Nutrition Research Reviews (2021), 34, 78–106 doi:10.1017/S0954422420000153

Scoping review of Paleolithic dietary patterns: a definition proposal

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Abstract

The Paleolithic diet (PaleoDiet) is an allegedly healthy dietary pattern inspired by the consumption of wild foods and animals assumed to be consumed in the Paleolithic era. Despite gaining popularity in the media, different operational definitions of this Paleolithic nutritional intake have been used in research. Our hypothesis is that specific components used to define the PaleoDiet may modulate the association of this diet with several health outcomes. We comprehensively reviewed currently applied PaleoDiet scores and suggested a new score based on the food composition of current PaleoDiet definitions and the theoretical food content of a staple dietary pattern in the Paleolithic age. In a PubMed search up to December 2019, fourteen different PaleoDiet definitions were found. We observed some common components of the PaleoDiet among these definitions although we also found high heterogeneity in the list of specific foods that should be encouraged or banned within the PaleoDiet. Most studies suggest that the PaleoDiet may have beneficial effects in the prevention of cardiometabolic diseases (type 2 diabetes, overweight/obesity, CVD and hyperlipidaemias) but the level of evidence is still weak because of the limited number of studies with a large sample size, hard outcomes instead of surrogate outcomes and long-term follow-up. Finally, we propose a new PaleoDiet score composed of eleven food items, based on a high consumption of fruits, nuts, vegetables, fish, eggs and unprocessed meats (lean meats); and a minimum content of dairy products, grains and cereals, and legumes and practical absence of processed (or ultra-processed) foods or culinary ingredients.

Keywords: Paleolithic diet: Cardiometabolic diseases: Dietary score: Comprehensive reviews: Interventional studies: Observational studies

(Received 26 November 2019; revised 6 May 2020; accepted 27 May 2020; accepted manuscript published online 2 June 2020)

Introduction

The Paleolithic diet (PaleoDiet) is a hunter–gatherer dietary pattern inspired by the consumption of wild foods that were consumed in the Paleolithic age[1], a period which lasted from 2·8 million years ago until 12 000 BC. Previous studies using isotopes have found that food consumption during this era provided a greater amount of nutrients and energy mainly from large terrestrial herbivores such as horses, pigs, boar and deer[2], from small and aquatic animals[2–6] and from wild plant foods[7]. However, the specific foods consumed were highly dependent upon the geographical area, the weather and soil conditions[8].

Some studies have hypothesised that the PaleoDiet may reduce the incidence of the metabolic syndrome[9], type 2 diabetes (T2D)[10], CVD[1] and cancer[11]. Moreover, several systematic reviews have shown the potential protective effect of the PaleoDiet on cardiovascular risk factors[12], on glucose metabolism and insulin homeostasis impairment[13] and on anthropometric measurements[14]. However, these associated potential benefits are not accepted without controversy, notably because of the restrictions of dairy products, legumes and grains, which generally are considered healthy foods[15]. From a public health perspective, this issue is very relevant because the PaleoDiet is becoming increasingly popular, especially among young adults and athletes[16].

To the best of our knowledge, no previous review has analysed current scientific evidence considering the definition of the PaleoDiet. In order to offer a realistic approach of the PaleoDiet, it has to balance the, sometimes limited, knowledge about the diet of our ancestors and the need to adapt this to our present food availability and preparation[17]. Therefore, different decisions can be made regarding which foods should be recommended or banned to follow the PaleoDiet and this may have an influence on the health effects associated with this dietary pattern.

In the present comprehensive review, our main objective was to assess PaleoDiet definitions currently published involving its food and nutritional composition and the consistency of these definitions with the ideal hunter–gatherer diet. A secondary

Abbreviations: ADA, American Diabetes Association; PaleoDiet, Paleolithic diet; T2D, type 2 diabetes.

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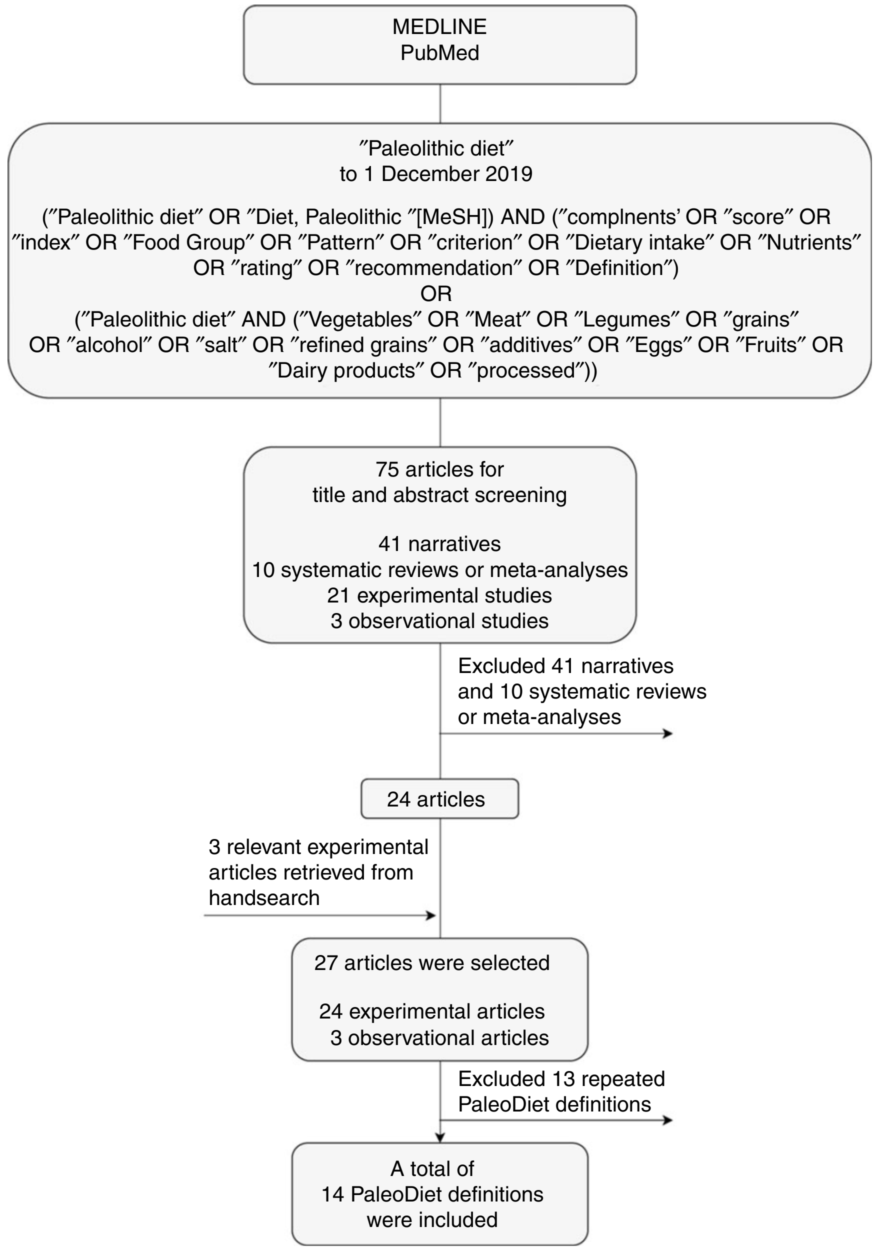

Fig. 1. Search strategy. MeSH, Medical Subject Headings; PaleoDiet, Paleolithic diet.

aim was to summarise the health effects of the PaleoDiet in the studies that have used these definitions of the PaleoDiet. In addition, we report a new definition of the PaleoDiet based on the most common items used to create previous PaleoDiet definitions and assuming those theoretical criteria that could better feature a diet with available foods during the Paleolithic era.

Methods

Our comprehensive review is based upon a search in PubMed database and a bibliographic search conducted until December 2019. According to our main objective, the inclusion criteria were studies conducted with human subjects, using an interventional or observational design, with an explicit definition of the PaleoDiet and where health-related effects were assessed. The exclusion criteria were narrative or systematic reviews or meta-analyses and articles published in languages other than Spanish or English.

Our search strategy combined the Medical Subject Headings (MeSH) term 'Paleolithic diet' and several terms related to the definition, components, recommendations or diet scores amongst others. To expand our search, we added a second search strategy where we combined the term 'Paleolithic diet' with a list of foods usually recommended (vegetables, fruits, meat, nuts, eggs), not allowed within the PaleoDiet (legumes, grains, refined grains, salt, additives, dairy products and processed foods) and alcohol. This list of foods is based on anthropological studies of the diet of our ancestors before agriculture started[18].

The flow diagram of the results of this search is shown in Fig. 1. From seventy-five articles initially retrieved, we excluded forty-one narrative reviews and ten systematic reviews[12,14,16,19–25]. We finally selected twenty-seven articles after adding four studies from our bibliographic search, which analyse the association between the PaleoDiet and health outcomes.

From these twenty-seven articles we found fourteen different PaleoDiet definitions. One definition was used in seven articles which analysed data from a 2-year intervention study conducted in seventy postmenopausal overweight or obese women[26–32]; another definition was used in three articles that used data from a parallel trial conducted in participants with T2D[33–35]; another three articles presented different results from a cross-over 12-week trial also with T2D participants[4,36,37]; and another in two studies explored different physiological mechanisms related to the PaleoDiet from a trial conducted in participants with T2D[38,39]. One common definition was found in three observational studies conducted in the USA[1,11,40]. Finally, nine different definitions were used in the other studies[9,10,41–47].

The assessment of the PaleoDiet definitions was independently performed by two reviewers (V.d. l. O. and M. R.-C.) and discrepancies were resolved by consensus.

Results

Definitions of the Paleolithic diet

In this section, we provide detailed information about the different definitions of the PaleoDiet patterns previously published. This issue is a relevant matter to better understand why this dietary pattern could be beneficial to prevent chronic diet-related diseases, but also to know if the definition of the PaleoDiet is consistent among previous epidemiological studies.

In this context, Table 1 presents the items used to define fourteen different versions of the PaleoDiet from the twenty-seven studies identified in the present review. We classified as different definitions those reported by Frassetto *et al.* in 2009[10] and 2013[38] because in the latter no component characteristic of the PaleoDiet was provided and we observed different foods that should be prohibited (added sugar and salt). However, these can be differences in the reporting but not in the definition of the PaleoDiet. Similarly, the definition reported by Pastore *et al.*[47] was adapted from the work by Jönsson *et al.*[37] and therefore these definitions could also be explained by differences in the reporting of the components used in the PaleoDiet definition.

Table 1 shows that most definitions included lean meat, eggs, fish, fruits, vegetables and nuts. Some definitions made a distinction between recommended, allowed or limited foods and some of them restricted the type of foods such as vegetables (i.e. cruciferous) or fruits (i.e. berries or coloured fruits). A common aspect in most definitions is the exclusion of grown foods from agriculture such as cereals or legumes, dairy products as well as added salt, sugar, processed foods and sweets. However, some contradictions were also found concerning the criteria used for some foods, such as potatoes[30,31,42,45,47] or alcohol[45,47], because some authors decided to exclude these foods or drinks as part of the PaleoDiet score definition. Regarding alcohol, one glass or less of wine was allowed in the PaleoDiet although it was not part of the PaleoDiet definition[30,31,42,45,47]. Conversely, there are also some items, such as mayonnaise[10,39], sugar-free tea[43], coffee[42,43], butter[44] or coconut products[44], that have been included in some of the definitions of the PaleoDiet, which should be a matter of debate.

Table 1 also shows the macronutrient distribution reported in some studies. Four studies[9,26,38,46] presented the *a priori* distribution of macronutrients according to the definition of the PaleoDiet and seven studies[11,33,42–45,47] showed the macronutrient distribution reported by participants as a measure of adherence to the PaleoDiet. The range for protein, carbohydrate and total fat intake was 18–30, 26–44 and 26·9–58 %, respectively.

