrates, milk peptides, vitamin D, antioxidant vitamins (C and E and carotenoids), flavonoids and phytoestrogens on inflammatory markers as reported in human studies, although often not in those with obesity. Finally, the paper descries the impact of an altered gut microbiota on inflammatory makers and the effects of pre and probiotics. As such, the paper provides a comprehensive overview of adipose tissue, obesity and inflammation and of nutrition and inflammation and attempts to integrate these. In this respect the paper was unique at the time of its publication. This probably explains its sustained high level of citations over the 10 years since its publication. However, as noted earlier citations have gone up during the period of the COVID-19 pandemic. Outcomes from COVID-19 are worse in those with higher inflammation [15,16], are worse in those living with obesity [17,18], and may be worse in those with poor nutrition

[19,20]. Because the paper by Calder et al. [1] brings obesity, inflammation and nutrition together, it remains an attractive paper to cite by those publishing about COVID-19.

In the ten years since the publication by Calder et al. [1], research in the area of adipose, tissue, obesity and inflammation has increased significantly (Table 1). Much more is known about inflammation within human adipose tissue including that visceral adipose tissue has a higher state of inflammation than subcutaneous [21] and that infiltrating cells other than macrophages, and including dendritic cells, T cells and B cells, make important contributions to adipose tissue inflammation [22]. There are interesting studies reporting altered concentrations of recently-discovered omega-3 fatty acid-derived lipid mediators that act to resolve ("turn off") inflammation in human adipose tissue [23], suggesting a nutritional strategy that could reduce adipose tissue inflammation with the aim of mitigating some of the co-morbidities associated with obesity. Earlier studies reported that omega-3 fatty acids (EPA+DHA) could decrease macrophage numbers, crown-like structures and expression of some inflammatory genes in human subcutaneous adipose tissue [24,25] and could increase concentrations of pro-resolving lipid mediators mainly in visceral adipose tissue [25]. A more recent study reported that omega-3 fatty acids could alter endocannabinoid and other lipid mediator concentrations ad gene expression in human subcutaneous adipose tissue but that adipose tissue from those living with obesity showed less profonde changes than that from healthy weight individuals [26,27]. This study has raised questions about better targeting of adipose tissue in those living with obesity. Against this background of advances in our understanding of adipose tissue biology, of obesity as a state of low grade inflammation, and of nutritional strategies to reduce the inflammatory state of adipose tissue, the paper by Calder et al. [1] will remain relevant for some time and seems likely to continue to be cited.

Conflicts of interest

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References

1. Calder PC, Ahluwalia N, Brouns F, Buetler T, Clement K, Cunningham K, Esposito K, Jönsson LS, Kolb H, Lansink M, Marcos A, Margioris A, Matusheski N, Nordmann H, O'Brien J, Pugliese G, Rizkalla S, Schalkwijk C, Tuomilehto J, Wärnberg J, Watzl B, Winklhofer-Roob BM (2011) Dietary factors and low-grade inflammation in relation to overweight and obesity. *Brit J Nutr* **106 Suppl 3**, S5-S78.
2. Calder PC, Albers R, Antoine JM, Blum S, Bourdet-Sicard R, Ferns GA, Folkerts G, Friedmann PS, Frost GS, Guarner F, Løvik M, Macfarlane S, Meyer PD, M'Rabet L, Serafini M, van Eden W, van Loo J, Vas Dias W, Vidry S, Winklhofer-Roob BM, Zhao J (2009) Inflammatory disease processes and interactions with nutrition. *Brit J Nutr* **101 Suppl 1**, S1-S45.
3. Calder PC, Ahluwalia N, Albers R, Bosco N, Bourdet-Sicard R, Haller D, Holgate ST, Jönsson LS, Latulippe ME, Marcos A, Moreines J, M'Rini C, Müller M, Pawelec G, van Neerven RJ, Watzl B, Zhao J (2013) A consideration of biomarkers to be used for evaluation of inflammation in human nutritional studies. *Brit J Nutr* **109 Suppl 1**, S1-S34.
4. Calder PC, Bosco N, Bourdet-Sicard R, Capuron L, Delzenne N, Doré J, Franceschi C, Lehtinen MJ, Recker T, Salvioli S, Visioli F (2017) Health relevance of the modification of low grade inflammation in ageing (inflammageing) and the role of nutrition. *Ageing Res Rev* **40**, 95-119.
5. Hotamisligil GS, Shargill NS, Spiegelman BM (1993) Adipose expression of tumour necrosis factor-alpha: direct role in obesity-linked insulin resistance. *Science* **259**, 87-91.
6. Wellen KF, Hotamisligil GS (2003) Obesity-induced inflammatory changes in adipose tissue. *J Clin Invest* **112**, 1785-1788.
7. Ziccardi P, Nappo F, Giugliano G, Esposito K, Marfella R, Cioffi M, D'Andrea F, Molinari AM, Giugliano D (2002) Reduction of inflammatory cytokine concentrations and improvement of endothelial functions in obese women after weight loss over one year. *Circulation* **105**, 804-809.
8. Straczkowski M, Dzienis-Straczkowska S, Stêpieñ A, Kowalska I, Szelachowska M, Kinalska I (2002) Plasma interleukin-8 concentrations are increased in obese subjects and related to fat mass and tumor necrosis factor-alpha system. *J Clin Endocrinol Metab* **87**, 4602-4606.

