Paleolithic nutrition for metabolic syndrome: systematic review and meta-analysis1,2

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ABSTRACT

Background: Paleolithic nutrition, which has attracted substantial public attention lately because of its putative health benefits, differs radically from dietary patterns currently recommended in guidelines, particularly in terms of its recommendation to exclude grains, dairy, and nutritional products of industry.

Objective: We evaluated whether a Paleolithic nutritional pattern improves risk factors for chronic disease more than do other dietary interventions.

Design: We conducted a systematic review of randomized controlled trials (RCTs) that compared the Paleolithic nutritional pattern with any other dietary pattern in participants with one or more of the 5 components of metabolic syndrome. Two reviewers independently extracted study data and assessed risk of bias. Outcome data were extracted from the first measurement time point (≥12 mo). A random-effects model was used to estimate the average intervention effect. The quality of the evidence was rated with the use of the Grading of Recommendations, Assessment, Development and Evaluation approach.

Results: Four RCTs that involved 159 participants were included. The 4 control diets were based on distinct national nutrition guidelines but were broadly similar. Paleolithic nutrition resulted in greater short-term improvements than did the control diets (random-effects model) for waist circumference (mean difference: −2.38 cm; 95% CI: −4.73, −0.04 cm), triglycerides (−0.40 mmol/L; 95% CI: −0.76, −0.04 mmol/L), systolic blood pressure (−3.64 mm Hg; 95% CI: −7.36, 0.08 mm Hg), diastolic blood pressure (−2.48 mm Hg; 95% CI: −4.98, 0.02 mm Hg), HDL cholesterol (0.12 mmol/L; 95% CI: −0.03, 0.28 mmol/L), and fasting blood sugar (−0.16 mmol/L; 95% CI: −0.44, 0.11 mmol/L). The quality of the evidence for each of the 5 metabolic components was moderate. The home-delivery (n = 1) and dietary recommendation (n = 3) RCTs showed similar effects with the exception of greater improvements in triglycerides relative to the control with the home delivery. None of the RCTs evaluated an improvement in quality of life.

Conclusions: The Paleolithic diet resulted in greater short-term improvements in metabolic syndrome components than did guideline-based control diets. The available data warrant additional evaluations of the health benefits of Paleolithic nutrition. This systematic review was registered at PROSPERO (www.crd.york.ac.uk/PROSPERO) as CRD42014015119. Am J Clin Nutr 2015;102:922–32.

Keywords: meta-analysis, Paleolithic diet, randomized controlled trials, systematic review, metabolic syndrome, cardiovascular risk, GRADE

INTRODUCTION

The metabolic syndrome is a cluster of 5 risk factors, including waist circumference, blood pressure, and serum concentrations of glucose, triglycerides, and HDL cholesterol in the fasting condition, which often occur in concert and predispose people to type 2 diabetes and cardiovascular disease. If ≥3 of these factors are in the pathological range, an individual is diagnosed with the metabolic syndrome (1). However, epidemiologic studies have consistently revealed that every single risk factor raises risks of diabetes and cardiovascular disease independent of the status of the other risk factors (2, 3).

Insulin resistance is believed to underlie most, if not all, of the components of the metabolic syndrome (4). Many ingredients of our modern (processed) food can induce low-grade inflammation and insulin resistance (5–7). Indeed, compelling evidence has supported the postulate that the macronutrient composition and numerous aspects of processing of modern nutrition are critically involved in the pathogenesis of metabolic disorders (8). Therefore, it is conceivable that the avoidance of modern food can ameliorate the metabolic anomalies that occur in the framework of the metabolic syndrome.

The nutritional patterns of our ancestors from the Paleolithic era (2.6 million to ~10,000 y ago), before the advent of modern (industrial) agriculture, differed considerably from current standards. However, there was no single Paleolithic nutritional pattern. Food choices critically depended on the geographical latitude and climate (8). Therefore, the diets of our Paleolithic ancestors varied considerably in the composition of macronutrients and the proportion of vegetable compared with animal foods. However, the food of our pre-agricultural ancestors was virtually devoid of cereals, newborns were fed breast milk, but children and adults never

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2Supplemental Tables 1–3 are available from the “Supplemental data” link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.
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touched milk products, and heating was probably the only significant food-processing procedure.