We have quantified the frequency of inclusion of foods considered characteristic of the PaleoDiet and those that should be excluded according to each of the fourteen PaleoDiet definitions. Tables 2 and 3 show thirty-nine food items in total included at least in one of the definitions of the PaleoDiet score: nineteen food items were positively considered as characteristic of this dietary pattern, while twenty food items were defined as items that should be excluded from the PaleoDiet.

As shown in Table 2, the most frequently used items were fruits, vegetables, meats (red meats and lean meats), fish, tree nuts and eggs, since they were included in at least eight out of fourteen definitions. Vegetable oils were included in six definitions although we have grouped in this category different oil sources including olive, flaxseed, rapeseed and canola. The least mentioned items were mainly specific foods such as poultry, honey, wine, potatoes, mayonnaise, sugarless coffee or tea, salt-free spices, butter, coconut products, almond milk and Ca. Some foods such as mayonnaise were included because they contained nutrient characteristics of the PaleoDiet[10,38,39].

Table 3 shows the twenty items that were defined as foods that should not be included as part of the PaleoDiet definition. The following items were included in at least eight out of fourteen definitions of the PaleoDiet: cereals and grains, dairy products, legumes, sugar and refined fats. Added salt was another culinary ingredient included in six studies. We grouped other foods in the category of processed or ultra-processed foods including soft drinks, alcohol (beer and liquor), candies, processed meats, products with KCl, bakery products, 'charcuterie' products, canned food, ice cream, sorbet, juices, syrups, eggs and processed seed oils. One definition of the PaleoDiet excluded specifically non-lean red meat[11]. Contrary to most definitions, eggs were excluded in a modified PaleoDiet used in a study on fatigue and multiple sclerosis because its elimination could improve the recovery of these patients[41].

All the PaleoDiet definitions, except one proposed by Whalen *et al.*[11], were used in clinical trials in which a list of encouraged/recommended and limited/prohibited foods was provided to participants as part of the nutritional intervention. Change in macronutrient intake was generally used to measure adherence to the PaleoDiet in participants assigned to this group intervention. Thus, an increase in protein and fat intake, especially MUFA and PUFA, and a decrease in carbohydrate intake were considered as criteria to measure adherence to the PaleoDiet. Some studies also checked an increase in other specific nutrients such as fibre, K, or n-3 fatty acids as well as a decrease in Na or n-6 fatty acid intake.

https://doi.org/10.1017/S0954422420000153 Published online by Cambridge University Press

Table 1. List of Paleolithic diet definitions

Study	Paleolithic diet pattern			Nutrient distributions
	Food and/or nutrients included	Food and/or nutrients excluded	Limited foods	
Boraxbekk *et al.* (2015)[26], Stomby *et al.* (2015)[27], Andersson *et al.* (2016)[28], Otten *et al.* (2016)[29], Blomquist *et al.* (2017)[30], Manousou *et al.* (2017)[31] and Otten *et al.* (2019)[32]	Lean meats, fish, fruits, vegetables, eggs, tree nuts, berries, avocado	Dairy products, cereals, refined salt, sugar and fats, soft drinks, bakery products	–	Protein*: 30 %E Carbohydrates: 30 %E Fat: 40 %E
Bisht *et al.* (2014)[41]	Recommended foods: green leafy vegetables, sulfur-containing vegetables, and intensely coloured fruits and vegetables Encouraged foods: plant and animal protein, seaweed, non-dairy milks	Dairy products, gluten-containing grains, eggs	–	
Bligh *et al.* (2015)[46]	Fresh protein (fish and tree nuts), fruits and vegetables	Dairy products, starchy cereals, legumes, refined fats and sugar	–	Protein*: 29 %E Carbohydrates: 43 %E Fat: 28 %E
Boers *et al.* (2014)[9]	Lean meat, fish, fruit, leafy and cruciferous vegetables, root vegetables, eggs and nuts	Dairy products, legumes, cereal grains, refined fats, extra salt and sugar	–	Protein*: 24 %E Carbohydrates: 35 %E Fat: 41 %E
Fontes-Villalba *et al.* (2016)[36], Jönsson *et al.* (2009)[37] and Jönsson *et al.* (2013)[4]	Lean meats, fish, fruit, dried fruit, leafy and cruciferous vegetables, root vegetables, eggs, nuts, potatoes, rapeseed or olive oil and wine	Dairy products, cereal grains, beans, refined fats, sugar, candies, soft drinks, beer and added salt	Eggs (≤2/d), nuts (preferentially walnuts), dried fruit, potatoes (≤1 medium-sized/d), rapeseed or olive oil (≤1 tablespoon/d), wine (≤1 glass/d)	
Frassetto *et al.* (2009)[10]	Meat, fish, poultry, eggs, fruits, vegetables, tree nuts, vegetable oils (for example, canola oil), mayonnaise, honey	Dairy products, legumes, cereals, grains, potatoes, products containing KCl	–	
Frassetto *et al.* (2013)[38] and Masharani *et al.* (2015)[39]	Meats, fish, fruits, poultry, eggs, vegetables, nuts, vegetable oils (for example, canola oil), mayonnaise, honey	Dairy products, cereals, grains, legumes, potatoes, added salt, refined sugars, products containing KCl	–	Protein*: 18 %E Carbohydrates: 44 %E Fat: 38 %E
Genoni *et al.* (2016)[43]	Lean meats, fish, eggs, fruits, vegetables, tree nuts, vegetable oils (for example, coconut and olive), sugarless coffee/tea and almond milk	Dairy products, legumes, cereals, grains, maize, white potatoes	Dried fruit was restricted (1 tablespoon/d)	Protein†: 27 %E Carbohydrates: 32 %E Fat: 40 %E Alcohol: 1 %E
Jospe *et al.* (2020)[44]	Meats, fish and sea food, fruits, vegetables, butter, coconut products, extra-virgin olive oil	Grains (both whole grains and refined grains), processed seed oils (for example, canola, margarines), sugar, other sweeteners, soft drinks	Nuts and seeds (partly limited because they are energy dense and widely available), dairy products (≤1 serving/d), legumes (≤1 serving/d), dark chocolate, honey, and fresh juices from fruits and vegetables	Protein†: 21 %E Carbohydrates: 34 %E Fat: 45 %E
Lindeberg *et al.* (2007)[45]	Lean meats, fish, eggs, fruits, leafy and cruciferous vegetables, root vegetables, tree nuts, wine	Dairy products, beans, cereals (including rice), sugar, bakery products, soft drinks, beer	Eggs (1/d), nuts (preferably walnuts), potatoes (2/d), rapeseed oil/olive (1 tablespoon/d), wine (1 cup/d)	Protein†: 27·9 %E Carbohydrates: 40·2 %E Fat: 26·9 %E

Table 1. (*Continued*)

Study	Paleolithic diet pattern		Limited foods	Nutrient distributions
	Food and/or nutrients included	Food and/or nutrients excluded		
Österdahl *et al.* (2008)[42]	Fresh or frozen fruits, berries and vegetables, canned tomatoes without additives except for citric acid, fresh or frozen unsalted fish, seafood, lean meats and minced meat, unsalted nuts (except groundnuts), fresh squeezed lemon or lime juice (as dressing), flaxseed or rapeseed oil (as dressing), coffee and tea (without sugar, honey, milk or cream), all salt-free spices, potatoes, honey	Dairy products, legumes (including groundnuts), grain products (including maize and rice), charcuterie products (sausages, pâtés), canned food (except tomatoes), candy, ice cream, sorbet, soft drinks, juices, syrups, liquor, sugar, salt	Dried fruits (2 d/week), salted seafood (once per week), meat with fat (once per week), potatoes (2 medium size/d), honey (once per week), cured meats (once per week), and mineral water only when the water was not drinkable	Protein†: 23·9 %E Carbohydrates: 40·3 %E Fat: 35·8 %E
Pastore *et al.* (2015)[47]	Lean meats, eggs, fruits, vegetables, tree nuts, wine, potatoes, dried fruit	Dairy products, legumes, grains	–	Protein†: 37 %E Carbohydrates: 23 %E Fat: 40 %E
Stomby *et al.* (2017)[33], Otten *et al.* (2017)[34] and Otten *et al.* (2018)[35]	Lean meats, fish, dried fruit, fruits, vegetables, eggs, tree nuts, berries	Dairy products, legumes, cereals, refined salt, sugar and fats	–	Protein†: 24 %E Carbohydrates: 34 %E Fat: 42 %E
Whalen *et al.* (2014)[11], (2016)[40] and (2017)[1]	Lean meats, fish, fruits, nuts, vegetable diversity, Ca	Dairy foods, grains and starches, sugar-sweetened beverages, red and processed meats, Na, baked goods, alcohol	–	Protein‡: 19·1 %E Carbohydrates: 53·7 %E Fat: 27·2 %E

%E, percentage of total energy intake.
* *A priori*-defined nutrient distribution.
† Reported after the intervention.
‡ Reported highest quintile.

Table 2. Frequency of foods considered as positive characteristics in Paleolithic diet definitions

Studies	Foods and nutrients included in Paleolithic diet scores from previous scientific articles																		
	Fruits (plus dried, lemon and berries)	Vegetables (plus tomatoes)	Lean meats*	Meats*	Fish	Nuts	Eggs	Vegetable oil (plus (extra) virgin olive oil, flaxseed/ rapeseed, canola)	Wine	Potatoes	Poultry	Honey	Mayonnaise	Sugarless coffee/tea	Salt-free spices	Butter	Coconut products	Almond milk	Ca
Boraxbekk *et al.* (2015)[26], Stomby *et al.* (2015)[27], Andersson *et al.* (2016)[28], Otten *et al.* (2016)[29], Blomquist *et al.* (2017)[30], Manousou *et al.* (2017)[31] and Otten *et al.* (2019)[32]	1	1	1	0	1	1	1	0	0	0	1	0	0	0	0	0	0	0	0
Bisht *et al.* (2014)[41]	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Bligh *et al.* (2015)[46]	1	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Boers *et al.* (2014)[9]	1	1	1	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0
Fontes-Villalba *et al.* (2016)[36], Jönsson *et al.* (2009)[37] and Jönsson *et al.* (2013)[4]	1	1	1	0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0
Frassetto *et al.* (2009)[10]	1	1	0	1	1	1	1	1	0	0	1	1	1	0	0	0	0	0	0
Frassetto *et al.* (2013)[38] and Masharani *et al.* (2015)[39]	1	1	0	1	1	1	1	1	0	0	1	1	1	0	0	0	0	0	0
Genoni *et al.* (2016)[43]	1	1	1	0	1	1	1	1	0	0	0	0	0	1	0	0	0	1	0
Jospe *et al.* (2020)[44]	1	1	0	1	1	0	0	1	0	0	0	0	0	0	0	1	1	0	0
Lindeberg *et al.* (2007)[45]	1	1	1	0	1	1	1	0	1	0	0	0	0	0	0	0	0	0	0
Österdahl *et al.* (2008)[42]	1	1	0	1	1	1	0	1	0	1	0	1	0	0	1	0	0	0	0
Pastore *et al.* (2015)[47]	1	1	1	0	0	1	1	0	1	1	0	0	0	0	0	0	0	0	0
Stomby *et al.* (2017)[33], Otten *et al.* (2017)[34], Otten *et al.* (2018)[35]	1	1	1	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0
Whalen *et al.* (2014)[11], (2016)[40], (2017)[1]	1	1	1	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1
Number of studies using this item	14	14	8	5	12	12	9	6	3	3	3	3	1	1	1	1	1	1	1

* Thirteen definitions included lean meat or any meat.

