Non-Classical Diet-Related Factors and Obesity

Subjects: Nutrition & Dietetics

Contributor: Georgia E. Samakidou , Chrysi C. Koliaki , Evangelos N. Liberopoulos , Nikolaos L. Katsilambros

Obesity is a chronic disease and a major public health problem due to its association with non-communicable diseases and all-cause mortality. An increased energy intake and decreased physical activity have been long recognized as the classical parameters that contribute to the development of obesity. However, several other, non-classical factors have also been associated with obesity through various complex mechanisms.Some of these factors are diet-related, such as diet quality, dietary habits and speed of eating.

obesity ultra-processed foods diet quality intermittent fasting

1. Diet Quality (What to Eat)

1.1. Ultra-Processed Foods (UPFs)

According to the Food and Agriculture Organization, ultra-processed foods (UPFs) are formulations of ingredients, mostly of exclusive industrial use, that result from a series of industrial processes, such as drying, boiling, crushing, grinding, roasting, freezing, pasteurization, refrigeration, smoking, canning or non-alcoholic fermentation. These products are rich in fats, sugars, salts and cosmetic additives that render them unhealthy, yet convenient and highly palatable [1]. UPFs may account for more than half of the total energy intake in certain high-income countries, including USA and Canada [1], while recent data from Europe state that ultra-processed food and drink consumption rates range from 14% to 44% [2]. UPF intake has been positively associated with many non-communicable diseases including obesity, type 2 diabetes, dementia, cancer, and all-cause mortality [3][4][5][6].

The link between obesity and UPFs has been observed in observational studies [7] and prospective cohort studies [6]. Several pathophysiological responsible mechanisms have been proposed. Apart from their high caloric content and reduced potential for satiety that can lead to a positive energy balance, these products promote the development of obesity by disrupting delicate endocrine and metabolic pathways [6][7]. Some mechanisms that have been studied are endocrine adaptations regarding the circulating levels of insulin and leptin and their effect on energy storage, reduced postprandial thermogenesis and interaction with the gut–brain axis and the reward circuits that modulate energy intake [6][8]. Specifically, a clinical study has shown that when the participants consumed likeable foods rich in carbohydrate and fat, an increased striatal response was observed, compared to the consumption of equally caloric, likeable foods rich in fat or carbohydrates alone. This increased response could be associated with food craving and overeating of processed foods [9]. Another plausible explanation is that the structure and physical properties of UPFs are responsible for increased energy absorption from the colon.

Interestingly, the importance of physical structure in energy absorption was evaluated in a clinical study where participants consumed peanuts in three different forms, whole peanuts, peanut butter or peanut oil, while the total amount of dietary fat remained stable. It was observed that the consumption of whole peanuts was associated with lower fat absorption compared to butter and oil (82% compared to 93% and 95%, respectively) [10]. Additionally, the included additives, as well as the packaging of UPFs, alter gut microbiota and contribute to dysbiosis, a state that has been associated with obesity through various mechanisms [6][7]. The importance of these non-nutritional components of a diet rich in UPFs has been demonstrated in a prospective cohort of 22,895 participants. In this cohort, where two distinct food classification systems were evaluated, higher mortality risk was related to food processing, but not to poor nutritional quality [11]. In conclusion, it is clear that UPFs can promote the development of obesity through a variety of mechanisms and dietary guidelines discourage their consumption [12]. It is therefore important that clinicians educate their patients in recognizing which foods are UPFs and, also, in understanding their harms and limiting their consumption.

1.2. Mediterranean Diet

The Mediterranean diet (MedDiet) is a dietary pattern that originates from the countries of Southern Europe. This pattern is defined by a high intake of vegetables, fruits, nuts, and whole grain cereals, the use of olive oil as the primary source of fat, a moderate intake of wine, especially with meals, and a low intake of red meat and saturated fats [13][14]. Numerous studies have been published emphasizing the importance of MedDiet in the prevention and management of chronic diseases such as cardiovascular diseases, cancer, depression, neurodegenerative diseases, obesity-related disorders such as diabetes mellitus and non-alcoholic fat liver disease and, of course, obesity per se [14][15][16][17][18]. It is believed that the beneficial effects of MedDiet arise from the synergistic interactions between its various components (including fats, starch, fibers, vitamins and bioactive molecules such as phytosterols, polyphenols and terpenes) and are extended beyond the actions of single compounds [15]. Interestingly, the relatively high content of fat in MedDiet has been considered by some investigators as a concern, as it has been speculated that it could lead to weight gain; however, this hypothesis has not been validated. On the contrary, accumulating evidence from systematic reviews and meta-analyses underscore that adherence to MedDiet is associated with modest weight loss and improvements in markers of central adiposity, such as waist circumference [19][20][21][22]. In a meta-analysis of 19 randomized controlled trials (RCTs), adherence to MedDiet significantly reduced body weight; this effect was stronger when MedDiet was followed for more than 6 months and also, when combined with energy restriction and increased physical activity [20]. Thus, taking into consideration the existing evidence, it seems that MedDiet is a healthy dietary pattern with several benefits in weight management and its adoption should be encouraged.