Paleolithic nutrition has gained popularity worldwide because of its putative health benefits. “Paleo” was the most searched diet-related term on Google in 2014 (9). However, a 2015 US News and World Report ranking of 35 diets with input from a panel of health experts placed the Paleolithic diet dead last, citing a lack of research evidence that showed clinical benefits (10). Several randomized trials have been published recently, but these have not, as yet, been systematically reviewed. The objective of this systematic review of randomized controlled trials (RCTs) was to evaluate whether current evidence supports the postulate that Paleolithic nutrition improves risk factors for chronic disease more than do other dietary interventions in people with one or more components of the metabolic syndrome.

METHODS

The protocol for this systematic review was registered in the PROSPERO database of prospectively registered systematic reviews in December 2014 (www.crd.york.ac.uk/PROSPERO; CRD42014015119) (11), and the completed review conforms to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (12).

Data sources and searches

We searched PubMed (http://www.ncbi.nlm.nih.gov/pubmed/), the Cochrane Central Register of Controlled Trials (http://www.cochranelibrary.com/), Embase (http://www.embase.com/), Literatura Latinoamericana y del Caribe en Ciencias de la Salud (http://lilacs.bvsalud.org/en/), the Science Citation Index (http://apps.webofknowledge.com), and Scopus (http://www.scopus.com/) from inception to January 2015 to identify published RCTs (11). To identify RCTs that may be relevant for possible future updates of this review, we also searched the following databases of ongoing trials: the US NIH’s clinicaltrials.gov, the WHO’s International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/), The Australian and New Zealand Clinical Trials Registry (http://www.anzctr.org.au), and the ISRCTN registry (www.isrctn.com). Two authors independently reviewed the studies identified in the searches for published trials (EWM and ZF) and ongoing trials (EWM and EJvZ) with no disagreements on the study selection. Experts in the field were contacted and asked if they were aware of any other potentially eligible trials.

Study selection

We included RCTs that compared Paleolithic nutrition with any other dietary intervention in participants with one or more of the 5 components of the metabolic syndrome (see Outcomes) but without a chronic (progressive) disease (11). We included RCTs in any language that were published as either full articles or abstracts. Crossover RCTs were eligible for inclusion, but we used data from only the first phase before the crossover occurred because we considered the risk of carryover effects to be high. Our specific inclusion criteria for a Paleolithic nutritional pattern were that it comprised vegetables (including root vegetables), fruit (including fruit oils, e.g., olive oil, coconut oil, and palm oil), nuts, fish, meat, and eggs, and it excluded dairy, grain-based foods, legumes, extra sugar, and nutritional products of industry (including refined fats and refined carbohydrates). Eligible trials could have either provided participants with advice to follow a Paleolithic nutritional pattern or delivered foods relevant to a Paleolithic nutritional pattern. For the comparison of the Paleolithic diet with the control diet, we included both isocaloric and ad libitum designs. Isocaloric diets are designed to have the same number of calories in each group. Ad libitum designs impose no calorie restriction in either group. We prespecified a minimum duration of the dietary intervention of 1 wk (11).

Data extraction and quality assessment

Two authors (EWM and EJvZ) independently extracted study details and outcome data with the use of predetermined forms designed for this purpose. The 2 authors only included data if there was an independently reached consensus, and a third author (ZF) was consulted in the event of any disagreement. To assess risk of bias, we used the Cochrane Collaboration’s domain-based evaluation tool as described in Chapter 8, Section 8.5, in the Cochrane Handbook for Systematic Reviews of Interventions. We specified “baseline imbalance” as the “other source of bias” domain for our assessments (11). Two authors (EWM and EJvZ) independently assessed risk of bias in the included trials. A third author (ZF) checked all risk-of-bias assessments and was involved in reaching a consensus for disagreements. We contacted the principal investigators of all of the trials with specific questions related to the design and outcomes of their trials. We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the quality of evidence for the various outcomes (13). Our GRADE assessment was not solely based on study hierarchy but also took into consideration additional key factors such as limitations in the study conduct, inconsistency, imprecision, directness of the evidence, and publication bias.