Table 3. Frequency of foods considered as negative characteristics in Paleolithic diet definitions

	Foods and nutrients included in Paleolithic diet scores from previous scientific articles																			
Studies	Cereals and/or grains	Dairy products	Legumes	Sugar*	Refined fats*	Added salt/Na*	Soft drinks†	Alcohol† (plus beer and liquor)	Candy†	Processed meats†	Bakery products†	Products with KCl†	Canned food†	Ice cream†	Sorbet†	Juices†	Syrups†	Potatoes	Eggs	Maize
Boraxbekk *et al.* (2015)[26], Stomby *et al.* (2015)[27], Andersson *et al.* (2016)[28], Otten *et al.* (2016)[29], Blomquist *et al.* (2017)[30], Manousou *et al.* (2017)[31] and Otten *et al.* (2019)[32]	1	1	0	1	1	1	1	0	0	0	1	0	0	0	0	0	0	0	0	0
Bisht *et al.* (2014)[41]	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Bligh *et al.* (2015)[46]	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Boers *et al.*l (2014)[9]	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Fontes-Villalba *et al.* (2016)[36], Jönsson *et al.* (2009)[37] and Jönsson *et al.* (2013)[4]	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0
Frassetto *et al.* (2009)[10]	1	1	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0
Frassetto *et al.* (2013)[38] and Masharani *et al.* (2015)[39]	1	1	1	1	0	1	0	0	0	0	0	1	0	0	0	0	0	1	0	0
Genoni *et al.* (2016)[43]	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1
Jospe *et al.* (2020)[44]	1	0	0	1‡	1§	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Lindeberg *et al.* (2007)[45]	1	1	1	1	0	0	1	1	0	0	1	0	0	0	0	0	0	0	0	0
Österdahl *et al.* (2008)[42]	1	1	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	0	0	0
Pastore *et al.* (2015)[47]	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Stomby *et al.* (2017)[33], Otten *et al.* (2017)[34] and Otten *et al.* (2018)[35]	1	1	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Whalen *et al.* (2014)[11], (2016)[40] and (2017)[1]	1	1	1	1	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0
Number of studies using this item	14	13	10	11	7	6	5	4	2	2	2	2	1	1	1	1	1	3	1	1

* Culinary ingredients (added sugar, salt/Na, or/and refined fats). Eleven studies included at least one culinary ingredient.
† Processed and ultra-processed foods. Five studies included at least one processed or ultra-processed food.
‡ Only Jospe *et al.* (2020)[44] rated 'sweeteners'.
§ Only Jospe *et al.* (2020)[44] rated 'processed seed oils'.

Only the definition by Whalen *et al.*[1,11,40] used a score to quantify the PaleoDiet. This definition was used in three different studies[1,11,40]. Participants were classified into quintiles according to their intake of seven components positively associated with this dietary pattern (vegetables, fruits, vegetable and fruit diversity, lean meats, fish, nuts and Ca) and seven items negatively associated with the PaleoDiet (non-lean red meats/processed meats, Na, dairy foods, grains and starches, baked goods, sugar-sweetened beverages, and alcohol). Thus, the range of possible scores was 14 to 70 points.

In summary, a great although not full agreement was found among the PaleoDiet definitions regarding the basic foods that should be included (vegetables, fruits, meat (preferably lean meat), fish, nuts and eggs) and excluded (grains/cereals, dairy products, legumes, added sugar, salt and refined fats). We identified a high heterogeneity in the criteria applied to define a PaleoDiet pattern regarding concrete foods that have 'positive characteristics' of this dietary pattern, such as honey or coconut products, as well as 'negative characteristics' such as canned food or ice cream. Moreover, no quantitative score was calculated in all definitions except in the one used in the studies by Whalen *et al.*[1,11,40].

Definitions of the Paleolithic diet in the context of the anthropological studies

The PaleoDiet is different from other dietary patterns because it is based on anthropological science[48]. For this reason, we explored the bibliography used in the studies included in the present review to assess how the characteristic components of the PaleoDiet were justified. Four definitions of the PaleoDiet[11,37,45,47] described in Table 1 referenced the study by Eaton *et al.*[49] where the paradigm of evolutionary health promotion was defended. Eaton & Konner[50] published one seminal article in 1985 proposing the PaleoDiet as an alternative to Western diets which are associated with higher incidence of chronic diseases. Then, 25 years later these authors revisited the PaleoDiet definition and they stated that there was a wide agreement to support that, compared with Western diets, the PaleoDiet was higher in total energy intake but lower energy density, higher in protein, lower in carbohydrate and similar in total fat (although lower n-6:n-3 ratio)[51]. Thus, the estimated percentage of daily energy in the PaleoDiet is 35–40 % for carbohydrates, 25–30 % for proteins and 20–35 % for total fats[51]. In some studies that showed the macronutrient percentage distribution, lower protein intake and higher fat intake were reported (Table 1).

The study by Boers *et al.*[9] supported their PaleoDiet definition according to an analysis of ethnographic studies which estimated that most hunter–gatherers consumed high amounts of animal foods (45–65 % of energy)[52]. These authors also referred to another study estimating that the PaleoDiet contained higher protein and n-3 fatty acid intakes[53]. In fact, Boers *et al.*[9] defined a PaleoDiet with 24 % of total energy coming from proteins and 82 % of total protein having an animal source. Finally, Genoni *et al.*[43] used a book by Cordain as a reference to define the PaleoDiet[54].

Paleolithic diet and health outcomes

We selected twenty-seven articles[1,4,9–11,26–47] published between 2007 and 2020. Table 4 shows the design, population, comparison group, main outcomes and results from twenty-four articles using an interventional design[4,9,10,26–39,41–47] and three using an observational epidemiological design[1,11,40].

Some of these twenty-seven studies analysed data from the same trial and, therefore, the descriptive characteristics shown in Table 4 are similar in some articles except that in some of them the total number and duration is not the same and each article is analysing different main outcomes. Among twenty-seven articles, nineteen of them included participants with some cardiometabolic disease such as T2D[4,34–39,45], overweight/obesity[9,26–31] and hyperlipidaemia[47], and the main outcomes were related to intermediate endpoints such as body weight, glucose, insulin resistance, glycosylated Hb or lipid profile. Only one study analysed the risk of hard endpoints such as cancer or CVD mortality with large follow-up[1].

Anthropometrics measurements and body composition. The results of long-term (up to 6 months) and short-term (14 d) PaleoDiet interventions on body weight, body fat and waist circumference suggest that this dietary pattern may have a positive impact. Table 5 shows the results comparing a PaleoDiet intervention with different control diets.

Eight studies assessed the effect of the PaleoDiet on body weight or weight loss and their results suggested that this diet may have a positive effect on the comparison of these variables in participants before and after following this diet[9,26,29,37,42–45]. However, no significant differences were observed when the PaleoDiet was compared with the Nordic Nutrition Recommendations after 6 months[26], with the Mediterranean diet[45] throughout the follow-up, with a low-fat diet after 24 months of follow-up[29] or in comparison with intermittent fasting or the Mediterranean diet[44].

Several studies[32,34,43–45] suggested a fat-mass reduction among participants within the PaleoDiet, except one study conducted with healthy participants with overweight[44]. No significant differences were observed between the Paleo Diet and control groups except in a trial conducted with obese postmenopausal women[32] and in a 4-week trial with Australian healthy overweight women[43].

Six studies analysed the effect of the PaleoDiet on waist circumference, an indicator of abdominal obesity. Three trials found a significant waist circumference reduction in the PaleoDiet group compared with the Mediterranean diet[45], the Australian Guide to Healthy Eating[43] or the diabetes diet[37]. Other two trials found significant reductions within participants when compared before and after exposure to the PaleoDiet[42,44]. Boers *et al.*[9] found a similar effect in the PaleoDiet and control groups.

Finally, studies on visceral fat deposition reported inconsistent findings[29,35,44]. Otten *et al.*[29] observed a significantly less marked increase in fatty liver in participants consuming the PaleoDiet compared with a low-fat diet after 6 months of intervention. In another study from the same research group[35],

https://doi.org/10.1017/S0954422420000153 Published online by Cambridge University Press

Table 4. Main characteristics of the studies showing an association between the Paleolithic diet (PaleoDiet) and different outcomes

Study and country	Design	Duration	Control diet group	Population	*n*	Median age	Sex	Main outcome	Main results
Participants with diseases or cardiometabolic risk factors									
Andersson *et al.* (2016), Sweden[28]	Parallel RCT	24 months	NNR	Postmenopausal overweight and obese women	68	61 years	Women	Myocardial TAG	Myocardial TAG content did not change over time compared with the control group
Bisht *et al.* (2014), USA[41]	Non-RCT (open-label intervention study)	12 months	–	Secondary progressive multiple sclerosis patients	13	52 years	Men, women	Fatigue (Fatigue Severity Scale score)	Significant improvement of fatigue with PaleoDiet
Blomquist *et al.* (2017), Sweden[30]	Parallel RCT	24 months	NNR	Postmenopausal overweight and obese women	70	61 years	Women	Insulin sensitivity, TAG, activity of proteins involved in lipogenesis in adipose tissue, gene expression of proteins involved in lipogenesis in adipose tissue	Compared with control group, PaleoDiet led to a more pronounced reduction of lipogenesis-promoting factors in SAT among postmenopausal women with overweight
Boers *et al.* (2014), Netherlands[9]	Parallel RCT	2 weeks	Dutch Health Council guidelines	Metabolic syndrome patients	34	18–70 years	Men, women	Body weight, insulin sensitivity, waist circumference, systolic blood pressure, diastolic blood pressure, glucose, LDL-cholesterol, HDL-cholesterol, TAG	PaleoDiet improved several cardiovascular risk factors compared with Dutch Health Council guidelines, although no differences between groups were observed except for body weight, HDL-cholesterol and TAG
Boraxbekk *et al.* (2015), Sweden[26]	Parallel RCT	24 months	NNR	Postmenopausal overweight and obese women	20	61 years	Women	Memory improvement following weight loss (0–24 remembered face–name pair) and weight loss	PaleoDiet induced more weight loss associated with decreased levels of plasma NEFA than NNR. No differences between groups were observed in improved episodic memory linked to increased hippocampal activity
Fontes-Villalba *et al.* (2016)[36]	Cross-over RCT	12 weeks	Diabetes diet	T2D patients	13	64 years	Men, women	Fasting plasma concentrations of hormones	PaleoDiet reduced fasting plasma leptin levels compared with diabetes diet
Frassetto *et al.* (2013), USA[38]	Parallel RCT	14 d	ADA recommendations	T2D patients	13	56 years	Men, women	Net acid excretion (amount of acid excreted in the urine per unit time)	Patients on PaleoDiet had lower net acid excretion in urine than those on ADA diet

Table 4. (*Continued*)

Study and country	Design	Duration	Control diet group	Population	*n*	Median age	Sex	Main outcome	Main results
Jönsson *et al.* (2009), Sweden[37]	Cross-over RCT	12 weeks	Diabetes diet	T2D patients	13	64 years	Men, women	Body weight, waist circumference, systolic blood pressure, diastolic blood pressure, HDL-cholesterol, TAG, HbA1c	PaleoDiet improved glycaemic control and cardiovascular risk factors better than control diet
Jönsson *et al.* (2013), Sweden[4]	Cross-over RCT	12 weeks	Diabetes diet	T2D patients	13	64 years	Men, women	Satiety	PaleoDiet was more satiating per unit energy than control diet
Lindeberg *et al.* (2007), Sweden[45]	Parallel RCT	12 weeks	MedDiet	IHD, glucose intolerance and T2D	29	57–65 years	Men	Body weight, waist circumference, fat mass, fat-free mass, AUC glucose	Glucose tolerance and waist circumference improved more with the PaleoDiet than control diet. No differences between groups were observed in body weight, fat mass and fat-free mass
Manousou *et al.* (2017), Sweden[31]	Parallel RCT	24 months	NNR	Postmenopausal overweight and obese women	70	60 years	Women	24 h urinary iodine concentration, 24 h urinary iodine excretion, free thyroxin, free triiodothyronine, free thyrotropin	PaleoDiet resulted in a higher risk of developing iodine deficiency than NNR. Thyrotropin, free thyroxin and free triiodothyronine levels did not differ between groups at any time except for free triiodothyronine at 6 months, which was lower in the PaleoDiet group
Masharani *et al.* (2015), USA[39]	Parallel RCT	14 d	ADA recommendations	T2D patients	24	58 years (PaleoDiet group), 56 years (ADA group)	Men, women	Fasting plasma glucose, HbA1c, cholesterol, LDL-cholesterol, HDL-cholesterol, TAG	Glucose control and lipid profile improved better on the PaleoDiet than control diet, but no differences between groups were observed
Otten *et al.* (2016), Sweden[29]	Parallel RCT	24 months	NNR	Postmenopausal overweight and obese women	70	61 years (PaleoDiet group), 62 years (LFD group)	Women	Body weight, liver fat, insulin sensitivity	PaleoDiet had a significant and persistent effect on liver fat and differed significantly from the conventional LFD. No differences were observed between groups at 24 months

