

1 **Unprocessed red meat and processed meat consumption: dietary guideline**  
2 **recommendations**

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65 **Running title:** Red and processed meat guideline recommendations

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77 **Description:** Dietary guideline recommendations require consideration of the certainty  
78 in the evidence, the magnitude of potential benefits and harms, and explicit  
79 consideration of peoples' values and preferences. We produced a set of  
80 recommendations regarding red meat and processed meat consumption based on five  
81 de novo systematic reviews that included consideration of all these issues.

82

83 **Methods:** We developed recommendations following the NutriRECS guideline  
84 development process that includes rigorous systematic review methodology, and the  
85 use of GRADE methods to rate the certainty of evidence for each outcome, and to move  
86 from evidence to recommendations. A panel including 14 members from seven  
87 countries, including three community members, voted on the final recommendations.  
88 Strict criteria limited the conflicts of interest among panel members. Considerations of  
89 environmental impact or animal welfare did not bear on the recommendations. We  
90 conducted four systematic reviews addressing the health effects associated with red  
91 meat and processed meat consumption, and one systematic review addressing people's  
92 health-related values and preferences regarding meat consumption.

93

94 **Recommendations:** The panel suggests that adults continue current unprocessed red  
95 meat consumption (weak recommendation, low certainty evidence). Similarly, the panel  
96 suggests adults continue current processed meat consumption (weak recommendation,  
97 low certainty evidence).

98

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100

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## 110 **Introduction**

111 Contemporary dietary guidelines recommend limiting consumption of  
112 unprocessed red meat and processed meat. For example, the 2015 Dietary Guidelines  
113 for Americans have recommended limiting red meat intake, including processed meat,  
114 to approximately one serving/day (1). Similarly, the UK dietary guidelines have endorsed  
115 limiting the intake of both red and processed meat to 70 g/day (2) while the World  
116 Cancer Research Fund/American Institute for Cancer Research have recommended  
117 limiting red meat consumption to moderate amounts and consuming very little  
118 processed meat (3). The World Health Organization International Agency for Research  
119 on Cancer has indicated that consumption of red meat is “probably carcinogenic” to  
120 humans while processed meat is considered “carcinogenic” to humans (4).

121 These recommendations are, however, primarily based on observational studies  
122 that are at high risk of confounding and thus are limited in establishing causal inferences  
123 nor do they report the absolute magnitude of any possible effects. Further, the  
124 organizations that produce guidelines have failed to conduct or access rigorous  
125 systematic reviews of the evidence, have been limited in addressing conflicts of interest,  
126 and have failed to explicitly address population values and preferences, raising  
127 questions regarding adherence to trustworthiness guideline standards (5-9).

128 A potential solution for the limitations of contemporary nutrition guidelines is  
129 for an independent group with clinical and nutritional content expertise and skilled in  
130 the methodology of systematic reviews and practice guidelines, methods that include  
131 careful management of conflicts of interest, to produce trustworthy recommendations  
132 based on the values and preferences of guideline users. We have developed the  
133 Nutritional Recommendations (NutriRECS) (7) international consortium to produce  
134 rigorous evidence-based nutritional recommendations adhering to trustworthiness  
135 standards (10-12).

136 To support our recommendations, we performed four parallel systematic  
137 reviews that focused both on randomized trials and observational studies addressing  
138 the possible impact of unprocessed red meat and processed meat consumption on  
139 cardiometabolic and cancer outcomes (13-16), and a fifth review addressing people’s

140 health-related values and preferences related to meat consumption (17). Based on  
141 these reviews, we developed recommendations for unprocessed red meat and  
142 processed meat consumption specific to health outcomes.

## 143 **Methods**

### 144 *Guideline Development Process*

145 We developed our recommendations following the NutriRECS guideline  
146 development process (7) that includes the use of GRADE methodology (18-20). To  
147 inform our guideline recommendations, systematic reviews were conducted based on a  
148 priori methods (21, 22).