Outcomes

Our prespecified primary outcome measures were changes from the baseline of each of the following 5 component variables of the metabolic syndrome: waist circumference, triglycerides, HDL cholesterol, blood pressure (systolic and diastolic), and fasting blood sugar (11). Two additional primary outcomes were participant-assessed changes in the quality of life and proportion of participants who reported an adverse event throughout the study period. Our prespecified secondary outcome measures were body weight and fasting plasma concentrations of insulin-like growth factor I, uric acid, C-reactive protein, insulin, and total cholesterol (11).

For short-term effects, we extracted data from the first outcome-assessment time point from each trial (11). The time point of interest for this review was the short-term effects of Paleolithic nutrition on metabolic risk factors. Our primary question was whether Paleolithic nutrition has any effect in improving metabolic risk factors. Short-term efficacy dietary trials are generally considered to be best suited to answer this question because they have higher compliance and fewer losses to follow-up.

Data synthesis and analysis

For all outcomes, we used the mean difference as the effect measure. We combined the mean differences with the use of the
random-effects model in RevMan software (version 5.3; Nordic Cochrane Centre). The random-effects model estimates the average mean difference by incorporating heterogeneity in clinically heterogeneous trials with different but related treatment effects. The 95% CI from the random-effects model describes the uncertainty in the location of the mean of systematically different mean differences in the different trials. When heterogeneity exists, the model assigns smaller studies more weight than they would receive in a fixed-effects model (14). The degree of statistical heterogeneity between studies was assessed with the use of the $I^2$ statistic. We reported statistical heterogeneity as important if it was at least moderate to substantial ($I^2 > 50$%) or if there was inconsistency across RCTs in the direction of effect (14). All outcome data were reported with their 95% CIs. We used individual patient data for any trials with discrepancies in the published analysis (15).

RESULTS

Four RCTs with a total of 159 randomly assigned participants met the inclusion criteria (15–18) (Figure 1). Table 1 shows the most-important characteristics of the included RCTs.

The Paleolithic nutritional patterns were broadly similar across RCTs and representative of the Paleolithic nutrition in current practice (i.e., comprising only unprocessed meat, fish, eggs, vegetables, fruit, and nuts in variable proportions). There were some minor variations in Paleo nutrition across the 4 RCTs. For example, 2 RCTs limited consumption of one (16) or 2 (15) eggs/d and oil to 1Tbsp/d (14.79 mL/d (15, 16), whereas the other 2 RCTs (17, 18) did not limit the consumption of eggs or oil. Only one of the 4 RCTs recommended macronutrient proportions for the Paleo-diet group (18), which were 30% of energy intake from protein, 40% of energy intake from fat, and 30% of energy intake from carbohydrates.

Control diets were based on current dietary guidelines and recommendations worldwide. Control diets used in the RCTs conducted in Sweden (18) and the Netherlands (17) were based on national dietary guidelines of Scandinavian countries (25) and the Netherlands (26), respectively. The control diet used in the RCT of Jonsson et al. (15) was based on an international dietary guideline for people with diabetes (27). The control diet used in the RCT of Lindeberg et al. (16) was termed a “Mediterranean-like Consensus” diet because participants were informed about the Lyon Heart study (28) and educated about the possible benefits of Mediterranean-like diets rich in whole grains (29).

Control-diet nutritional patterns were, in general, similar across RCTs. They all advocated increased consumption of cereals and low-fat dairy products, the restriction of saturated fat from <10% (15, 17, 18) to 15% (16) of total daily energy, and the allowance of refined vegetable oils and processed foods. There were some differences in the specifics of their macronutrient-proportion recommendations. Although the control diets in the RCT of Jonsson et al. (15) and Mellberg et al. (18) explicitly recommended that carbohydrate intake range between 45% and 60% of total energy (15, 18), between 10% and 20% of energy from protein (15, 18), and between 25% and 30% (18) or $\leq 35$% (15) of energy from total fat, the control diets in the RCTs of Lindeberg et al. (16) and Boers et al. (17) did not provide specific recommendations on the proportion of energy derived from each macronutrient. Full details of the Paleolithic nutritional patterns and control diets used in the 4 RCTs are included in Supplemental Table 1.