Table 4. (*Continued*)

Study and country	Design	Duration	Control diet group	Population	*n*	Median age	Sex	Main outcome	Main results
Otten *et al.* (2017), Sweden[34]	Parallel RCT	12 weeks	PaleoDiet + exercise	T2D individuals with overweight and obesity	32	60 years (male group), 61 years (female group)	Men, women	Fat mass, fasting insulin, fasting glucose, leptin	PaleoDiet improved fat mass, metabolic balance (insulin sensitivity, glycaemic control and leptin). Exercise may not have enhanced the effects on these outcomes, but preserved lean mass in men and increases cardiovascular fitness
Otten *et al.* (2018), Sweden[35]	Parallel RCT	12 weeks	PaleoDiet + exercise	T2D individuals with overweight and obesity	32	61 years	Men, women	Ectopic fat deposition, peripheral and adipose tissue insulin sensitivity	PaleoDiet reduced liver fat and IMCL content, while there was a tissue-specific heterogeneous response to added exercise training
Otten *et al.* (2019), Sweden[32]	Parallel RCT	24 months	NNR	Postmenopausal overweight and obese women	48	60 years	Women	Fat mass, GLP-1 responses, GIP, glucagon	Weight loss caused an increase in postprandial GLP-1 levels and a further rise occurred during weight maintenance. Postprandial GIP levels increased only after the PaleoDiet. Reduced postprandial glucagon suppression may be caused by a catabolic state
Pastore *et al.* (2015), USA[47]	Cross-over RCT	4 months	AHA recommendations	Non-diabetic adults with hyperlipidaemia	20	53 years (male group), 52 years (female group)	Men, women	Cholesterol, LDL-cholesterol, HDL-cholesterol, TAG	Cholesterol, LDL and TAG significantly decreased more, although HDL increased, by PaleoDiet, independent of changes in body weight compared with control diet
Stomby *et al.* (2015), Sweden[27]	Parallel RCT	24 months	NNR	Postmenopausal overweight and obese women	49	60 years	Women	Tissue-specific glucocorticoid metabolism in arbitrary units for 5α-glucocorticoid metabolites and 11βHSD1	*Ad libitum* PaleoDiet caused an increased excretion of 5α-reduced glucocorticoid metabolites and decreased expression of 11βHSD1 in SAT

Table 4. (*Continued*)

Study and country	Design	Duration	Control diet group	Population	*n*	Median age	Sex	Main outcome	Main results
Stomby *et al.* (2017), Sweden[33]	Parallel RCT	12 weeks	PaleoDiet + exercise	T2D patients	49	60 years	Men, women	Functional brain response	Both interventions were associated with increased functional brain responses within the right anterior hippocampus, right inferior occipital gyrus and increased volume of the right posterior hippocampus
Healthy participants									
Bligh *et al.* (2015), UK[46]	Cross-over RCT	6 weeks	Usual diet	Healthy adults	24	18–60 years	Men	Gut hormone responses, appetite	PaleoDiet increased incretin and anorectic gut hormones and increased perceived satiety more than usual diet
Frassetto *et al.* (2009), USA[10]	Non-RCT	20 d	Usual diet	Non-obese sedentary healthy patients	9	38 years	Men, women	Blood pressure, cholesterol, TAG, LDL-cholesterol, plasma insulin *v.* time AUC (during OGTT)	PaleoDiet improved blood pressure and glucose tolerance, decreased insulin secretion, increased insulin sensitivity and improved lipid profiles without weight loss
Genoni *et al.* (2016), Australia[43]	Parallel RCT	4 weeks	AGHE	Healthy adults	39	47 years	Women	Anthropometric measurements (body weight, fat mass, fat-free mass, waist circumference) and blood pressure	PaleoDiet induced greater changes in body composition over the short-term intervention than AGHE diet, but no differences in cardiovascular and metabolic markers between groups were found
Jospe *et al.* (2020), New Zealand[44]	Parallel RCT	12 months	Intermittent Fasting diet/MedDiet	Overweight healthy adults	250	43 years	Men, women	Weight loss, fat mass, visceral fat, waist circumference, systolic blood pressure, diastolic blood pressure, HbA1c, cholesterol, LDL-cholesterol, HDL-cholesterol, TAG	Small differences in metabolic outcomes were apparent in participants following self-selected diets without intensive ongoing dietary support and the between-group differences in most outcomes were not significant

Table 4. (*Continued*)

Study and country	Design	Duration	Control diet group	Population	*n*	Median age	Sex	Main outcome	Main results
Österdahl *et al.* (2008), Sweden[42]	Non-RCT	3 weeks	–	Healthy adults	14	20–40 years	Men, women	Body weight, BMI, waist circumference, systolic blood pressure, diastolic blood pressure, cholesterol, TAG, HDL-cholesterol, LDL-cholesterol	PaleoDiet in healthy volunteers showed some favourable effects on cardiovascular risk factors
Whalen *et al.* (2014), USA[11]	Case–control study	–	–	Patients with no prior history of colorectal neoplasm	2301	46–58 years	Men, women	Incident of sporadic colorectal adenomas	PaleoDiet pattern may be associated with lower risk of incident sporadic colorectal adenomas
Whalen *et al.* (2016), USA[40]	Cross-sectional study	–	–	Elective out-patient colonoscopy populations (MAPI and MAPII)	642	≥45 years	Men, women	High-sensitivity C-reactive protein, F2-isoprostane	PaleoDiet may be associated with lower levels of systemic inflammation and oxidative stress
Whalen *et al.* (2017), USA[1]	Cohort study	6·25 years	–	Black and white adults (REGARDS cohort)	21	423	≥45 years	Men, women	PaleoDiet pattern may be inversely associated with all-cause and cause-specific mortality (cardiovascular, cancer and non-injury)
PaleoDiet pattern may be inversely associated with all-cause and cause-specific mortality (cardiovascular, cancer and non-injury)									

11βHSD1, 11β hydroxysteroid dehydrogenase type 1; ADA, American Diabetes Association; AGHE, Australian Guide to Healthy Eating; AHA, American Heart Association; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; IMCL, intramyocellular lipid; LFD, low-fat diet; MAPI, Markers of Adenomatous Polyps I; MAPII, Markers of Adenomatous Polyps II; MedDiet, Mediterranean diet; NNR, Nordic Nutrition Recommendations; OGTT, oral glucose tolerance test; RCT, randomised controlled trial; REGARDS, REasons for Geographic and Racial Differences in Stroke; SAT, subcutaneous adipose tissue; T2D, type 2 diabetes.

Table 5. Main results of the studies analysing the effect of the Paleolithic diet (PaleoDiet) on different outcomes

Study	Outcome	Time	Results of the intervention group	*P* within (intervention)	Results of the control group	*P* within (control)	*P* between groups
Participants with diseases or cardiometabolic risk factors							
Anderson *et al.* (2016)[28]			PaleoDiet		Nordic Nutrition Recommendations		
	Myocardial TAG	0–24 months	Myocardial TAG content did not change over time	0·11	Myocardial TAG content did not change over time	0·98	–
Bisht *et al.* (2014)[41]			PaleoDiet		–		
	Fatigue in patients with secondary progressive multiple sclerosis (Fatigue Severity Scale score)	Baseline	Score = 5·7		–		
		At 12 months	Score = 3·32	<0·001	–	–	–
Blomquist *et al.* (2017)[30]			PaleoDiet (mean ± SD)		Control diet (mean ± SD)		
	Insulin sensitivity HOMA-IR	Baseline	1·8 ± 1·1		2·2 ± 1·0		
		Change 0–6 months	−0·32 ± 1·3	<0·01	−0·08 ± 1·3		<0·001
	TAG (mmol/l)	Baseline	1·2 ± 0·53		1·3 ± 0·55		
		Change 0–6 months	−0·39 ± 0·41	<0·001	−0·11 ± 0·38		<0·001
	Activity of proteins involved in lipogenesis in adipose tissue	0–24 months	Decreased significantly in the PaleoDiet group after 6 and 24 months, and there were significant differences in changes of lipoprotein lipase activity between the diet groups at both 6 and 24 months	–	–	–	–
	Gene expression of proteins involved in lipogenesis in adipose tissue	0–6 months	Gene expressions of lipoprotein lipase were significantly decreased in the PaleoDiet group, but no between-group differences were found	–	–	–	–
Boers *et al.* (2014)[9]			PaleoDiet (mean ± SD)		Dutch Health Council guidelines (mean ± SD)		
	Body weight (kg)	Baseline	98 ± 18·2		86 ± 14·2		
		At 14 d	95·3 ± 17·5	–	84·3 ± 12·5	–	0·010
	Insulin sensitivity HOMA-IR	Baseline	3·3 ± 1·7		2·7 ± 1·8		
		At 14 d	2·4 ± 1·6	–	2·4 ± 1·3	–	0·280
	Waist circumference (cm)	Baseline	114·7 ± 11·5		107·7 ± 9·4		
		At 14 d	111·6 ± 12·3	–	104·7 ± 8·7	–	0·690
	Systolic blood pressure (mmHg)	Baseline	131 ± 15		134 ± 15		
		At 14 d	122 ± 10	–	129 ± 14	–	0·020
	Diastolic blood pressure (mmHg)	Baseline	87 ± 9		86 ± 13		
		At 14 d	79 ± 6	–	83 ± 9	–	0·040
	Glucose (mmol/l)	Baseline	6·1 ± 0·8		5·8 ± 0·7		
		At 14 d	5·7 ± 0·8	–	5·5 ± 0·8	–	0·680

Table 5. (*Continued*)