1.3. Nuts Intake

Nut consumption is generally considered as a “healthy habit” and nuts are essential components of certain dietary patterns that confer substantial health benefits, such as the Mediterranean diet and the Dietary Approaches to Stop Hypertension (DASH) diet [14][23]. Nuts are rich in dietary fiber, monounsaturated fatty acids (MUFAs), vitamins and bioactive compounds such as phytosterols and are favorably associated with several health outcomes, including

coronary heart disease and diabetes [24]. However, nuts are energy-dense foods, and concerns have been raised about their potential obesogenic effect. Therefore, their consumption is advised in limited amounts. Contrary to this common notion, evidence from RCTs and meta-analyses does not support an obesogenic action of nuts; it is rather proposed that nut consumption may be protective against obesity. A network meta-analysis of 105 RCTs aimed to analyze the effect of tree nuts and peanuts on markers of adiposity, such as waist circumference, body weight, body mass index (BMI) and body fat percentage. Nut consumption was not associated with an increase in the aforementioned parameters (except for an increase in waist circumference with diets high in hazelnut); on the other hand, almond consumption was related to a reduction in waist circumference [25]. This result is consistent with earlier research demonstrating the positive benefits of nut consumption on long-term weight change and blood lipids [26][27]. Furthermore, a meta-analysis and meta-regression of prospective studies and RCTs reported an inverse relationship between nut consumption and body weight [28]. A possible explanation of this inverse association is that nuts often replace other snacks that are high in sugars and fats [26]. Moreover, additional mechanisms have been postulated. Despite being energy-dense, nuts are less bioaccessible due to their physical properties and their fiber content, leading to less energy absorption [28]. Additionally, the consumption of nuts requires effort for oral processing, which, along with their high fiber content, delays gastric emptying and promotes satiety. Finally, nuts are rich in MUFAs and polyunsaturated fatty acids (PUFAs), which are believed to increase postprandial thermogenesis and energy expenditure [28]. Thus, according to the existing evidence, the daily consumption of nuts as part of a healthy diet should not be discouraged in the fear of promoting weight gain. On the contrary, provided they are consumed in moderation, these natural products could be valuable assets in the fight against obesity.

1.4. Unrefined Compared to Refined Grains

An increased whole grain consumption has been consistently promoted as a key component of a healthy dietary pattern in recent decades, as it has been linked to a reduction in non-communicable diseases and all-cause mortality [29]. Specifically, the Dietary Guidelines for Americans recommend that at least half of the grains that are daily consumed should be whole grain [30]. The association between whole grain consumption and obesity has been extensively studied in observational studies and RCTS and the results are often conflicting. Consumption of high-fiber whole grain foods was associated with less weight gain over a 12-year follow-up period in a prospective cohort of 74,091 female nurses [31]. Furthermore, in a prospective cohort of middle-aged adults, eating at least three servings of whole grains per day resulted in a 10% lower volume of visceral adipose tissue, a marker of central obesity [32]. Apart from observational studies, the relation between whole grains and several metabolic parameters has been evaluated in RCTs. In a RCT of 81 participants, whole grains increased resting metabolic rate and stool energy excretion, effects that translated to a 92 kcal higher net daily energy loss [33], while in a small RCT of 14 subjects, a diet with approximately 5–6 servings of whole grain per day increased whole body protein turnover and net protein balance [34]. Additionally, a RCT that evaluated the metagenomics profile of gut microbiota after 8 weeks of dietary intervention rich in whole grains concluded that, despite no significant changes in the microbiome, weight loss and attenuation of systemic low-grade inflammation were observed [35]. Several mechanisms concerning the effect of whole grain intake on energy regulation have been proposed, including the reduction in energy intake (due to attenuation of energy absorption from the gastrointestinal track and increased

satiety), the action of certain ingredients of whole grains (such as minerals and phytosterols) on adipocyte functions and thermogenesis, as well as the fermentation by the gut microbiota and the production of secondary metabolites, such as short-chain fatty acids [36][37]. Despite the positive results from observational studies and the plausibility of the aforementioned mechanisms, evidence from systematic reviews and RCTs is rather inconclusive and causality cannot be proven [38][39]. Nonetheless, in accordance with current dietary guidelines, health professionals should promote the consumption of whole grains and should assist their patients in incorporating them in their daily routine (by recommending, for instance, the substitution of white bread, plain flour and regular pasta by their whole grain versions).

1.5. Macronutrients: Low-Carbohydrate and Low-Fat Diets

The importance of distinct macronutrients (carbohydrates, fat and protein) in human metabolism and weight management has been addressed in several studies. The scientific hypothesis is that isocaloric diets with different proportions of macronutrients, such as low-carbohydrate or low-fat diets, will lead to distinct energy balances [40]. There are several underlying pathophysiological mechanisms in support of this hypothesis, including discrepancies in energy absorption, effects on gut microbiota, postprandial thermogenesis and secretion of hormones and peptides regulating metabolism of nutrients and satiety [40][41][42][43][44][45]. Despite being intriguing, this hypothesis cannot be robustly supported by the existing evidence, as studies that compare low-fat with low-carbohydrate diets often yield conflicting results. A meta-analysis of 38 RCTs and 6449 participants with BMI ranging from 22.0 to 43.9 kg/m^2, concluded that low-carbohydrate diets were associated with a more significant weight reduction at 12 months; however, this effect was attenuated at 24 months [44]. Similarly, a more recent meta-analysis of 3939 overweight and obese participants, that included 33 RCTS with duration of at least 6 months, reported that low-carbohydrate diets were more effective at weight loss compared to low-fat diets; nevertheless, no difference was observed after 24 months [43]. On the contrary, it seems that the most important attribute of a diet is whether it consists of healthy foods, such as whole grains and unsaturated fats, instead of unhealthy foods, such as refined sugars and saturated fatty acids (SAFAs). A prospective cohort study of 37,233 adults showed that both low-fat and low-carbohydrate diets were associated with increased mortality when they comprised of unhealthy foods, while the opposite effect was observed for both diets when they were based on healthy foods [46]. In addition, it should be noted that in the case of very low-carbohydrate diets, the fat content is necessarily very high. The long-term effects on health and the cardiovascular system, especially when the included fats are mostly of animal origin, represent a serious concern [47]. In conclusion, current evidence tends to downgrade the significance of the macronutrient content of the diet and supports that macronutrient composition is not important for long-term weight loss. Clinicians should emphasize to their patients that in order to achieve long-term, sustainable weight loss, they should focus on the overall quality and caloric content of their diet instead of the distinct macronutrients.