In 3 trials (15, 16, 18), the intervention was dietary information and advice. Ad libitum consumption of both diets was advised and with no recommended restriction on caloric intake. The trial of Boers et al. (17) provided home-delivered Paleolithic- and control-diet meals to participants; isocaloric meals were delivered at baseline, but additional snacks were provided to participants who lost $>2$ kg body weight without being hungry.

Risk of bias

A risk-of-bias summary is presented in Figure 2. All 4 RCTs used adequate methods of random-sequence generation and allocation concealment. Three RCTs were judged to be at low risk of bias because of incomplete outcome data that were based on low numbers of losses to follow-up (15, 17, 18), and one RCT was judged to be at unclear risk (16). The lack of blinding of participants and personnel in all RCTs might possibly have influenced how patients were treated by the physician and other study personnel (i.e., performance bias); therefore, we judged this domain as having unclear risk of bias for all 4 RCTs. One RCT had a clear baseline imbalance, with the Paleolithic diet group having statistically significant worse values at baseline for 5 outcome variables, and therefore, we judged this domain as being at high risk (17). Detailed explanations for our judgments for each risk-of-bias domain are included as Supplemental Table 2.

Effects of interventions

The Paleolithic diet resulted in greater pooled improvements than did control diets for our primary outcomes of waist
<table>
<thead>
<tr>
<th>Study, year of publication, country (reference)</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindeberg et al., 2007, Sweden (16)</td>
<td>38 randomly assigned (29 analyzed) men with ischemic heart disease with waist circumferences &gt; 94 cm and increased blood glucose or known diabetes Mean age: 65 y (group A); 57 y (group B)</td>
<td>12 wk (6-wk time point for meta-analysis) Dietary advice on: A) Paleolithic diet B) Consensus Mediterranean-like diet Ad libitum food consumption in both groups</td>
<td>Waist circumference Triglycerides Systolic blood pressure Diastolic blood pressure C-reactive protein Total cholesterol Fasting blood sugar Body weight Fasting insulin</td>
</tr>
<tr>
<td>Jönsson et al., 2009, Sweden (15)</td>
<td>17 randomly assigned (13 analyzed) adults with type 2 diabetes Mean age: 66 y (group A); 63 y (group B)</td>
<td>6 mo (3-mo time point for meta-analysis) Dietary advice on: A) Paleolithic diet B) Diabetes diet in accordance with current guidelines Ad libitum food consumption in both groups</td>
<td>Waist circumference Triglycerides HDL cholesterol Systolic blood pressure Diastolic blood pressure Fasting blood sugar Body weight C-reactive protein Fasting insulin Total cholesterol</td>
</tr>
<tr>
<td>Mellberg et al., 2014, Sweden (18)</td>
<td>70 randomly assigned (61 analyzed) obese postmenopausal women Mean age: 59 y (group A); 60 y (group B)</td>
<td>2 y (6-mo time point for meta-analysis) Dietary advice on: A) Paleolithic diet B) Nordic Nutrition Recommendations diet Ad libitum food consumption in both groups</td>
<td>Waist circumference Triglycerides HDL cholesterol Systolic blood pressure Diastolic blood pressure Fasting blood sugar Adverse events Body weight C-reactive protein Fasting insulin Total cholesterol</td>
</tr>
<tr>
<td>Boers et al., 2014, Netherlands (17)</td>
<td>34 randomly assigned (34 analyzed) adults with ≥ 2 components of the metabolic syndrome Mean age: 52 y (group A); 55 y (group B)</td>
<td>2 wk Provision of meals for: A) Paleolithic diet B) Dutch Health Council guidelines for a healthy diet Delivery of isocaloric meals at baseline with snacks added for participants who lost ≥ 2 kg body weight without being hungry (n = 7 in group A; n = 2 in group B)</td>
<td>Waist circumference Triglycerides HDL cholesterol Systolic blood pressure Diastolic blood pressure Fasting blood sugar Body weight C-reactive protein Fasting insulin Total cholesterol</td>
</tr>
</tbody>
</table>
circumference, triglycerides, blood pressure (systolic and diastolic), HDL cholesterol, and fasting blood sugar (Figure 3). However, the greater pooled improvements were NS for 2 of the 5 components [i.e., HDL-cholesterol ($P = 0.11$) and fasting blood sugar ($P = 0.24$)].