Study	Outcome	Time	Results of the intervention group	*P* within (intervention)	Results of the control group	*P* within (control)	*P* between groups
	LDL-cholesterol (mmol/l)	Baseline	3·5 ± 0·7		3·9 ± 1·4		
		At 14 d	3·2 ± 0·8	–	3·9 ± 1·1	–	0·560
	HDL-cholesterol (mmol/l)	Baseline	1·3 ± 0·4		1·6 ± 0·4		
		At 14 d	1·3 ± 0·4	–	1·4 ± 0·4	–	0·010
	TAG (mmol/l)	Baseline	1·9 ± 1·4		1·3 ± 0·6		
		At 14 d	1 ± 0·6	–	1·4 ± 0·6	–	<0·01
Boraxbekk *et al.* (2015)[26]			PaleoDiet (mean ± SD)		Nordic Nutrition Recommendations (mean ± SD)		
	Memory improvement following weight loss (0–24 remembered face–name pairs)	Baseline	16·7 ± 3·3		16·7 ± 3·3		
		At 6 months	18·5 ± 2·0	0·010	18·5 ± 2·0	0·010	≥0·05
	Weight loss (kg)	Baseline	84·8 ± 5·6		85·1 ± 4·8		
		At 6 months	75·1 ± 5·8	0·001	79·1 ± 4·9	0·001	≥0·05
Fontes-Villalba *et al.* (2016)[36]			PaleoDiet (mean ± SD)		Diabetes diet (mean ± SD)		
	Fasting plasma leptin (ng/ml)	Baseline	9·84 ± 12·18		9·84 ± 12·18		
		At 3 months	5·1 ± 4·9	–	7·4 ± 8·3	–	0·023
Frassetto *et al.* (2013)[38]			PaleoDiet (mean ± SD)		American Diabetes Association (mean ± SD)		
	Net acid excretion (mEq/d)	Baseline	94 ± 32		31 ± 22		
		At 14 d	118 ± 48	0·010	112 ± 52	0·800	0·002
Jönsson *et al.* (2009)[37]			PaleoDiet (mean ± SD)		Diabetes diet (mean ± SD)		
	Body weight (kg)	Baseline	82 ± 13		92 ± 20		
		At 3 months	81 ± 13	0·005	84 ± 15	0·052	0·010
	Waist circumference (cm)	Baseline	97 ± 9		109 ± 17		
		At 3 months	94 ± 9	0·010	98 ± 11	0·020	0·020
	TAG (mmol/l)	Baseline	1·4 ± 0·5		1·7 ± 0·8		
		At 3 months	1·0 ± 0·5	0·003	1·5 ± 0·7	0·700	0·003
	HDL-cholesterol (mmol/l)	Baseline	1·28 ± 0·25		1·28 ± 0·19		
		At 3 months	1·34 ± 0·30	0·200	1·26 ± 0·23	0·700	0·030
	Systolic blood pressure (mmHg)	Baseline	156 ± 23		144 ± 18		
		At 3 months	140 ± 12	0·048	149 ± 22	0·700	0·130
	Diastolic blood pressure (mmHg)	Baseline	83 ± 11		84 ± 9		
		At 3 months	79 ± 6	0·060	83 ± 9	0·700	0·030
	HbA1c (%, Mono S assay)	Baseline	6·2 ± 0·2		6·9 ± 0·7		
		At 3 months	5·5 ± 0·7	<0·001	5·9 ± 0·9	<0·001	0·020

Table 5. *(Continued)*

Study	Outcome	Time	Results of the intervention group	*P* within (intervention)	Results of the control group	*P* within (control)	*P* between groups
Jönsson *et al.* (2013)[4]			PaleoDiet (mean ± SD)		Diabetes diet (mean ± SD)		
	Satiety quotient for glycaemic load per meal (RS/kg)	At 12 weeks	297 ± 138		153 ± 170		0·020
	Satiety quotient for energy per meal (RS/MJ)	At 12 weeks	1·8 ± 0·7	–	1·5 ± 0·5	–	0·004
	Satiety quotient for energy density per meal (RS/g per kJ)	At 12 weeks	0·5 ± 0·2	–	0·4 ± 0·1	–	0·010
Lindeberg *et al.* (2007)[45]			PaleoDiet (mean ± SD)		MedDiet (mean ± SD)		
	Body weight (kg)	Baseline	91·7 ± 11·2		96·1 ± 12·4		
		Change 0–6 weeks	−3·7 ± 2·2	<0·001	−2·5 ± 2·3	<0·001	0·200
		Change 6–12 weeks	−1·4 ± 2·1	0·030	−1·3 ± 1·1	<0·001	0·900
		Change 0–12 weeks	−5·0 ± 3·3	<0·001	−3·8 ± 2·4	<0·001	0·300
	Waist circumference (cm)	Baseline	105·8 ± 7·6		106·6 ± 8·0		
		Change 0–6 weeks	−3·0 ± 1·8	<0·001	−1·5 ± 2·0	0·020	0·040
		Change 6–12 weeks	−2·6 ± 2·4	0·001	−1·5 ± 1·8	0·003	0·200
		Change 0–12 weeks	−5·6 ± 2·8	<0·001	−2·9 ± 3·1	0·004	0·030
	Fat mass (kg)	Baseline	28·7 ± 5·4		33·0 ± 8·6		
		At 6 weeks	26·5 ± 4·5	<0·05	31·7 ± 8·5	<0·05	0·160
		At 12 weeks	24·9 ± 4·5	<0·05	30·8 ± 8·7	≥0·05	0·120
		Change 0–12 weeks	−3·9 ± 2·9	<0·007	−2·3 ± 1·0	<0·001	0·180
	Fat-free mass (kg)	Baseline	66·6 ± 6·3		66·7 ± 4·8		
		At 6 weeks	64·8 ± 6·1	≥0·05	66·6 ± 4·9	≥0·05	0·500
		At 12 weeks	65·6 ± 6·6	<0·05	66·9 ± 4·9	≥0·05	0·700
		Change 0–12 weeks	−1·0 ± 2·7	0·300	+0·2 ± 0·9	≥0·05	0·300
	AUC glucose 0–120 (mmol/l × min)	Baseline	1104 ± 118		1145 ± 298		
		Change 0–6 weeks	−220 ± 206	0·002	−120 ± 255	<0·001	0·300
		Change 6–12 weeks	−70 ± 156	0·120	+41 ± 179	0·400	0·090
		Change 0–12 weeks	−290 ± 143	<0·001	−80 ± 168	0·090	0·001
Manousou *et al.* (2017)[31]			PaleoDiet (medians)		Nordic Nutrition Recommendations (medians)		
	24 h urinary iodine concentration (µg/l)	Baseline	71		71		
		At 6 months	36	–	71	–	0·001

Table 5. (*Continued*)

Study	Outcome	Time	Results of the intervention group	*P* within (intervention)	Results of the control group	*P* within (control)	*P* between groups
		At 24 months	57	–	71	–	0·010
	24 h urinary iodine excretion (µg/d)	Baseline	136		136		
		At 6 months	77	–	136	–	0·001
		At 24 months	113·5	–	136	–	0·026
	Free thyroxin, triiodothyronine and thyrotropin	–	Thyrotropin, free thyroxin and free triiodothyronine levels did not differ between groups at any time except for free triiodothyronine at 6 months, which was lower in the PaleoDiet group	–	–	–	–
Masharani *et al.* (2015)[39]			PaleoDiet (mean ± SD)		American Diabetes Association (mean ± SD)		
	Fasting plasma glucose (mmol/l)	Baseline	7·7 ± 2·5		8·4 ± 4·2		
		Change 0–14 d	−1·3 ± 1·4	0·008	+0·6 ± 1·8	0·400	0·300
	HbA1c (%, Mono S assay)	Baseline	7·0 ± 1·5		7·3 ± 2·1		
		Change 0–14 d	−0·3 ± 0·49	0·040	−0·18 ± 0·24	0·040	0·500
	Cholesterol (mg/dl)*	Baseline	192 ± 52		176 ± 50		
		Change 0–14 d	−26 ± 27	0·003	−9 ± 25	0·200	0·200
	LDL-cholesterol (mg/dl)*	Baseline	114 ± 41		92 ± 40		
		Change 0–14 d	−15 ± 22	0·020	−7 ± 17	0·200	0·400
	HDL-cholesterol (mg/dl)*	Baseline	51 ± 12		46 ± 13		
		Change 0–14 d	−8 ± 7	0·001	−6 ± 8	0·030	0·500
	TAG (mg/dl)*	Baseline	149 ± 75		149 ± 73		
		Change 0–14 d	−23 ± 46	0·080	−5 ± 63	0·800	0·500
Otten *et al.* (2016)[29]			PaleoDiet (mean ± SEM)		Low-fat diet (mean ± SEM)		
	Body weight (kg)	Baseline	85·9 ± 10·9		84·0 ± 7·7		
		At 6 months	76·8 ± 10·7	<0·001	79·7 ± 9·2	<0·001	<0·001
		At 24 months	77·9 ± 11·7	<0·001	79·0 ± 9·7	<0·001	≥0·05
	Liver fat (%)	Baseline	4·6 ± 5·2		8·6 ± 8·7		
		At 6 months	1·2 ± 1·2	<0·001	5·2 ± 7·9	<0·001	<0·01
		At 24 months	1·6 ± 1·8	<0·001	4·3 ± 6	<0·001	≥0·05
	Insulin sensitivity HOMA-IR	Baseline	1·97 ± 1·06		2·15 ± 1·08		
		At 6 months	1·31 ± 0·50	<0·001	2·10 ± 1·07	≥0·05	≥0·05
		At 24 months	1·79 ± 0·91	≥0·05	2·56 ± 1·48	≥0·05	≥0·05
Otten *et al.* (2017)[34]			PaleoDiet (median and interquartile range)		PaleoDiet + exercise (median and interquartile range)		
	Fat mass (%)	Baseline	37·8 (33·1 to 40·8)		37·7 (34·7 to 43·1)		
		Change 0–12 weeks	−3·5 (−4·4 to −2·6)	<0·001	−4·1 (−5·8 to −3·4)	<0·001	≥0·05
	Fasting insulin (mIU/l)	Baseline	23 (15 to 30)		16 (11 to 20)		
		Change 0–12 weeks	−8 (−16 to −3)	<0·01	−4 (−8 to −2)	<0·001	≥0·05
	Fasting glucose (mmol/l)	Baseline	8·0 (7·2 to 8·4)		8·9 (7·9 to 10·5)		
		Change 0–12 weeks	−0·9 (−1·7 to −0·2)	<0·05	−2·0 (−3·2 to −1·1)	<0·01	≥0·05

Table 5. *(Continued)*

Study	Outcome	Time	Results of the intervention group	*P* within (intervention)	Results of the control group	*P* within (control)	*P* between groups
	Leptin (ng/ml)	Baseline	13·8 (6·4 to 26·5)		13·3 (7·2 to 16·7)		
		Change 0–12 weeks	–8·5 (–12·2 to –2·6)	<0·001	–5·6 (–9·4 to –3·5)	<0·001	≥0·05
Otten *et al.* (2018)[35]			PaleoDiet		PaleoDiet + exercise		
	Ectopic fat deposition	At 12 weeks	Hepatic lipid reduction was 74 % for the PaleoDiet group		Hepatic lipid reduction was 32 % for the PaleoDiet + exercise group		<0·05
	Peripheral and adipose tissue insulin sensitivity	At 12 weeks	Peripheral insulin sensitivity increased by 53 % for the PaleoDiet group	≥0·05	Peripheral insulin sensitivity increased by 42 % for the PaleoDiet + exercise group	<0·01	≥0·05
Otten *et al.* (2019)[32]			PaleoDiet (mean ± SEM)		Control diet (mean ± SEM)		
	Fat mass (kg)	Baseline	39·2 ± 1·5		39·2 ± 1·1		
		At 6 months	31·9 ± 1·5	<0·001	35·3 ± 1·4	<0·001	<0·001
		At 24 months	33·8 ± 1·6	<0·001	35·7 ± 1·5	<0·001	<0·05
	GLP-1 responses (incremental AUC (120 min × pmol/l))	Baseline	1084 ± 99		933 ± 106		
		At 6 months	1449 ± 111	<0·01	1036 ± 134	≥0·05	≥0·05
		At 24 months	1572 ± 233	<0·05	1488 ± 266	<0·05	≥0·05
	GIP (incremental AUC (120 min × pmol/l))	Baseline	4708 ± 426		4629 ± 349		
		At 6 months	5804 ± 622	<0·05	4503 ± 334	≥0·05	≥0·05
		At 24 months	5799 ± 540	<0·01	5151 ± 534	≥0·05	≥0·05
	Glucagon (total AUC (120 min × pmol/l))	Baseline	496 ± 36		526 ± 42		
		At 6 months	558 ± 42	<0·05	580 ± 37	<0·05	≥0·05
		At 24 months	539 ± 34	≥0·05	636 ± 37	≥0·05	≥0·05
Pastore *et al.* (2015)[47]			PaleoDiet (mean ± SD)		American Heart Association (mean ± SD)		
	Cholesterol (mmol/l)	Baseline	6·1 ± 0·6		6·1 ± 0·6		
		At 4 months	4·7 ± 0·7	<0·001	5·9 ± 5·9	<0·001	<0·001
	LDL-cholesterol (mmol/l)	Baseline	4·0 ± 0·6		4·0 ± 0·6		
		At 4 months	2·5 ± 0·7	<0·001	3·9 ± 0·6	<0·001	<0·001
	HDL-cholesterol (mmol/l)	Baseline	1·17 ± 0·33 in men; 1·59 ± 0·48 in women		1.17 ± 0.33 in men; 1.59 ± 0.48 in women		
		At 4 months	1·62 ± 0·37 in men; 1·97 ± 0·25 in women	<0·001 in men and women	1·14 ± 0·29 in men; 1·52 ± 0·50 in women	≥0·05 in men and women	<0·001 in men and women
	TAG (mmol/l)	Baseline	1·6 ± 0·7		1·6 ± 0·7		
		At 4 months	0·9 ± 0·3	<0.001	1·6 ± 0·6	≥0·05	<0·001
Stomby *et al.* (2015)[27]			PaleoDiet		Nordic Nutrition Recommendations		
	Glucocorticoid metabolites in 24 h urine samples	At 24 months	Increased 12 %	<0.001	Increased 19 %	<0·001	≥0·05