9. Kim CS, Park HS, Kawada T, Kim JH, Lim D, Hubbard NE, Kwon BS, Erickson KL, Yu R (2006) Circulating levels of MCP-1 and IL-8 are elevated in human obese subjects and associated with obesity-related parameters. *Int J Obes* **30**, 1347-1355.
10. Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB (1999) Elevated C-reactive protein levels in overweight and obese adults. *JAMA* **282**, 2131-2135.
11. Breton J, Galmiche M, Déchelotte P (2022) Dysbiotic gut bacteria in obesity: an overview of the metabolic mechanisms and therapeutic perspectives of next-generation probiotics. *Microorganisms* **10**, 452.
12. Singh RK, Chang HW, Yan D, Lee KM, Ucmak D, Wong K, Abrouk M, Farahnik B, Nakamura M, Zhu TH, Bhutani T, Liao W (2017) Influence of diet on the gut microbiome and implications for human health. *J Transl Med* **15**, 73.
13. Malesza IJ, Malesza M, Walkowiak J, Mussin N, Walkowiak D, Aringazina R, Bartkowiak-Wieczorek J, Mądry E (2021) High-fat, western-style diet, systemic inflammation, and gut microbiota: a narrative review. *Cells* **10**, 3164.
14. Burdge GC, Calder PC (2005) Plasma cytokine response during the postprandial period: a potential causal process in vascular disease? *Brit J Nutr* **93**, 3-9.
15. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B (2020) Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 395, 1054-1062.
16. Ruan Q, Yang K, Wang W, Jiang L, Song J (2020) Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med* **46**, 846.
17. Popkin BM, Du S, Green WD, Beck MA, Algaith T, Herbst CH, Alsukait RF, Alluhidan M, Alazemi N, Shekar M (2020) Individuals with obesity and COVID-19: A global perspective on the epidemiology and biological relationships. *Obes Rev* **21**, e13128-e131848.
18. Zhang X, Lewis AM, Moley JR, Brestoff JR (2021) Systematic review and meta-analysis of obesity and COVID-19 outcomes. *Sci Rep* **11**, 7193.
19. Calder PC (2020) Nutrition, immunity and COVID-19. *BMJ Nutr Prev Health* **3**, 74-92.
20. Calder PC (2021) Nutrition and immunity: lessons for COVID-19. *Eur J Clin Nutr* **75**, 1309-1318.