We extracted the shortest time-point data from each trial for the meta-analyses for greater comparability in the duration of treatments across trials (11). However, the durations still varied from 2 wk (17) to 6 mo (18) (Table 1); the effects on primary outcomes were not associated with durations as evidenced by the relatively homogeneous and consistent benefits across RCTs and outcomes (Figure 3).

The home-delivery ($n = 1$) and dietary recommendation ($n = 3$) RCTs showed similar effects with the exception of greater improvements in triglycerides relative to control with home delivery ($I^2$ test for subgroup difference $= 85.6\%$). Although there was substantial heterogeneity in triglyceride effect sizes across RCTs, the heterogeneity was largely due to the larger benefits in the RCT of Boers et al. (17), which provided meals and, therefore, likely had greater adherence to the Paleolithic dietary pattern.

The quality of life and adverse effects were additional primary outcomes, but none of the included studies assessed the quality of life, and only one study (17) reported on adverse effects, highlighting gaps in the evidence (Table 2). The Paleolithic diet also resulted in greater pooled improvements than the control diets for the secondary outcomes (Table 3), but the pooled improvement was statistically significant only for body weight.

### Quality of evidence

Tables 2 and 3 present results of all outcomes in GRADE summary-of-findings tables. Included RCTs were methodologically sound and showed general consistency in the direction of effect. A baseline imbalance posed the greatest threat to the internal validity in these RCTs, and we judged this as being at high risk of bias in one RCT (17) and unclear risk in 2 other RCTs (15, 16). The baseline imbalances in these 3 RCTs were not explained by an inappropriate sequence generation, lack of allocation concealment, or exclusion of participants and, therefore, were unlikely to have been due to a selection bias. These baseline imbalances were not likely to lead to important exaggerations (or understatements) of mean differences, which were based on changes from baseline values and used objective outcome data. In addition, for the RCT of Boers et al. (17), we used outcome values from the mixed model, which adjusted for the baseline value of the specific outcome variable as appropriate (30). Despite these risks of bias, the overall high methodologic quality of the RCTs and the consistency in the direction of the effect for all outcomes supported our confidence in the quality of the evidence and the internal validity of the results of this review. The most-common reason for downgrading the quality of the evidence for outcomes was due to a low precision in the pooled estimate of effect (Tables 2 and 3). However, conclusions on the basis of results from even a small RCT may be more reliable than conclusions that are based on large cohort studies, which are much more vulnerable to a selection bias and confounding (31).

There are 2 ongoing RCTs, one of which has a large target sample size ($n = 150$; status: recruitment not begun) and the other of which has a small target sample size ($n = 15$; status: ongoing analysis) (Supplemental Table 3).

### DISCUSSION

#### Summary of main results

In this systematic review and meta-analysis of 4 RCTs, Paleolithic nutrition resulted in greater short-term pooled improvements on each of the 5 components of the metabolic syndrome than did currently recommended guideline-based control diets. However, the greater pooled improvements did not reach significance for 2 of the 5 components (i.e., HDL cholesterol and fasting blood sugar). For each metabolic syndrome component, the quality of the evidence for the pooled estimate for improvement was moderate. Furthermore, there was moderate quality evidence for greater weight loss on Paleolithic nutrition relative to the control diet. The absence of an assessment of both adverse events [with one exception (17)] and the quality of life by the trial investigators in all of these studies appears to have been a critical oversight.