Table 5. *(Continued)*

Study	Outcome	Time	Results of the intervention group	*P* within (intervention)	Results of the control group	*P* within (control)	*P* between groups
Stomby *et al.* (2017)[33]			PaleoDiet		PaleoDiet + exercise		
	Functional brain response	At 12 weeks	PaleoDiet intervention was associated with increased functional brain responses within the right anterior hippocampus (no data available)	–	PaleoDiet intervention with exercise was associated with increased functional brain responses within the right anterior hippocampus (no data available)	–	<0·001
Healthy participants							
Bligh *et al.* (2015)[46]			PaleoDiet		Usual diet		
	GLP-1 responses (in 0–180 min)	–	GLP-1 concentration was significantly increased across 180 min for both PAL1 (*P*=0·001) and PAL2 (*P*=0·011) compared with the reference meal	0·001 (PAL1); 0·011 (PAL2)	–	–	
	Peptide YY responses (in 0–180 min)	–	Increased across 180 min	<0·001 (PAL1); 0·003 (PAL2)	–	–	
	Appetite (electronic visual analogue scale score in 0–180 min)	–	More satiety	<0·05 (PAL1 and PAL2)	–	–	
Frassetto *et al.* (2009)[10]			PaleoDiet (mean ± SD)		Usual diet		
	Mean arterial pressure (mmHg)	10 d	−3·1 ± 2·9	<0·01	–	–	
	Cholesterol (mmol/l)	10 d	−0·8 ± 0·6	0·007	–	–	–
	TAG (mmol/l)	10 d	−0·3 ± 0·3	0·010	–	–	–
	LDL-cholesterol (mmol/l)	10 d	−0·7 ± 0·5	0·030	–	–	–
	Plasma insulin *v.* time AUC (during OGTT)	10 d	–	0·006	–	–	
Jospe *et al.* (2020)[44]			PaleoDiet (mean and 95 % CI; mean ± SD)		Intermittent fasting diet/MedDiet (mean and 95 % CI; mean ± SD)		
	Weight loss	Baseline	–		–		
		Change 0–6 months	−2·8 (−4·8, −0·9)	<0·05	−4·2 (−5·2, −3·2)/−2·1 (−3·7, −0·6)	<0·05/<0·05	0·067
		Change 0–12 months	−1·8 (−4·0, 0·5)	≥0·05	−4·0 (−5·1, −2·8)/−2·8 (−4·4, −1·2)	<0.05/<0.05	0·167
	Fat mass (%)	Baseline	41 ± 6·6		40·4 ± 7·5/39·4 ± 7·6		
		Change 0–6 months	–		–		
		Change 0–12 months	−1·6 (−3·0, 0·2)	≥0·05	−1·6 (−2·4, −0·9)/−1·9 (−2·8, −0·9)	<0·05/<0·05	0·939
	Visceral fat (cm^3)	Baseline	1281 ± 979		1534 ± 930/1429 ± 957		
		Change 0–6 months	–		–		
		Change 0–12 months	−182 (−388, 25)	≥0·05	−243 (−351, −136)/−252 (−397, −108)	<0·05/<0·05	0·846

Table 5. (*Continued*)

Study	Outcome	Time	Results of the intervention group	*P* within (intervention)	Results of the control group	*P* within (control)	*P* between groups
	Waist circumference (cm)	Baseline	–		–		
		Change 0–6 months	−3·5 (−5·6, −1·4)	<0·05	−4·1 (−5·2, −3·0)/−2·8 (−4·5, −1·2)	<0·05/<0·05	0·419
		Change 0–12 months	−2·4 (−4·8, −0·02)	<0·05	−3·9 (−5·2, −3·0)/−4·0 (−5·7, −2·3)	<0·05/<0·05	0·499
	Systolic blood pressure (mmHg)	Baseline	121 ± 14		122 ± 14/126 ± 16		
		Change 0–6 months	−3·0 (−6·9, 0·8)	≥0·05	−0·9 (−3·0, 1·1)/−3·0 (−6·0, 0·1)	≥0·05/≥0·05	0·444
		Change 0–12 months	−1·6 (−6·0, 2·7)	≥0·05	−4·9 (−7·2, −2·6)/−5·9 (−9·0, −2·7)	<0·05/<0·05	0·296
	Diastolic blood pressure (mmHg)	Baseline	79 ± 11		78 ± 10/79 ± 10		
		Change 0–6 months	−2·5 (−5·4, 0·4)	≥0·05	−1·7 (−3·3, 0·2)/−2·6 (−4·8, −0·3)	≥0·05/<0·05	0·794
		Change 0–12 months	−3·1 (−6·4, −0·2)	<0·05	−2·9 (−4·6, −1·2)/−3·3 (−5·6, −0·9)	<0·05/<0·05	0·967
	HbA1c (%, Mono S assay)	Baseline	33·3 ± 3		33·8 ± 3.2/33·4 ± 2.7		
		0–6 months	–		–		
		Change 0–12 months	−0·2 (−0·7, 0·3)	≥0·05	−0·2 (−0·5, 0·1)/−0·8 (−1·2, −0·4)	≥0·05/<0·05	0·036
	Cholesterol (mmol/mol)	Baseline	5·4 ± 1		5·3 ± 0·8/5·5 ± 1·1		
		Change 0–6 months	–		–		
		Change 0–12 months	−0·3 (−0·6, −0·02)	<0·05	−0·1 (−0·2, 0·01)/−0·3 (−0·5, −0·1)	≥0·05/<0·05	0·188
	LDL-cholesterol (mmol/mol)	Baseline	3·4 ± 0·9		3·4 ± 0·8/3·6 ± 1		
		Change 0–6 months	–		–		
		Change 0–12 months	−0·3 (−0·6, −0·01)	<0·05	−0·1 (−0·2, 0·01)/−0·2 (−0·4, −0·03)	≥0·05/<0·05	0·144
	HDL-cholesterol (mmol/mol)	Baseline	1·4 ± 0·4		1·3 ± 0·3/1·3 ± 0·3		
		Change 0–6 months	–		–		
		Change 0–12 months	0·06 (−0·02, 0·14)	≥0·05	0·06 (0·02, 0·10)/−0·1 (−0·07, 0·05)	<0·05/≥0·05	0·139
	TAG (mmol/mol)	Baseline	1·4 ± 0·7		1·4 ± 0·5/1·4 ± 0·5		
		Change 0–6 months	–		–		
		Change 0–12 months	−0·2 (−0·4, 0·04)	≥0·05	−0·2 (−0·3, −0·1)/−0·1 (−0·2, 0·1)	<0·05/≥0·05	0·716

Table 5. (*Continued*)

Study	Outcome	Time	Results of the intervention group	*P* within (intervention)	Results of the control group	*P* within (control)	*P* between groups
Genoni *et al.* (2016)[43]			PaleoDiet (mean ± SD; mean and 95 % CI)		Australian Guide to Healthy Eating (mean ± SD; mean and 95 % CI)		
	Body weight (kg)	Baseline	73·8 ± 13·3		73·0 ± 12·3		
		Change 0–4 weeks	−3·20 (−3·8, −2·6)	<0·01	−1·21 (−2·0, −0·5)	<0·01	<0·01
	Fat mass (%)	Baseline	34·1 ± 8·9		31·5 ± 6·2		
		Change 0–4 weeks	−1·48 (−2·2, −0·8)	<0·01	−0·14 (−1·1, 0·9)	≥0·05	<0·05
	Fat mass (kg)	Baseline	26.2 ± 10.8		23·6 ± 7·5		
		Change 0–4 weeks	−2·14 (−2·7, −1·6)	<0·01	−0·46 (−1·4, 0·4)	≥0·05	<0·01
	Weight loss (%)	Baseline	–		–		
		Change 0–4 weeks	−4·28 ± 1·7	≥0·05	−1·66 ± 1·9	≥0·05	<0·01
	Waist circumference (cm)	Baseline	85·9 ± 14·9		83·0 ± 9·0		
		Change 0–4 weeks	−3·35 (−4·2, −2·5)	<0·01	−1·55 (−2·6, −0·4)	<0·05	<0·01
	Systolic blood pressure (mmHg)	Baseline	119 ± 14·5		115 ± 11·1		
		Change 0–4 weeks	−3·32 (−9·1, 2·5)	≥0·05	−0·71 (−5·2, 3·8)	≥0·05	≥0·05
	Diastolic blood pressure (mmHg)	Baseline	77·8 ± 9·0		71·7 ± 6·7		
		Change 0–4 weeks	−1·87 (−6·4, 2·7)	≥0·05	1·65 (−1·0, 4·3)	≥0·05	≥0·05
Österdahl *et al.* (2008)[42]			PaleoDiet (mean and 95 % CI)		–		
	Body weight (kg)	Baseline	65·2		–		
		Change 0–3 weeks	−2·3 (−2·7, −1·8)	<0·001	–	–	–
	BMI (kg/m^2)	Baseline	22·2		–		
		Change 0–3 weeks	−0·8 (−0·9, −0·6)	<0·001	–	–	–
	Waist circumference (cm)	Baseline	74·3		–		
		Change 0–3 weeks	−1·5 (−2·3, −0·7)	0·001	–	–	–
	Systolic blood pressure (mmHg)	Baseline	110·1		–		
		Change 0–3 weeks	−3·0 (−5·7, −0·3)	0·030	–	–	–
	Diastolic blood pressure (mmHg)	Baseline	65		–		
		Change 0–3 weeks	−2·4 (−4·9, 0·1)	>0·05	–	–	–

Table 5. (*Continued*)

Study	Outcome	Time	Results of the intervention group	*P* within (intervention)	Results of the control group	*P* within (control)	*P* between groups
	Cholesterol (mmol/l)	Baseline	4·3		–		
		Change 0–3 weeks	−0·2 (−0·4, 0·1)	–	–	–	–
	TAG (mmol/l)	Baseline	0·8		–		
		Change 0–3 weeks	−0·1 (−0·2, 0)	–	–	–	–
	HDL-cholesterol (mmol/l)	Baseline	1·4		–		
		Change 0–3 weeks	−0·1 (−0·2, 0)	0·063	–	–	–
	LDL-cholesterol (mmol/l)	Baseline	2·5		–		
		Change 0–3 weeks	−0·1 (−0·3, 0·2)	>0·05	–	–	–
Whalen *et al.* (2014)[11]			PaleoDiet (OR and 95 % CI)		–		
	Incidence of sporadic colorectal adenomas	–	Q5 *v.* Q1: 0·71 (0·50, 1·02)	–	–	–	–
Whalen *et al.* (2016)[40]			PaleoDiet (OR and 95 % CI)		–		
	High-sensitivity C-reactive protein	–	Q5 *v.* Q1: 0·61 (0·36, 1·05)	–	–	–	–
	F2-isoprostane	–	Q5 *v.* Q1: 0·51 (0·27, 0·95)	–	–	–	–
Whalen *et al.* (2017)[1]			PaleoDiet (HR and 95 % CI)				
	All-cause mortality	–	Q5 *v.* Q1: 0·77 (0·67, 0·89)	–	–	–	–
	Cardiovascular-specific mortality	–	Q5 *v.* Q1: 0·78 (0·61, 1·00)	–	–	–	–
	Cancer-specific mortality	–	Q5 *v.* Q1: 0·72 (0·55, 0·95)	–	–	–	–
	Non-injury-specific mortality	–	Q5 *v.* Q1: 0·77 (0·60, 0·98)	–	–	–	–

GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; HOMA-IR, homeostatic model assessment of insulin resistance; HR, hazard ratio; MedDiet, Mediterranean diet; OGTT, oral glucose tolerance test; PAL1, Palaeolithic-type meal 1; PAL2, Palaeolithic-type meal 2; Q1, quintile 1; Q5, quintile 5; RS, Rating Scale units.