1.6. Nutritional Ingredients Associated with White Adipose Tissue (WAT) Browning and Brown Adipose Tissue (BAT) Activation

In humans, three types of adipose tissue have been identified: white, brown, and brown-like or beige adipose tissue. White adipose tissue (WAT) is the most abundant type, and its primary functions are energy storage and

adipokine secretion. Brown adipose tissue has been found in adult humans in small amounts (mostly in the cervical-supraclavicular region) and has thermogenic properties, which are mediated by the expression of the uncoupling protein 1 (UCP1). Beige adipocytes express UCP1 and induce thermogenesis, but have different origins from the brown ones; specifically, they develop in white adipose tissue depots under certain stimuli, such as cold exposure and adrenergic stimulation, a process known as “browning” [48][49]. The induction of thermogenesis and the subsequent increased energy expenditure has been considered as a potential strategy in the management of obesity [50]. Interestingly, several bioactive nutritional elements have been studied as possible modulators of BAT activation and WAT “browning”. Some of these compounds are capsaicin and capsinoids, resveratrol, green tea catechins, berberine, curcumin, omega-3 PUFAs, menthol and retinoic-acid. These molecules have been tested in experimental settings and found to induce thermogenesis by modulating multiple signaling pathways [48][49][50][51][52]. However, for a variety of reasons, translating these findings into clinical practice remains very difficult. First and foremost, high-quality human studies are lacking, as the majority of evidence comes from cell lines and experimental trials. Furthermore, these molecules have been tested at extremely high doses, making it unclear whether such doses could be used and whether bioavailability or safety issues would arise. Finally, the true benefit of increased thermogenesis in humans, as well as the potential activation of counter-regulatory mechanisms such as increased energy intake, must be determined [50]. In conclusion, despite the intriguing concept and pathophysiological mechanisms involved, the use of molecules aimed at BAT activation or WAT “browning” for the management of obesity cannot be recommended in clinical practice until the aforementioned issues are resolved.

2. Dietary Habits (When to Eat)

2.1. Intermittent Fasting

In recent years, intermittent fasting diets have gained popularity as weight loss strategies, as they are typically simpler and easier to adhere to than conventional calorie-restricted diets [53]. There are various diverse intermittent fasting protocols. Alternate-day fasting (ADF), 5:2 fasting, and time-restricted eating (TRE) have been examined the most [53][54]. In the zero-calorie ADF protocol, a day of total fasting is followed by a day of unlimited eating, while in the modified ADF protocol, a day of decreased caloric intake (no more than 500–600 kcal) is followed by a day of unrestricted eating. The 5:2 pattern consists of 2 consecutive or non-consecutive days in which calorie intake is restricted to 500–1000 kcal, followed by 5 days of unrestricted eating (feast days). TRE does not restrict caloric intake; rather, eating is restricted to specific times of the day. The most common TRE schedule consists of 16 h of fasting and 8 h of eating (16:8). Early TRE is a variation of TRE in which calorie intake is restricted to the morning and lunch time and no meals are consumed after 3:00 p.m. [53].

The metabolic switch from glucose to ketones is considered a key mediator of the health benefits of intermittent fasting. Hepatic glycogen depletion after prolonged fasting triggers utilization of fat as energy fuel, oxidation of free fatty acids and production of ketones [53][55][56]. Numerous advantageous metabolic adaptations have been attributed to intermittent fasting including enhanced mitochondrial function, attenuation of oxidative stress, downregulation of anabolic processes such as lipogenesis, increased hepatic and skeletal muscle glycogenolysis and modulation of adipokine secretion (elevated adiponectin and lower levels of leptin) [54]. Chrononutrition and

synchronization of food intake with the biological circadian rhythms are also studied as mediators of the health benefits of TRE, particularly when eating windows are restricted to daylight hours [53]. In addition, an unvoluntary restriction of caloric intake in feeding periods has been documented [56]. Changes in gut microbiota that provoke white adipose tissue browning and increased energy expenditure via non-shivering thermogenesis have also been reported in an experimental study of intermittent fasting [57].