#### Agreements and disagreements with other studies

To our knowledge, this is the first systematic review of RCTs of the effects of Paleolithic nutrition. Other lines of evidence also have
suggested benefits of the Paleolithic nutritional pattern. First, 3 uncontrolled trials reported that participants’ metabolic risk factors improved after only a short time consuming the Paleolithic diet (22–24). The durations of these trials ranged from 10 d to 5 wk, and the participants were healthy volunteers. Second, medical and anthropologic studies have shown that hunter-gatherer societies are largely free of the degenerative diseases of Western civilization, and this has been attributed partly to their diets (32). Third, anthropologic and medical research has shown that, when primitive cultures encounter civilization and adopt Western diets, their health worsens (33–35). For example, O’Dea (35) reported that, when Australian Aborigines transitioned from a traditional hunter-gatherer style to a westernized lifestyle, they developed high prevalence rates for obesity, diabetes, and related metabolic anomalies, all of which had previously been rare conditions in the Aborigines. Fourth, a temporary reversion to a traditional diet and lifestyle has been shown to result in marked improvement in metabolic risk factors in studies that involved Australian aborigines (36, 37).
Biological foundations of Paleolithic nutritional benefits

It has been proposed that insulin resistance has evolved as an adaptation to relatively low carbohydrate foods consumed by our ancestors for millions of years (38). The accrual of body fat, when food was plenty in the summer, rendered our ancestors [and today’s contemporaries who still carry the (epi)genetic architecture that predisposes them] insulin resistant, which facilitated survival in the winter by hampering the uptake of scarce carbohydrates in peripheral tissues, thereby leaving these carbohydrates for combustion by the brain. The agricultural revolution, yielding carbohydrate-rich crops as staple foods just 10,000 y ago, relaxed the selection pressure. The subsequent industrial revolution enabled the skyrocketing of agricultural production, which provided a continuous (over)supply of calories for every society member for the first time in human history. Moreover, food processing introduced massive amounts of simple carbohydrates into our dietary repertoire. Although myriad signs indicate that our gene pool rapidly adapts to the novel nutritional environment (39), many of us still carry gene variants that promote insulin resistance. In such individuals, overconsumption of processed (high–glycemic index) foodstuffs and (even whole-grain) cereals overloads the metabolic machinery with carbohydrates, yielding hyperglycemia and other metabolic anomalies. Paleolithic nutrition is virtually devoid of high–glycemic index carbohydrates (40).

Yet another distinction between Paleolithic nutrition and other diets (including low carbohydrate ones) that may contribute to its health benefits is the fact that it exclusively comprises non-processed foods. Food-processing procedures often entail the addition of salt and a variety of vegetable oils that contain a relative surplus of omega-6 (ω-6) fatty acids, shifting the ω-6 over ω-3 balance unfavorably upwards (6). High intakes of salt are associated with high blood pressure (41), and a high ω-6:ω-3 fatty acid ratio may induce chronic inflammation (7). Thus, the absence of processed food may contribute to the health benefits of Paleolithic nutrition.

Safety concerns

Paleolithic nutrition has been criticized as being too low in calcium intake. However, in the RCT of Boers et al. (17) they showed that, although calcium intake was indeed lower in the Paleolithic diet group, magnesium intake was higher, and the lower calcium intake was compensated for by lower calcium and magnesium excretions, which led the authors to speculate that “calcium homeostasis was unlikely to have become compromised.” One of the noncontrolled Paleolithic diet–intervention studies also showed a decrease from baseline in calcium excretion after 10 d consumption of the Paleolithic diet (22). The low-salt, high-protein, and alkalizing properties of Paleo nutrition may substantially contribute to a healthy calcium balance (42–44).

Implications for practice

Although there is moderate quality evidence from randomized controlled intervention studies to suggest that the Paleolithic diet can improve metabolic syndrome components, we believe that more studies are required before Paleolithic nutrition can be recommended in future guidelines.