### 149 *Guideline team structure*

150 This work involved three teams:

- 151 1. A core NutriRECS leadership team was responsible for supervision and coordination  
152 of the project, and for drafting of the research questions, guideline protocol and  
153 manuscripts;
- 154 2. A guideline panel included experts in health research methodology, nutritional  
155 epidemiology, dietetics, basic and translational research, family medicine, and  
156 general internal medicine. The panel included three members from outside the  
157 medical and health care communities. Panelists resided in high income countries  
158 (Canada, England, Germany, New Zealand, Poland, USA, Spain);
- 159 3. A literature review team drafted the protocols for the systematic reviews,  
160 completed the literature search and eligibility review, abstracted data and  
161 conducted data analysis and produced narrative and tabular summaries of the  
162 results.

### 163 *Framework for panel construction and guideline recommendations*

164 The core leadership team applied safeguards against competing interests (7).  
165 After generating a list of potential panel members without perceived vested interests,  
166 we contacted prospective candidates from North America, Western Europe and New  
167 Zealand. Those who expressed interest completed a detailed form enumerating  
168 potential financial or intellectual conflicts during the previous three years. If important  
169 competing issues were identified (one interested individual had financial conflicts), they

170 were not invited to participate. **Table 1** includes a summary of the conflict of interest  
171 forms, with full competing interests available upon request.

172         Prior to our initial guideline panel meeting, the methods editor and panel chair  
173 contacted panelists, shared the draft questions, and received and incorporated  
174 feedback. At the initial meeting, the guideline panel discussed the scope of the project,  
175 and agreed on the research questions and subgroups of interest. The panel focused on  
176 health outcomes thought to be associated with unprocessed red meat and processed  
177 meat and chose not to consider animal welfare and environmental issues related to  
178 meat consumption in making recommendations. The panel chose to exclusively focus on  
179 health outcomes because environmental and animal welfare concerns are very different  
180 issues, extremely challenging to integrate with health concerns, possibly more societal  
181 rather than personal issues, and with extreme variability in the extent to which people  
182 find these issues a priority. Finally, to consider these issues rigorously would require  
183 systematic reviews that we were not resourced to undertake. The panel also chose to  
184 make separate recommendations for unprocessed red meat and processed meat given  
185 the potential for differential health effects, and differing values and preferences  
186 members of the public may have to unprocessed meat versus processed meat.

#### 187 *Target audience for recommendations*

188         The target audience for our guidance statement was individuals who consume  
189 unprocessed red meat or processed meat as part of their diet. The panel took the  
190 perspective of individual decision-making rather than a public health perspective.

#### 191 *Key principles for PICO question and study eligibility criteria*

192         Each NutriRECS project addresses a single nutrition question or topic, in this case  
193 guidance regarding the potential harms, benefits and health-related values and  
194 preferences related to consuming unprocessed red meat and processed meat. We  
195 conducted a series of systematic reviews to inform our recommendations addressing  
196 the following questions: i) *Among adults, what is the impact of diets and dietary*  
197 *patterns lower in red or processed meat versus diets higher in red or processed meat*  
198 *intake on the risk of outcomes important to community members?* and ii) *What are their*  
199 *health-related values and preferences for red and processed meat consumption?*

200 The panel considered all-cause mortality, major cardiometabolic outcomes (e.g.  
201 cardiovascular mortality, stroke, myocardial infarction, diabetes), cancer incidence and  
202 mortality (i.e. gastrointestinal, prostate, female cancers), quality of life and willingness  
203 to change unprocessed red or processed meat consumption as *critically important* for  
204 developing recommendations. *Important* outcomes included surrogate outcomes  
205 (weight, body mass index, blood lipids, blood pressure, hemoglobin, anemia) and  
206 reasons for eating unprocessed red meat and processed meat.

### 207 *Methods for systematic reviews*

208 In consultation with an expert librarian, we searched the major literature  
209 databases to identify all relevant studies on harms, benefits and health-related values  
210 and preferences on unprocessed red meat and processed meat. Each database was  
211 searched from inception until July 2018 without restrictions on language or date of  
212 publication (see respective systematic reviews in this issue (13-17)).