* To convert cholestereol in mg/dl to mmol/l, multiply by 0·0259. To convert TAG in mg/dl to mmol/l, multiply by 0·0113.

a more pronounced reduction in liver fat deposition in the PaleoDiet group was found compared with a group where PaleoDiet and physical exercise recommendations were implemented. Another study found that visceral fat decreased more in those who followed the control diet (MedDiet or intermittent fasting diet) than in the PaleoDiet group although there were no significant differences between groups in the long term[44].

Cardiometabolic risk factors. Total cholesterol, LDL- and HDL-cholesterol, TAG and blood pressure were the most common cardiometabolic risk factors analysed in the studies included in the present review (Table 5).

A significant total blood cholesterol reduction was observed in five studies[10,39,42,44,47]. Pastore *et al.* (2015)[47] observed significant differences between the PaleoDiet group and control group following American Heart Association recommendations, but no difference was observed in other studies when the PaleoDiet was compared with American Diabetes Association (ADA) recommendations in a short-term study[39] and when it was compared with intermittent fasting or the Mediterranean diet after 12 months of follow-up[44].

LDL-cholesterol was assessed in six studies[9,10,39,42,44,47]. These studies suggested a reduction in LDL blood concentrations in the PaleoDiet group, although only a significant difference between this diet and a control group was observed in Pastore *et al.* (2015)[47].

The effect of the PaleoDiet on HDL-cholesterol levels compared with different control diets was evaluated in six studies[9,37,39,42,44,47], but with unclear results. Jönsson *et al.*[37] and Pastore *et al.*[47] observed a significant increment in HDL-cholesterol levels in the PaleoDiet group, while a null effect with a PaleoDiet intervention was observed in the studies of Boers *et al.*[9] and Jospe *et al.* (2020)[44]. A reduction in HDL-cholesterol levels after a short-term PaleoDiet intervention was observed although with no significant differences between the Paleo Diet and control diet following the ADA recommendations[39]. Osterdahl *et al.*[42] found a non-significant change in HDL-cholesterol levels after 3 weeks of a PaleoDiet intervention.

Blood TAG levels were analysed in nine studies[9,10,28,30,37,39,42,44,47]. Most studies showed a higher reduction of TAG levels in the PaleoDiet group compared with the control groups[9,10,30,37,42,47]. However, no significant difference was observed in another three studies[28,39,44].

Finally, the PaleoDiet significantly reduced blood pressure over time in five studies[9,10,37,42,43]. One study[44] showed similar results when the PaleoDiet intervention was compared with the Mediterranean diet or the intermittent fasting diet.

Type 2 diabetes markers. The characteristics and the strength of association found in experimental studies that evaluated the effects of diets on T2D risk markers are shown in Table 5.

HbA1c levels were reduced after a PaleoDiet intervention in a short-term study although a non-significant difference was observed in comparison with the ADA recommendations[39]. On the contrary, a higher reduction of HbA1c levels was found in the diabetes diet and Mediterranean diet compared with the PaleoDiet after 3 and 12 months of follow-up, respectively[37,44].

A short-term reduction in glucose levels was observed related with the PaleoDiet[9,34,39] with no significant differences compared with control groups. Lindeberg *et al.*[45] observed a higher improvement in glucose tolerance after 12 weeks in the PaleoDiet group compared with the Mediterranean diet group.

Six intervention studies[9,10,29,30,34,35] compared the effect of a PaleoDiet and other control diets on insulin sensitivity. Several studies did not find significant results[9,29]. Frassetto *et al.*[10] found a significant reduction in a very short intervention. A significantly higher improvement was observed in the PaleoDiet group compared with a control group after 6 months of follow-up[30].

Mortality and cancer. One longitudinal cohort study assessed the association between a PaleoDiet score and the risk of all-cause and cause-specific deaths during a median follow-up of 6·25 years[1]. The results suggested that a PaleoDiet may reduce the risk of all-cause mortality and also cardiovascular, cancer and non-injury-specific mortality (Table 5).

The association between colorectal neoplasm and the PaleoDiet was assessed in a case–control study (Table 4)[11]. This study found a non-significant inverse association in the comparison between the lowest and highest quintile of adherence to a PaleoDiet score after adjusting for other risk factors (Table 5).

Cognitive and brain function. One small pilot study investigated the feasibility of a multimodal intervention with a modified PaleoDiet and its effect on perceived fatigue in patients with secondary multiple sclerosis[41]. This study showed that a PaleoDiet intervention significantly improved fatigue in these patients after 12 months of follow-up.

Cognitive function was analysed in two studies[26,33]. The first study found increased brain activity in postmenopausal obese women following the PaleoDiet and compared with a group following a standard diet (Table 5)[26]. Similar results were found in another small-sized study with diabetics which found that both a PaleoDiet and PaleoDiet plus physical exercise could increase some functional brain responses after weight loss and improved insulin sensitivity[33].

Mechanisms underlying the effect of the Paleolithic diet. Several studies found in the present review were focused on different mechanisms that could explain the potential beneficial effects of the PaleoDiet[27,30,32,34,36,38,40,46].

One parallel and a small cross-over trial investigated PaleoDiet consumption and the influence over the concentrations of glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), leptin and peptide YY (PYY) (Table 5)[32,46]. An increase in PYY was observed during 0–180 min in the PaleoDiet group compared with the usual diet[46]. Both studies showed a significant increment in GLP-1 and GIP concentration after a PaleoDiet intervention, suggesting that the effect of the PaleoDiet on weight loss and T2D prevention could be mediated through these actions on GLP-1, GIP and PYY.

One small cross-over trial and a parallel trial investigated the effect of the PaleoDiet on fasting plasma leptin levels[34,36].

Otten *et al.*[34] found improvements in leptin concentrations among participants with a PaleoDiet + exercise intervention, but Fontes-Villalba *et al.*[36] did not find differences between diets when comparing the PaleoDiet with the diabetes diet.

In a controlled trial, postmenopausal overweight and obese woman were randomised to eat an *ad libitum* PaleoDiet-style diet or a control diet for 24 months with the objective to study the gene expression and activity of proteins involved in lipogenesis and lipolysis in adipose tissue[30]. After 6 and 24 months, a significant decrease within the PaleoDiet group and significant differences in changes of lipoprotein lipase activity compared with the control diet were observed. Moreover, the gene expressions of lipoprotein lipase were significantly decreased in the PaleoDiet group, although no between-group differences were found.

One parallel trial analysed glucocorticoid metabolites and urinary excretion in postmenopausal overweight and obese women[27]. A long-term (24 months) weight-loss intervention with a PaleoDiet caused a 12 % increase in the excretion of 5α-reduced glucocorticoid metabolites and decreased expression of 11βHSD1 (11β hydroxysteroid dehydrogenase type 1) in subcutaneous adipose tissue (Table 5).

One intervention study with T2D patients analysed the amount of acid excreted in the urine per unit time following a PaleoDiet compared with nutritional recommendations from the ADA[38]. They observed that after a short-term intervention (14 d), the net acid load of the patients on the PaleoDiet was lower than that of those following the nutritional recommendations from the ADA[38].

Finally, in a cross-sectional study of men and women undergoing a colonoscopy, plasma high-sensitivity C-reactive protein and F2-isoprostane concentrations were measured according to levels of adherence to the PaleoDiet[40]. A lower probability of systemic inflammation and oxidative stress was associated with a higher adherence to the PaleoDiet (Table 5).

In summary, a number of studies have presented different mechanistic insights related to the beneficial effect of the PaleoDiet on cardiometabolic diseases, especially overweight/obesity and T2D.

Micronutrient intake associated with the Paleolithic diet. Several trials provided information about micronutrient intake and the changes observed after PaleoDiet intervention. A number of these studies showed a lower intake of Na after the PaleoDiet intervention[10,34,39,42–45], and higher intake of K[10,39,42].

One parallel trial in postmenopausal overweight and obese woman analysed iodine deficiency and free thyroxine (FT4), free triiodothyronine (FT3) and thyrotropin (TSH)[31]. They found that short-term (6 months) PaleoDiet intervention resulted in lower FT3 than the Nordic Nutrition Recommendations diet. Moreover, a long-term PaleoDiet intervention resulted in a higher risk of developing mild iodine deficiency compared with a control diet (Table 5). Genoni *et al.*[43] also observed a lower of iodine in the PaleoDiet group in a 4-week randomised trial.

Jospe *et al.*[44] found that Ca intake was significantly higher in the Mediterranean diet group compared with the PaleoDiet group after 6 and 12 months of follow up A lower intake of Ca was also found in a 4-week trial with healthy women[43] and in a 3-week pilot study with healthy volunteers[42].

The Paleolithic diet in perspective with other healthy dietary patterns. According to the present review, current evidence suggests that the PaleoDiet may have potential benefits in the prevention of obesity and T2D, although this evidence is limited due to small sample size, the short follow-up of most studies, and it is based on surrogate outcomes. Different studies analysed in the present review compared the PaleoDiet with other healthy diets such as the American Heart Association, ADA, or Nordic Nutrition Recommendations, the Dutch Health Council guidelines, the Mediterranean diet, the diabetes diet or the Australian Guide to Healthy Eating diet. As shown in Table 5, the improvement associated with the PaleoDiet was statistically significant in comparison with some of these dietary patterns regarding body weight[9,37,43], HBA1c levels and cholesterol levels[44], and satiety[42]. However, in most of these comparisons the follow-up was short (14 d to 4 months). Moreover, non-significant differences were found in other comparisons in different studies[9,26–28,39,44,45]. Of course, these negative results cannot be interpreted as a demonstration of equivalence between these dietary patterns since the sample size is small.

The PaleoDiet, similar to other dietary patterns, measures the overall and synergistic effect of all its components. The potential beneficial effects of the PaleoDiet could be attributed to a high consumption of fruits, vegetables, fish and nuts, which are important sources of fibre, MUFA and PUFA, as well as to a very limited or no consumption of processed and ultra-processed food, and limited intake of added sugar, salt and refined oils.

The PaleoDiet is characterised by relatively high protein intake and high consumption of meat, especially lean meat. Most studies included both red and white meat as part of this diet, although with preference for lean meats. However, getting the difference between lean and non-lean meat to the general population can be tricky. Moreover, the nutrient composition of meat available today is probably different from meat consumed in the Paleolithic era, which was low in saturated fats and higher in n-3 fatty acids, particularly α-linolenic acid, as animals would have been free range[52]. In fact, the consumption of animal protein (especially red meat) during the Paleolithic age may conflict with current nutritional guidelines and studies supporting the reduction of meat intake for both health and environmental reasons. Different studies have already shown the increased risk of cancer with a higher consumption of red and ultra-processed meats[55–59]. However, since the PaleoDiet supports the consumption of non-processed meats, more studies are needed to explore the relevance of the quality of protein intake, such as for example the healthy *v.* the unhealthy sources of protein, beyond the quantity of protein, that would be acceptable for the general population[60]. In any case, a higher intake of non-processed meat could be associated with an increased cost and it would not be feasible to recommend this diet for the general population[61], and also for the environmental consequences of animal food consumption[62].