21. Bruun JM, Lihn AS, Madan AK, Pedersen SB, Schiøtt KM, Fain JN, Richelsen B (2004) Higher production of IL-8 in visceral vs. subcutaneous adipose tissue. Implication of nonadipose cells in adipose tissue. *Am J Physiol Endocrinol Metab* **286**, E8-E13.
22. Kintscher U, Hartge M, Hess K, Foryst-Ludwig A, Clemenz M, Wabitsch M, Fischer-Posovszky P, Barth TF, Dragun D, Skurk T, Hauner H, Blüher M, Unger T, Wolf AM, Knippschild U, Hombach V, Marx N (2008) T-lymphocyte infiltration in visceral adipose tissue: a primary event in adipose tissue inflammation and the development of obesity-mediated insulin resistance. *Arterioscler Thromb Vasc Biol* **28**, 1304-1310.
23. Clària J, López-Vicario C, Rius B, Titos E (2017) Pro-resolving actions of SPM in adipose tissue biology. *Mol Aspects Med* **58**, 83-92.
24. Spencer M, Finlin BS, Unal R, Zhu B, Morris AJ, Shipp LR, Lee J, Walton RG, Adu A, Erfani R, Campbell M, McGehee RE Jr, Peterson CA, Kern PA (2013) Omega-3 fatty acids reduce adipose tissue macrophages in human subjects with insulin resistance. *Diabetes* **62**, 1709-1717.
25. Itariu BK, Zeyda M, Hochbrugger EE, Neuhofer A, Prager G, Schindler K, Bohdjalian A, Mascher D, Vangala S, Schranz M, Krebs M, Bischof MG, Stulnig TM (2012) Long-chain n-3 PUFAs reduce adipose tissue and systemic inflammation in severely obese nondiabetic patients: a randomized controlled trial. *Am J Clin Nutr* **96**, 1137-1149.
26. Fisk HL, Childs CE, Miles EA, Ayres R, Noakes PS, Paras-Chavez C, Kuda O, Kopecký J, Antoun E, Lillycrop KA, Calder PC (2021) Dysregulation of endocannabinoid concentrations in human subcutaneous adipose tissue in obesity and modulation by omega-3 polyunsaturated fatty acids. *Clin Sci* **135**, 185-200.
27. Fisk HL, Childs CE, Miles EA, Ayres R, Noakes PS, Paras-Chavez C, Kuda O, Kopecký J, Antoun E, Lillycrop KA, Calder PC (2022) Modification of subcutaneous white adipose tissue inflammation by omega-3 fatty acids is limited in human obesity – a double blind, randomised clinical trial. *EBioMed*, in press.

Table 1. Numbers of publications identified in PubMed using different search terms. Searches conducted 27 February 2022.

	Search terms used			
Years covered	Obesity AND Inflammation	Adipose tissue AND Inflammation	Obesity AND Low grade inflammation	Adipose tissue AND Low grade inflammation
1980-1989	65	89	1	0
1990-1999	159	190	3	1
2000-2009	3961	1892	473	232
2010-2019	19801	9940	2301	1156
2020-now	7433	3272	809	334

Figure 1. Abstract of Calder *et al.* [1].

Low-grade inflammation is a characteristic of the obese state, and adipose tissue releases many inflammatory mediators. The source of these mediators within adipose tissue is not clear, but infiltrating macrophages seem to be especially important, although adipocytes themselves play a role. Obese people have higher circulating concentrations of many inflammatory markers than lean people do, and these are believed to play a role in causing insulin resistance and other metabolic disturbances. Blood concentrations of inflammatory markers are lowered following weight loss. In the hours following the consumption of a meal, there is an elevation in the concentrations of inflammatory mediators in the bloodstream, which is exaggerated in obese subjects and in type 2 diabetics. Both high-glucose and high-fat meals may induce postprandial inflammation, and this is exaggerated by a high meal content of advanced glycation end products (AGE) and partly ablated by inclusion of certain antioxidants or antioxidant-containing foods within the meal. Healthy eating patterns are associated with lower circulating concentrations of inflammatory markers. Among the components of a healthy diet, whole grains, vegetables and fruits, and fish are all associated with lower inflammation. AGE are associated with enhanced oxidative stress and inflammation. SFA and *trans*-MUFA are pro-inflammatory, while PUFA, especially long-chain *n*-3 PUFA, are anti-inflammatory. Hyperglycaemia induces both postprandial and chronic low-grade inflammation. Vitamin C, vitamin E and carotenoids decrease the circulating concentrations of inflammatory markers. Potential mechanisms are described and research gaps, which limit our understanding of the interaction between diet and postprandial and chronic low-grade inflammation, are identified.