Implications for research

Longer-term RCTs that compare currently recommended diets with Paleolithic nutrition and evaluate outcomes that are components of the metabolic syndrome as well as changes in the quality of life and adverse events should be conducted. Potential barriers to maintaining Paleolithic nutrition over the long term include the restriction of entire food groups (e.g., grains and dairy) and costs that are higher but still feasible on a limited budget (45). Preliminary evidence from this review suggests that the Paleolithic dietary pattern can be maintained at least as easily as currently recommended dietary patterns. In the RCT of Boers et al. (17), 89% of the Paleolithic group was motivated to continue the diet at the end of the...
<table>
<thead>
<tr>
<th>Primary outcomes</th>
<th>Anticipated absolute effects (95% CIs)</th>
<th>Participants (studies), n</th>
<th>Quality of evidence, GRADE</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference assessed in cm; follow-up range: 2–26 wk</td>
<td>Mean change in waist circumference ranged from −1.5 to −6.0 cm</td>
<td>137 (4 RCTs)</td>
<td>★ ★ ★, moderate</td>
<td>Paleolithic nutrition was more effective than the control diet was in reducing waist circumference</td>
</tr>
<tr>
<td>Triglyceride concentrations assessed in mmol/L; follow-up range: 2–26 wk</td>
<td>Mean change in triglyceride concentrations ranged from 0.1 to −0.45 mmol/L</td>
<td>137 (4 RCTs)</td>
<td>★ ★ ★, moderate</td>
<td>Paleolithic nutrition was more effective than the control diet was in reducing triglycerides</td>
</tr>
<tr>
<td>HDL-cholesterol concentrations assessed in mmol/L; follow-up range: 2–26 wk</td>
<td>Mean change in HDL-cholesterol concentrations ranged from −0.04 to −0.2 mmol/L</td>
<td>108 (3 RCTs)</td>
<td>★ ★ ★, moderate</td>
<td>Higher HDL values indicated reduced risk of metabolic disease</td>
</tr>
<tr>
<td>Systolic blood pressure assessed in mm Hg; follow-up range: 2–26 wk</td>
<td>Mean change in systolic blood pressure ranged from 1.33 to −8.5 mm Hg</td>
<td>137 (4 RCTs)</td>
<td>★ ★ ★, moderate</td>
<td>Paleolithic nutrition was more effective than the control diet was in reducing systolic blood pressure</td>
</tr>
<tr>
<td>Diastolic blood pressure assessed in mm Hg; follow-up range: 2–26 wk</td>
<td>Mean change in diastolic blood pressure ranged from −0.83 to −5 mm Hg</td>
<td>137 (4 RCTs)</td>
<td>★ ★ ★, moderate</td>
<td>Paleolithic nutrition was more effective than the control diet was in reducing diastolic blood pressure</td>
</tr>
<tr>
<td>Fasting blood sugar concentrations assessed in mmol/L; follow-up range: 2–26 wk</td>
<td>Mean change in fasting blood sugar concentrations ranged from 0.05 to −1.30 mmol/L</td>
<td>137 (4 RCTs)</td>
<td>★ ★ ★, moderate</td>
<td>Greater reductions in fasting blood sugar indicated reduced risk of metabolic disease</td>
</tr>
<tr>
<td>Quality of life was not assessed</td>
<td>—</td>
<td>0 (0)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Adverse effects assessed in proportion of participants who reported an adverse event</td>
<td>—</td>
<td>34 (1 RCT)</td>
<td>★ ★ ★, moderate</td>
<td>Boers et al. (17) reported no treatment-related adverse events and only one adverse event that was unrelated to treatment in the control-diet group</td>
</tr>
</tbody>
</table>

1Patient or population included participants with one or more components of the metabolic syndrome. The setting included outpatients at health clinics. The intervention was the Paleolithic diet, and the comparison was the control diet. GRADE, Grading of Recommendations Assessment, Development and Evaluation; RCT, randomized controlled trial GRADE levels are as follows: ★ ★ ★, high; ★ ★, moderate; ★, low; ★ ★ ★ ★, very low.

2Downgraded one level because of serious imprecision. The pooled 95% CI came very close to no effect (mean difference at the upper bound), and thus, there was low precision in the pooled estimate of a benefit.

3Downgraded one level for serious inconsistency ($I^2 = 73\%$). The RCT of Lindberg et al. (16) showed a qualitative difference in effect.