2.2. Skipping Breakfast

Many authors consider that breakfast is the most important meal of the day [58]. Some studies have associated skipping breakfast with several health outcomes, including the development of obesity, dyslipidemia, type 2 diabetes, cardiovascular and all-cause mortality [59]. In a meta-analysis of 45 cross-sectional and cohort studies, breakfast skipping increased the risk of overweight and obesity, as well as abdominal obesity [60]. In addition, in a cross-sectional analysis of 23,758 participants, eating breakfast was negatively associated with obesity and Dietary Inflammatory Index (DII), a score developed to quantify the inflammatory burden of a diet [61]. However, when the importance of breakfast consumption in weight management is evaluated in RCTs, the results are often contradictory. A meta-analysis of RCTs found that breakfast skipping may lead to a significant but small weight loss of 0.5 kg but no significant differences in other cardiometabolic parameters, except for a rise in low-density lipoprotein (LDL) cholesterol [62]. Another meta-analysis of 13 RCTs concluded that breakfast skippers had a lower total energy intake and a small difference in weight compared to participants who consumed breakfast. The authors acknowledge that there was inconsistency across the trials results and that their findings should be cautiously interpreted; nevertheless, they suggest that the inclusion of breakfast might not be a good weight loss strategy [63].

Several mechanisms linking breakfast skipping and obesity have been postulated, including decreased satiety, which could lead to overeating, impaired insulin sensitivity after meals throughout the day [64], as well as differences in postprandial thermogenesis [65]. Behavioral factors could also be implicated, as breakfast consumption may indicate a healthier and more active lifestyle [66]. Moreover, the quality of breakfast seems to play an important role, as the consumption of a “healthy breakfast”, consisting of fruits and fiber-rich carbohydrates may be the cause of the aforementioned beneficial metabolic effects [64]. In a Swiss cross-sectional study, a “prudent” breakfast consisting of fruits, unprocessed and unsweetened cereal flakes, nuts/seeds and yogurt was negatively associated with abdominal obesity. This association could be due to the adoption of a healthy dietary pattern throughout the rest of the day [67]. In conclusion, the evidence regarding the clinical importance of breakfast in the management of obesity is conflicting and more well-designed studies focusing on the composition of breakfast and its long-term effects are required. Until then, clinicians should focus on the quality of foods that are consumed as breakfast and educate their patients in adopting a “healthy” breakfast that contains for example, fruits, yogurt and whole grains instead of an “unhealthy” breakfast rich in refined sugars and trans fats.

3. Speed of Eating (How to Eat)

“Eating slowly” has been traditionally advocated as a healthy eating behavior that would protect individuals against obesity. Interestingly, this argument is not just an anecdotal advice; instead, scientific evidence points to that direction too. The association between the speed of eating and the risk of obesity was investigated in a meta-analysis of 23 epidemiological studies [68]. The included studies were cross-sectional and longitudinal and the rate of eating was evaluated with self-reporting measures in 22 studies and with an eating monitor in 1 study. This meta-analysis reported that increased speed of eating was associated with significantly higher BMI and increased risk of being obese [68]. In addition, a more recent narrative review suggested that faster eating could increase the risk of abdominal obesity and metabolic syndrome in children and adults [69]. A plausible underlying pathophysiological mechanism is that faster eating could lead to excess energy intake due to reduced oral processing and delayed transfer of satiety signals from the gastrointestinal tract to the brain (gut–brain axis) [68][70][71]. Distinct eating behaviors provoke changes in the secretory patterns of the enteroendocrine hormones, such as glucagon-like peptide-1 (GLP-1), peptide tyrosine tyrosine (PYY) and ghrelin. Further, slower eating has been associated with higher secretion of the anorexic hormones PPY and GLP-1 [70], as well as lower levels of ghrelin in some studies [71]. This link between eating rate and energy intake was studied in a meta-analysis of controlled laboratory trials; this meta-analysis reported that slower eating was associated with less energy intake compared to faster eating [72]. A clinical question that arises after the consideration of the above data is whether the manipulation of eating behavior through interventions and educational programs could be feasible and efficient against obesity. A narrative review that addressed this matter of eating manipulation concluded that, in most cases, the energy intake and the feeling of fullness is not modified in subsequent meals, neither is the intermeal interval; therefore, it is still unclear whether acute changes that occur after eating manipulation would provoke significant long sustained changes in weight [73]. In addition, a very recent study found that a 5-week intervention of lessons that aimed to modify eating behavior of overweight and obese women led to reduced laboratory measured eating rate and prolonged meal duration; no changes in overall energy intake or body weight were observed. As the authors highlight, it is possible that a multifactorial approach that would combine eating pace instruction with diet and physical activity could be useful [74]. Thus, it can be said that current evidence supports that increased speed of eating is associated with certain pathophysiological changes that could promote obesity. Further research from long-term and high-quality studies is needed for these findings to be incorporated in clinical practice interventions and guidelines. Until then and due to the plausibility of the pathophysiological mechanisms, “eat slowly” may be prudent advice for patients in everyday clinical practice.

References

1. Monteiro, C.A.; Cannon, G.; Levy, R.B.; Moubarac, J.-C.; Louzada, M.L.C.; Rauber, F.; Khandpur, N.; Cediel, G.; Neri, D.; Martinez-Steele, E.; et al. Ultra-processed foods: What they are and how to identify them. Public. Health Nutr. 2019, 22, 936–941.
2. Mertens, E.; Colizzi, C.; Peñalvo, J.L. Ultra-processed food consumption in adults across Europe. Eur. J. Nutr. 2022, 61, 1521–1539.