The recommendation to exclude legumes and whole grains in the PaleoDiet is another source of controversy if compared with recommendations from other healthy diets. Some studies

Table 6. Proposal of the new Paleolithic diet (PaleoDiet) score for observational studies

Components of the PaleoDiet score (g/d)	Range	Criteria for minimum points of each item (1)	Criteria for maximum points of each item (5)
Food groups with direct score			
Fruits	1–5	Lowest quintile	Highest quintile
Tree nuts	1–5	Lowest quintile	Highest quintile
Vegetables	1–5	Lowest quintile	Highest quintile
Fish	1–5	Lowest quintile	Highest quintile
Eggs	1–5	Lowest quintile	Highest quintile
Unprocessed meats (lean meats)	1–5	Lowest quintile	Highest quintile
Food groups with inverse score			
Dairy products	5–1	Highest quintile	Lowest quintile
Cereals and grains	5–1	Highest quintile	Lowest quintile
Legumes	5–1	Highest quintile	Lowest quintile
Culinary ingredients (added sugar, salt and refined oils)	5–1	Highest quintile	Lowest quintile
Processed and ultra-processed foods	5–1	Highest quintile	Lowest quintile
Total range scoring	11–55		

have shown the beneficial effects of legumes, such as risk reduction of IHD[63], LDL-cholesterol[64], systolic blood pressure[65], body fat[66], and the reduction of oxidative stress, pro-inflammatory marker C-reactive protein and cholesterol levels[67,68]. Moreover, the consumption of legumes is beneficial for environment sustainability because they are N-fixing and therefore they increase soil fertility[69].

The promotion of a relatively high-protein diet may have negative consequences for a long-term adherence of the PaleoDiet. A recent study has shown that total protein intake is quite stable in many countries: about 16 % of total energy, independent of lifestyle and demographic factors[70]. According to the 'protein leverage theory', humans and other animals avoid high- and low-protein diets and they strongly regulate protein intake in comparison with other macronutrients[71]. This fact may help to understand the low level of adherence when free-living humans are advised to change their macronutrient intake, especially protein intake. In fact, compliance with the PaleoDiet can be difficult, especially in the long term[43].

Finally, restriction of some foods within the PaleoDiet could determine the adequate intake of some specific micronutrients. According to the definition of the PaleoDiet, this diet could provide the recommended daily intake of all micronutrients[72,73]. In fact, one positive aspect of this restriction is the lower intake of Na and higher intake of K in comparison with other diets. However, a lower intake of iodine could be related to the restriction of iodised table salt and dairy products[74] and the restriction of dairy products could also explain the lower intake of Ca[75,76].

Proposal of the Paleolithic diet score

In the present review we found that only one definition proposed a score to quantify adherence to the PaleoDiet[11]. As we have described before, these authors scored PaleoDiet adherence with fourteen items and participants were classified into quintiles according to these items. Among the positive items, two of them were probably based on health reasons but not as a characteristic of the original PaleoDiet. One item was fruit and vegetable diversity, and another was the intake of Ca from sources other than dairy products. On the one hand, the PaleoDiet was dependent of the geographical, seasonal, weather and soil conditions and therefore in most cases it would be not possible to achieve this diversity. On the other hand, in Whalen's score[1,11,40], Ca intake was indirectly measured in the item on fruit and vegetable intake and the item on fruit and vegetable diversity. Moreover, Ca intake was calculated as residuals from the linear regression of total Ca intake and this also included Ca supplements. The score by Whalen *et al.*[1,11,40] only included beef meet as red lean meat (plus skinless chicken and turkey) and all non-lean red meat was excluded. However, the general opinion is that any red lean meat was characteristic of the diet among hunter–gatherer societies[77]. Finally, in this score only sugar-sweetened beverages and baked goods were used as sources of added sugar. In our score described below, we included an item such as processed and ultra-processed foods (that includes other foods that are not sweet but with added sugar and salt) and another item to refer to the culinary ingredients (added sugar, salt and refined fats).

We propose a new definition of the PaleoDiet based on those foods that were most frequently used in the definitions we have identified (items found in ≥50 % of the PaleoDiet definitions), and also considering foods which are consistent with the theoretical definition of the PaleoDiet. As anthropologists have described the PaleoDiet as the diet existing before the development of agriculture[50], foods from wild animals and plants were mostly accounted for in our new definition. Also, a numeric score was calculated in order to measure adherence to this dietary pattern.

The new PaleoDiet score that we promote encompasses eleven items: six items refer to foods that should be part of a PaleoDiet: fruits, nuts, fish, vegetables, eggs and meats (lean meats); and another five items refer to dietary variables that should be excluded from the PaleoDiet definition: cereals and grains, dairy products, legumes, culinary ingredients (added sugar, salt and refined oils) and ultra-processed foods (Table 6). We defined a score following a similar approach applied in other dietary patterns such as the Dietary

Approaches to Stop Hypertension (DASH)[78] score, a Mediterranean diet score[79] and the previous PaleoDiet score[11]. Thus, each of the eleven items was categorised according to quintiles of intake. Those items promoted within the PaleoDiet received a minimum of 1 point for the lowest quintile and a maximum of 5 points for the highest quintile. In contrast, those items negatively associated with the PaleoDiet definition received a maximum of 5 points for the lowest quintile and 1 point for the highest quintile. Finally, we constructed the PaleoDiet score by summing all the values, ranging from 11 (lowest adherence) to 55 (highest adherence). This quantified score could be applied in any observational study once food intake has been derived from FFQ or other method of dietary assessment.

Limitations and strengths

The scoping review

The main limitation of our scoping review is that we have not followed a more thorough methodology such as the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Nevertheless, systematic reviews and meta-analyses are usually focused on specific aims according to one main independent variable (for example, PaleoDiet) and a specific outcome. Our scoping review had a broader perspective since we were focused on the different definitions of the PaleoDiet and secondarily we reviewed the association between these PaleoDiet definitions and several outcomes. Furthermore, our search identified several systematic reviews that included a smaller number of studies related to the PaleoDiet[12,14,16], and our comprehensive review used literature review methods that are specific and thorough to avoid outcome bias[80]. In addition, information extracted from the selected studies in this review was independently performed by two reviewers, who resolved their discrepancies by consensus.

The Paleolithic diet definition

The promotion of the PaleoDiet is based on the concept of evolutionary health promotion[49]. According to this concept, human lifestyles, including diet, have evolved more rapidly than human genetic evolution. Basically, this dissonance may explain the increased morbidity and mortality in our Modern times since the origin of agriculture. According to this, the recovery of the diet of our ancestors should become a new paradigm to reduce the burden of chronic and degenerative diseases associated with our lifestyle.

One important limitation of the PaleoDiet is our partial knowledge about the diet of our ancestors during the Paleolithic age. Anthropological and archeological studies have shed new light about the human diet during this time. For example, an anthropological study about food consumption during this period observed a disparity in relation to the consumption of starch and the heterogeneity of food habits among different populations[81]. An archeological study has found evidence of cooked starchy plant foods in Africa 170 000 years ago[82]. As a consequence, the PaleoDiet will be always defined with some level of uncertainty and without taking into account other characteristics of a hunger–gatherer lifestyle.

Another limitation is the variability of the PaleoDiet due to the availability of food depending on the geographical area and the long period of the Paleolithic era with their respective variations in food consumption and nutritional composition of the diet. Moreover, diets based on ancient civilisations are always dependent on the adaptation of the animal and vegetable species available nowadays. The differences between domestic/supermarket meat *v.* lean meat and wild plants *v.* cultivated plants are factors that are difficult to control.

A new Paleolithic diet score

The PaleoDiet was already popular before solid scientific evidence was available. The present review has shown that this dietary pattern may have beneficial effects, especially in relation to cardiometabolic diseases although the evidence is still limited. The definition and adaptation of the PaleoDiet are key aspects as well as the need of a pragmatic and realistic approach to follow a healthy diet[17]. Similar questions are faced with the promotion of traditional diets such as Japanese or Mediterranean diets. However, this is more challenging when we try to restore a diet from ancient times, sometimes with some halo of mysticism such as the Avicennian diet[83].

Both interventional and observational epidemiological studies are needed to support the promotion of any dietary pattern with scientific evidence. The development of diet scores is a common strategy to evaluate the level of adherence and also as simple assessment tools to promote traditional healthy diets[84,85]. We have previously discussed the limitations of the PaleoDiet score found in the present review[11]. In this review we propose a new score which follows a similar approach to score the PaleoDiet according to the quintiles of adherence to different items. However, we have used a lower number of items and we have modified some of them. Our score is based on a systematic search of previous definitions and the analysis of the theoretical definition of the PaleoDiet. Thus, we have eliminated the use of fruit/vegetable diversity and Ca as components of the PaleoDiet. We have added the use of ultra-processed foods as they have a high content of saturated fats, added salt and sugar as well as low content of fibre[86,87]. Therefore, we consider that ultra-processed foods are representative of the group of foods that should not be part of the PaleoDiet in addition to grains, legumes and dairy products.

One limitation of our score is that no quantitative information is proposed to determine the amount that should be consumed of each food group. Therefore, this score could not be used as a self-administered score to assess adherence to the PaleoDiet. However, we think more epidemiological research is needed before we can promote the PaleoDiet as a healthy diet and also to establish clear recommended cut-offs of each food within this diet. Our proposed score is aimed to measure the PaleoDiet and to quantify the longitudinal relationship of the overall diet with chronic diseases. The use of FFQ is the best approach to capture the usual intake and to explore whether the dietary recommendations are met over time in large populations. The general problem is that these questionnaires are usually based on self-reported information and they have important limitations in capturing the absolute intake of foods and nutrients[88].

Another limitation is the use of population-specific values (quintiles) as cut-off levels for scoring each item of the PaleoDiet. This approach limits the comparison of PaleoDiet scores across populations but when fixed cut-off levels are defined it is possible that some components do not contribute to the overall score because all participants receive the same score[89]. Our approach allows all score components to contribute to the overall PaleoDiet score. An alternative could be the development of a weighted PaleoDiet score, for example with weights according to the burden of disease associated with each component, but more research is needed to use objective weights that can be implemented in different populations[90].

Conclusion

According to our scoping review, scientific evidence suggests beneficial effects of predefined PaleoDiet patterns in lipid markers, obesity, insulin and glucose altered levels, appetite and satiety, and improvements in patients with neurological diseases. However, current evidence about the PaleoDiet is limited because most of the experimental studies are focused on intermediate outcomes, such as body weight or fat mass, instead of hard endpoints such as T2D, CVD or cancer.

We have found that almost all definitions of the PaleoDiet include fruits, nuts, vegetables, fish, eggs and lean meats as characteristic foods of the PaleoDiet. Similarly, dairy products, cereals and grains, legumes and culinary ingredients (added salt, sugar and refined fats) were discouraged foods in most PaleoDiet definitions. However, we have observed a high heterogeneity regarding specific foods that should be added or excluded within the PaleoDiet definition and sometimes with some contradictory criteria such as the exclusion of eggs or potatoes. In this review, we report a simplified operational definition of this dietary pattern and a quantification system mode that could be used in observational studies.

Finally, more nutritional epidemiology research is needed to demonstrate the nutrient adequacy and long-term association of a higher adherence to this PaleoDiet score with the prevention of the most prevalent chronic diseases.

Acknowledgements

The present review received no specific grant from any funding agency, commercial or non-profit sectors.

V. d. l. O. participated in the conception and design of the study, conducted the critical review of current literature and the assessment and wrote the first draft of the manuscript. M. R.-C. and I. Z. developed the concept and design of the present review and supervised the analysis of the results and the writing of the manuscript, J. A. M., S. S., S. C. and M. A. Z. contributed to the design and implementation of the research, to the critical analysis of the results and to the writing of the manuscript. All included authors were involved in the review and subsequent approval of the final version of the manuscript.

There are no conflicts of interest.

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