4Downgraded one level because of serious imprecision. The pooled 95% CI came close to showing a significant pooled benefit (mean difference at the upper bound), and thus, there was low precision in the pooled estimate of no significant benefit.

5Downgraded one level because of serious imprecision. There was a low occurrence of events and a low sample size.
### TABLE 3
Summary of secondary outcomes and findings of the Paleolithic diet compared with guideline-based control diets for metabolic syndrome

<table>
<thead>
<tr>
<th>Secondary outcomes</th>
<th>Anticipated absolute effects (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight assessed in kg; follow-up range: 2–26 wk</td>
<td>Mean change in body weight ranged across control groups from −1.23 to −3.00 kg. Mean reduction in body weight in the intervention group was 2.69 kg greater (4.87, 0.52 kg greater)</td>
</tr>
<tr>
<td>C-reactive protein assessed in mg/L; follow-up range: 2–26 wk</td>
<td>Mean change in C-reactive protein concentrations ranged across control groups from 1.35 to −6.30 mg/L. Mean reduction in C-reactive protein concentrations in the intervention group was 0.28 mg/L greater (0.76 mg/L lower, 0.21 mg/L higher)</td>
</tr>
<tr>
<td>Fasting insulin assessed in pmol/L; follow-up range: 2–26 wk</td>
<td>Mean change in fasting insulin concentrations ranged across control groups from 3.52 to −23.0 pmol/L. Mean reduction in fasting insulin concentrations in the intervention group was 12.87 pmol/L greater (32.28 pmol/L lower, 6.54 pmol/L higher)</td>
</tr>
<tr>
<td>Total cholesterol assessed in mmol/L; follow-up range: 2–26 wk</td>
<td>Mean change in total cholesterol concentrations ranged across control groups from 0.1 to −0.61 mmol/L. Mean reduction in total cholesterol concentrations in the intervention group was 0.24 mmol/L greater (0.56 mmol/L lower, 0.09 mmol/L higher)</td>
</tr>
</tbody>
</table>

1. Participants or population included participants with one or more components of the metabolic syndrome. The setting included outpatients at health clinics. The intervention was the Paleolithic diet, and the comparison was the control diet. GRADE, Grading of Recommendations Assessment, Development and Evaluation; RCT, randomized controlled trial GRADE levels are as follows: ⊗ ⊗ ⊗ ⊗, high; ⊗ ⊗ ⊗, moderate; ⊗ ⊗ ∗ ⊗, low; ⊗ ⊗ ⊗ ⊗, very low.

2. Downgraded one level because of serious imprecision. The pooled 95% CI came very close to no effect (mean difference at the upper bound), and thus, there was low precision in the pooled estimate of a benefit.

3. Downgraded one level because of serious imprecision. The pooled 95% CI came close to showing a significant pooled benefit (mean difference at the upper bound), and thus, there was low precision in the pooled estimate of no significant benefit.

4. Downgraded one level for serious inconsistency ($I^2 = 69\%$). The RCT of Lindeberg et al. (16) showed a qualitative difference in effect.
2-wk intervention period compared with 64% of the Dutch Health Council reference group. In the RCT of Mellberg et al. (18), there were fewer dropouts in the Paleolithic diet group than in the Nordic Nutrition Recommendations Group at 6 mo (n = 1 compared with 8, respectively) and at 2 y (n = 8 compared with 13, respectively).

In conclusion, state-of-the-art nutritional science readily explains the metabolic benefits of a (modest) restriction of carbohydrates, a lack of high-glycemic index products, low ω-6 over ω-3 fatty acid balance, and a reduction of salt intake in patients with insulin resistance and the metabolic syndrome. In contrast, it is less clear whether the avoidance of whole grains and dairy products is a prerequisite for the optimal control of metabolism. Although numerous small-scale pathophysiologic studies have highlighted their potential adverse health effects (46, 47), large-scale epidemiologic data suggest that whole grain– and (fermented) dairy consumption protects against diabetes (48). Future studies should carefully examine the importance for health of avoiding these food groups in the context of Paleolithic nutrition.

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