3. Li, H.; Li, S.; Yang, H.; Zhang, Y.; Zhang, S.; Ma, Y.; Hou, Y.; Zhang, X.; Niu, K.; Borne, Y.; et al. Association of Ultraprocessed Food Consumption With Risk of Dementia: A Prospective Cohort. Neurology 2022, 99, e1056–e1066.
4. Wang, L.; Du, M.; Wang, K.; Khandpur, N.; Rossato, S.L.; Drouin-Chartier, J.-P.; Steele, E.M.; Giovannucci, E.; Song, M.; Zhang, F.F. Association of ultra-processed food consumption with colorectal cancer risk among men and women: Results from three prospective US cohort studies. BMJ 2022, 378, e068921.
5. Nilson, E.A.F.; Ferrari, G.; Louzada, M.L.C.; Levy, R.B.; Monteiro, C.A.; Rezende, L.F.M. Premature Deaths Attributable to the Consumption of Ultraprocessed Foods in Brazil. Am. J. Prev. Med. 2023, 64, 129–136.
6. Konieczna, J.; Morey, M.; Abete, I.; Bes-Rastrollo, M.; Ruiz-Canela, M.; Vioque, J.; Gonzalez-Palacios, S.; Daimiel, L.; Salas-Salvadó, J.; Fiol, M.; et al. Contribution of ultra-processed foods in visceral fat deposition and other adiposity indicators: Prospective analysis nested in the PREDIMED-Plus trial. Clin. Nutr. 2021, 40, 4290–4300.
7. Askari, M.; Heshmati, J.; Shahinfar, H.; Tripathi, N.; Daneshzad, E. Ultra-processed food and the risk of overweight and obesity: A systematic review and meta-analysis of observational studies. Int. J. Obes. 2020, 44, 2080–2091.
8. Fernandes, A.E.; Rosa, P.W.L.; Melo, M.E.; Martins, R.C.R.; Santin, F.G.O.; Moura, A.; Coelho, G.; Sabino, E.C.; Cercato, C.; Mancini, M.C. Differences in the gut microbiota of women according to ultra-processed food consumption. Nutr. Metab. Cardiovasc. Dis. 2023, 33, 84–89.
9. Small, D.M.; DiFeliceantonio, A.G. Processed foods and food reward. Science 2019, 363, 346–347.
10. Levine, A.S.; Silvis, S.E. Absorption of whole peanuts, peanut oil, and peanut butter. N. Engl. J. Med. 1980, 303, 917–918.
11. Bonaccio, M.; Di Castelnuovo, A.; Ruggiero, E.; Costanzo, S.; Grosso, G.; De Curtis, A.; Cerletti, C.; Donati, M.B.; de Gaetano, G.; Iacoviello, L. Joint association of food nutritional profile by Nutri-Score front-of-pack label and ultra-processed food intake with mortality: Moli-sani prospective cohort study. BMJ 2022, 378, e070688.
12. Koios, D.; Machado, P.; Lacy-Nichols, J. Representations of Ultra-Processed Foods: A Global Analysis of How Dietary Guidelines Refer to Levels of Food Processing. Int. J. Health Policy Manag. 2022, 11, 2588–2599.
13. Trichopoulou, A.; Lagiou, P. Healthy traditional Mediterranean diet: An expression of culture, history, and lifestyle. Nutr. Rev. 1997, 55 Pt 1, 383–389.
14. Trichopoulou, A.; Costacou, T.; Bamia, C.; Trichopoulos, D. Adherence to a Mediterranean diet and survival in a Greek population. N. Engl. J. Med. 2003, 348, 2599–2608.

15. Dominguez, L.J.; Di Bella, G.; Veronese, N.; Barbagallo, M. Impact of Mediterranean Diet on Chronic Non-Communicable Diseases and Longevity. Nutrients 2021, 13, 2028.
16. Yaskolka Meir, A.; Tsaban, G. Dietary Strategies to Reduce Obesity Burden-Polyphenols as a Game-Changer? Healthcare 2022, 10, 2430.
17. Yaskolka Meir, A.; Rinott, E.; Tsaban, G.; Zelicha, H.; Kaplan, A.; Rosen, P.; Shelef, I.; Youngster, I.; Shalev, A.; Blüher, M.; et al. Effect of green-Mediterranean diet on intrahepatic fat: The DIRECT PLUS randomised controlled trial. Gut 2021, 70, 2085–2095.
18. Estruch, R.; Ros, E.; Salas-Salvadó, J.; Covas, M.-I.; Corella, D.; Arós, F.; Gómez-Gracia, E.; Ruiz-Gutiérrez, V.; Fiol, M.; Lapetra, J.; et al. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. N. Engl. J. Med. 2018, 378, e34.
19. Kastorini, C.-M.; Milionis Haralampos, J.; Esposito, K.; Giugliano, D.; Goudevenos John, A.; Panagiotakos Demosthenes, B. The Effect of Mediterranean Diet on Metabolic Syndrome and its Components. J. Am. Coll. Cardiol. 2011, 57, 1299–1313.
20. Esposito, K.; Kastorini, C.M.; Panagiotakos, D.B.; Giugliano, D. Mediterranean diet and weight loss: Meta-analysis of randomized controlled trials. Metab. Syndr. Relat. Disord. 2011, 9, 1–12.
21. Mancini, J.G.; Filion, K.B.; Atallah, R.; Eisenberg, M.J. Systematic Review of the Mediterranean Diet for Long-Term Weight Loss. Am. J. Med. 2016, 129, 407–415.e4.
22. Bendall, C.L.; Mayr, H.L.; Opie, R.S.; Bes-Rastrollo, M.; Itsiopoulos, C.; Thomas, C.J. Central obesity and the Mediterranean diet: A systematic review of intervention trials. Crit. Rev. Food Sci. Nutr. 2018, 58, 3070–3084.
23. Chiavaroli, L.; Viguiliouk, E.; Nishi, S.K.; Blanco Mejia, S.; Rahelić, D.; Kahleová, H.; Salas-Salvadó, J.; Kendall, C.W.; Sievenpiper, J.L. DASH Dietary Pattern and Cardiometabolic Outcomes: An Umbrella Review of Systematic Reviews and Meta-Analyses. Nutrients 2019, 11, 338.
24. Ros, E. Health benefits of nut consumption. Nutrients 2010, 2, 652–682.
25. Fernández-Rodríguez, R.; Mesas, A.E.; Garrido-Miguel, M.; Martínez-Ortega, I.A.; Jiménez-López, E.; Martínez-Vizcaíno, V. The Relationship of Tree Nuts and Peanuts with Adiposity Parameters: A Systematic Review and Network Meta-Analysis. Nutrients 2021, 13, 2251.
26. Liu, X.; Li, Y.; Guasch-Ferré, M.; Willett, W.C.; Hu, F.B.; Tobias, D.K. Abstract 14327: Changes in Nut Consumption Influence Long-Term Weight Changes in US Men and Women. Circulation 2018, 138 (Suppl. S1), A14327.
27. Liu, K.; Hui, S.; Wang, B.; Kaliannan, K.; Guo, X.; Liang, L. Comparative effects of different types of tree nut consumption on blood lipids: A network meta-analysis of clinical trials. Am. J. Clin. Nutr.

2020, 111, 219–227.

28. Nishi, S.K.; Viguiliouk, E.; Blanco Mejia, S.; Kendall, C.W.C.; Bazinet, R.P.; Hanley, A.J.; Comelli, E.M.; Salas Salvadó, J.; Jenkins, D.J.A.; Sievenpiper, J.L. Are fatty nuts a weighty concern? A systematic review and meta-analysis and dose-response meta-regression of prospective cohorts and randomized controlled trials. Obes. Rev. 2021, 22, e13330.
29. Reynolds, A.; Mann, J.; Cummings, J.; Winter, N.; Mete, E.; Te Morenga, L. Carbohydrate quality and human health: A series of systematic reviews and meta-analyses. Lancet 2019, 393, 434–445.
30. Phillips, J.A. Dietary Guidelines for Americans, 2020–2025. Workplace Health Saf. 2021, 69, 395.
31. Liu, S.; Willett, W.C.; Manson, J.E.; Hu, F.B.; Rosner, B.; Colditz, G. Relation between changes in intakes of dietary fiber and grain products and changes in weight and development of obesity among middle-aged women. Am. J. Clin. Nutr. 2003, 78, 920–927.
32. McKeown, N.M.; Troy, L.M.; Jacques, P.F.; Hoffmann, U.; O'Donnell, C.J.; Fox, C.S. Whole- and refined-grain intakes are differentially associated with abdominal visceral and subcutaneous adiposity in healthy adults: The Framingham Heart Study. Am. J. Clin. Nutr. 2010, 92, 1165–1171.
33. Karl, J.P.; Meydani, M.; Barnett, J.B.; Vanegas, S.M.; Goldin, B.; Kane, A.; Rasmussen, H.; Saltzman, E.; Vangay, P.; Knights, D.; et al. Substituting whole grains for refined grains in a 6-wk randomized trial favorably affects energy-balance metrics in healthy men and postmenopausal women. Am. J. Clin. Nutr. 2017, 105, 589–599.
34. Mey, J.T.; Godin, J.P.; Scelsi, A.R.; Kullman, E.L.; Malin, S.K.; Yang, S.; Floyd, Z.E.; Poulev, A.; Fielding, R.A.; Ross, A.B.; et al. A Whole-Grain Diet Increases Whole-Body Protein Balance Compared with a Macronutrient-Matched Refined-Grain Diet. Curr. Dev. Nutr. 2021, 5, nzab121.
35. Roager, H.M.; Vogt, J.K.; Kristensen, M.; Hansen, L.B.S.; Ibrügger, S.; Mærkedahl, R.B.; Bahl, M.I.; Lind, M.V.; Nielsen, R.L.; Frøkiær, H.; et al. Whole grain-rich diet reduces body weight and systemic low-grade inflammation without inducing major changes of the gut microbiome: A randomised cross-over trial. Gut 2019, 68, 83–93.
36. Wu, D.; Wang, H.; Xie, L.; Hu, F. Cross-Talk Between Gut Microbiota and Adipose Tissues in Obesity and Related Metabolic Diseases. Front. Endocrinol. 2022, 13, 908868.
37. Sanders, L.M.; Zhu, Y.; Wilcox, M.L.; Koecher, K.; Maki, K.C. Effects of Whole Grain Intake, Compared with Refined Grain, on Appetite and Energy Intake: A Systematic Review and Meta-Analysis. Adv. Nutr. 2021, 12, 1177–1195.
38. Maki, K.C.; Palacios, O.M.; Koecher, K.; Sawicki, C.M.; Livingston, K.A.; Bell, M.; Nelson Cortes, H.; McKeown, N.M. The Relationship between Whole Grain Intake and Body Weight: Results of Meta-Analyses of Observational Studies and Randomized Controlled Trials. Nutrients 2019, 11, 1245.

39. Sadeghi, O.; Sadeghian, M.; Rahmani, S.; Maleki, V.; Larijani, B.; Esmaillzadeh, A. Whole-Grain Consumption Does Not Affect Obesity Measures: An Updated Systematic Review and Meta-analysis of Randomized Clinical Trials. Adv. Nutr. 2020, 11, 280–292.
40. Ebbeling, C.B.; Feldman, H.A.; Klein, G.L.; Wong, J.M.W.; Bielak, L.; Steltz, S.K.; Luoto, P.K.; Wolfe, R.R.; Wong, W.W.; Ludwig, D.S. Effects of a low carbohydrate diet on energy expenditure during weight loss maintenance: Randomized trial. Bmj 2018, 363, k4583.
41. Koliaki, C.; Spinos, T.; Spinou, M.; Brinia, M.E.; Mitsopoulou, D.; Katsilambros, N. Defining the Optimal Dietary Approach for Safe, Effective and Sustainable Weight Loss in Overweight and Obese Adults. Healthcare 2018, 6, 73.
42. Koliaki, C.; Kokkinos, A.; Tentolouris, N.; Katsilambros, N. The effect of ingested macronutrients on postprandial ghrelin response: A critical review of existing literature data. Int. J. Pept. 2010, 2010, 710852.
43. Lei, L.; Huang, J.; Zhang, L.; Hong, Y.; Hui, S.; Yang, J. Effects of low-carbohydrate diets versus low-fat diets on metabolic risk factors in overweight and obese adults: A meta-analysis of randomized controlled trials. Front. Nutr. 2022, 9, 935234.
44. Chawla, S.; Tessarolo Silva, F.; Amaral Medeiros, S.; Mekary, R.A.; Radenkovic, D. The Effect of Low-Fat and Low-Carbohydrate Diets on Weight Loss and Lipid Levels: A Systematic Review and Meta-Analysis. Nutrients 2020, 12, 3774.
45. San-Cristobal, R.; Navas-Carretero, S.; Martínez-González, M.; Ordovas, J.M.; Martínez, J.A. Contribution of macronutrients to obesity: Implications for precision nutrition. Nat. Rev. Endocrinol. 2020, 16, 305–320.
46. Shan, Z.; Guo, Y.; Hu, F.B.; Liu, L.; Qi, Q. Association of Low-Carbohydrate and Low-Fat Diets With Mortality Among US Adults. JAMA Intern. Med. 2020, 180, 513–523.
47. Noto, H.; Goto, A.; Tsujimoto, T.; Noda, M. Low-carbohydrate diets and all-cause mortality: A systematic review and meta-analysis of observational studies. PLoS ONE 2013, 8, e55030.
48. Okla, M.; Kim, J.; Koehler, K.; Chung, S. Dietary Factors Promoting Brown and Beige Fat Development and Thermogenesis. Adv. Nutr. 2017, 8, 473–483.
49. Moreno-Aliaga, M.J.; Villarroya, F. Nutritional and metabolic regulation of brown and beige adipose tissues. J. Physiol. Biochem. 2020, 76, 181–184.
50. Kuryłowicz, A.; Puzianowska-Kuźnicka, M. Induction of Adipose Tissue Browning as a Strategy to Combat Obesity. Int. J. Mol. Sci. 2020, 21, 6241.
51. El Hadi, H.; Di Vincenzo, A.; Vettor, R.; Rossato, M. Food Ingredients Involved in White-to-Brown Adipose Tissue Conversion and in Calorie Burning. Front. Physiol. 2018, 9, 1954.

52. Fernández-Galilea, M.; Félix-Soriano, E.; Colón-Mesa, I.; Escoté, X.; Moreno-Aliaga, M.J. Omega-3 fatty acids as regulators of brown/beige adipose tissue: From mechanisms to therapeutic potential. J. Physiol. Biochem. 2020, 76, 251–267.
53. Koliaki, C.C.; Katsilambros, N.L. Are the Modern Diets for the Treatment of Obesity Better than the Classical Ones? Endocrines 2022, 3, 603–623.
54. Katsarou, A.L.; Katsilambros, N.L.; Koliaki, C.C. Intermittent Energy Restriction, Weight Loss and Cardiometabolic Risk: A Critical Appraisal of Evidence in Humans. Healthcare 2021, 9, 495.
55. Papakonstantinou, E.; Oikonomou, C.; Nychas, G.; Dimitriadis, G.D. Effects of Diet, Lifestyle, Chrononutrition and Alternative Dietary Interventions on Postprandial Glycemia and Insulin Resistance. Nutrients 2022, 14, 823.
56. Tsitsou, S.; Zacharodimos, N.; Poulia, K.A.; Karatzi, K.; Dimitriadis, G.; Papakonstantinou, E. Effects of Time-Restricted Feeding and Ramadan Fasting on Body Weight, Body Composition, Glucose Responses, and Insulin Resistance: A Systematic Review of Randomized Controlled Trials. Nutrients 2022, 14, 4778.
57. Li, G.; Xie, C.; Lu, S.; Nichols, R.G.; Tian, Y.; Li, L.; Patel, D.; Ma, Y.; Brocker, C.N.; Yan, T.; et al. Intermittent Fasting Promotes White Adipose Browning and Decreases Obesity by Shaping the Gut Microbiota. Cell. Metab. 2017, 26, 672–685.e4.
58. O'Neil, C.E.; Byrd-Bredbenner, C.; Hayes, D.; Jana, L.; Klinger, S.E.; Stephenson-Martin, S. The role of breakfast in health: Definition and criteria for a quality breakfast. J. Acad. Nutr. Diet. 2014, 12 (Suppl. S12), S8–S26.
59. Rong, S.; Snetselaar, L.G.; Xu, G.; Sun, Y.; Liu, B.; Wallace, R.B.; Bao, W. Association of Skipping Breakfast With Cardiovascular and All-Cause Mortality. J. Am. Coll. Cardiol. 2019, 73, 2025–2032.
60. Ma, X.; Chen, Q.; Pu, Y.; Guo, M.; Jiang, Z.; Huang, W.; Long, Y.; Xu, Y. Skipping breakfast is associated with overweight and obesity: A systematic review and meta-analysis. Obes. Res. Clin. Pract. 2020, 14, 1–8.
61. Sun, M.; Wang, X.; Wang, L.; Hu, W.; Yang, Y.; Yao, N.; Li, J.; Xie, Z.; Guo, R.; Wang, Y.; et al. The Mediating Role of Dietary Inflammatory Index in the Association between Eating Breakfast and Obesity: A Cross-Sectional Study. Nutrients 2022, 14, 4378.
62. Bonnet, J.P.; Cardel, M.I.; Cellini, J.; Hu, F.B.; Guasch-Ferré, M. Breakfast Skipping, Body Composition, and Cardiometabolic Risk: A Systematic Review and Meta-Analysis of Randomized Trials. Obesity 2020, 28, 1098–1109.
63. Sievert, K.; Hussain, S.M.; Page, M.J.; Wang, Y.; Hughes, H.J.; Malek, M.; Cicuttini, F.M. Effect of breakfast on weight and energy intake: Systematic review and meta-analysis of randomised controlled trials. BMJ 2019, 364, l42.

64. Timlin, M.T.; Pereira, M.A. Breakfast frequency and quality in the etiology of adult obesity and chronic diseases. Nutr. Rev. 2007, 65 Pt 1, 268–281.
65. Richter, J.; Herzog, N.; Janka, S.; Baumann, T.; Kistenmacher, A.; Oltmanns, K.M. Twice as High Diet-Induced Thermogenesis After Breakfast vs Dinner On High-Calorie as Well as Low-Calorie Meals. J. Clin. Endocrinol. Metab. 2020, 105, dgz311.
66. Wicherski, J.; Schlesinger, S.; Fischer, F. Association between Breakfast Skipping and Body Weight-A Systematic Review and Meta-Analysis of Observational Longitudinal Studies. Nutrients 2021, 13, 272.
67. Chatelan, A.; Castetbon, K.; Pasquier, J.; Allemann, C.; Zuber, A.; Camenzind-Frey, E.; Zuberbuehler, C.A.; Bochud, M. Association between breakfast composition and abdominal obesity in the Swiss adult population eating breakfast regularly. Int. J. Behav. Nutr. Phys. Act. 2018, 15, 115.
68. Ohkuma, T.; Hirakawa, Y.; Nakamura, U.; Kiyohara, Y.; Kitazono, T.; Ninomiya, T. Association between eating rate and obesity: A systematic review and meta-analysis. Int. J. Obes. 2015, 39, 1589–1596.
69. Garcidueñas-Fimbres, T.E.; Paz-Graniel, I.; Nishi, S.K.; Salas-Salvadó, J.; Babio, N. Eating Speed, Eating Frequency, and Their Relationships with Diet Quality, Adiposity, and Metabolic Syndrome, or Its Components. Nutrients 2021, 13, 1687.
70. Kokkinos, A.; le Roux, C.W.; Alexiadou, K.; Tentolouris, N.; Vincent, R.P.; Kyriaki, D.; Perrea, D.; Ghatei, M.A.; Bloom, S.R.; Katsilambros, N. Eating slowly increases the postprandial response of the anorexigenic gut hormones, peptide YY and glucagon-like peptide-1. J Clin Endocrinol Metab 2010, 95, 333–337.
71. Slyper, A. Oral Processing, Satiation and Obesity: Overview and Hypotheses. Diabetes Metab. Syndr. Obes. 2021, 14, 3399–3415.
72. Robinson, E.; Almiron-Roig, E.; Rutters, F.; de Graaf, C.; Forde, C.G.; Tudur Smith, C.; Nolan, S.J.; Jebb, S.A. A systematic review and meta-analysis examining the effect of eating rate on energy intake and hunger. Am. J. Clin. Nutr. 2014, 100, 123–151.
73. Argyrakopoulou, G.; Simati, S.; Dimitriadis, G.; Kokkinos, A. How Important Is Eating Rate in the Physiological Response to Food Intake, Control of Body Weight, and Glycemia? Nutrients 2020, 12, 1734.
74. Melanson, K.J.; Matsumoto, C.N.; Greene, G.W. Eating pace instruction is effective in slowing eating rate in women with overweight and obesity. Eat. Behav. 2023, 48, 101701.