213 For harms and benefits, we included any randomized trial, as well as cohort  
214 studies including 1,000 or more adults assessing diets with varying quantities of  
215 unprocessed red meat (e.g., servings or times/week, g/day) and/or processed meat  
216 (meat preserved by smoking, curing, salting, or by the addition of preservatives) (23) for  
217 a duration of six months or more. Studies in which more than 20% of the sample was  
218 pregnant or had cancer or a chronic health condition, other than cardiometabolic  
219 diseases, were excluded. The review articles report our methods for screening, data  
220 abstraction, risk of bias assessment and data analysis (13-17).

221 Panelists considered 3 servings per week as a realistic reduction in meat  
222 consumption (e.g. moving from 7 to 4, or 4 to 1 servings) based on the average intake of  
223 2 to 4 servings per week in North America and Western Europe (24-28). We therefore  
224 framed the evidence regarding the potential reduced risks associated with a decrease of  
225 3 servings per week of both unprocessed red meat and processed meat.

226 We used GRADEpro software to formulate GRADE summary of findings (SoF)  
227 tables for each PICO question (29). The overall certainty of evidence was evaluated  
228 using the GRADE approach (18). For estimates of risk with current levels of meat  
229 consumption we used population estimates from the Emerging Risk Factors

230 Collaboration study for cardiometabolic outcomes (30), and we used population  
231 estimates from Globocan for cancer outcomes (31). Using these resources, our  
232 estimates for cardiometabolic mortality and incidence outcomes are based on an  
233 average of 10.8 years of follow-up, while for cancer mortality and incidence our  
234 estimates are for the overall lifetime risk.

235         Complementing existing GRADE standards and to determine if we should rate up  
236 for a dose-response effect, we assessed the plausibility of a causal relationship between  
237 meat and adverse health outcomes contrasting results from two bodies of evidence (7,  
238 22): cohort studies specifically addressing red meat and processed meat intake, and  
239 cohort studies addressing dietary patterns associated with varying red meat and  
240 processed meat consumption. We hypothesized that if red meat and processed meat  
241 were indeed causally related to adverse health outcomes, we would find stronger  
242 associations in studies that specifically addressed red meat and processed meat intake  
243 versus studies addressing dietary patterns (7).

244         To address health-related values and preferences related to red meat and  
245 processed meat, we included qualitative (e.g. interviews, focus groups) and quantitative  
246 (e.g. cross-sectional survey) studies conducted in adults. We independently screened,  
247 abstracted data and assessed risk of bias (17) and synthesized the data into narrative  
248 themes and tabulated summaries, and again assessed the certainty of evidence using  
249 GRADE (18, 32).

250         To assist our three public panel members without health science backgrounds,  
251 the method's editor conducted electronic meetings with them prior to the guideline  
252 panel meetings to explain the systematic review results and the GRADE approach for  
253 assessing the certainty of evidence and for moving from evidence to recommendations.  
254 During the guideline panel meetings, the leads of each of the systematic reviews shared  
255 the summary data and certainty of evidence for each of our outcomes with the  
256 guideline panel, and the panel chair answered any questions as necessary.

#### 257 *Moving from evidence to recommendations*

258         Prior to our final guideline panel meeting, we asked each panellist to complete a  
259 GRADE Evidence to Decision (EtD) framework. The purpose of EtD frameworks is to help



260 panelists use the evidence summaries in a structured and transparent way to develop  
261 the final recommendations. In doing so the panellists considered evidence summaries  
262 for health effects, values and preferences, and also considered the cost, acceptability,  
263 and feasibility of a recommendation to decrease meat consumption (33). During the  
264 final meeting, the panel reviewed the results of the EtD survey and considered the  
265 implications of those judgments for their recommendations.

266 *Recommendation for unprocessed red meat*

267 For adults 18 years of age or older, we suggest continuing current unprocessed  
268 red meat consumption (weak recommendation, low certainty evidence). Eleven of 14  
269 panelists voted for a continuation of current unprocessed red meat consumption, while  
270 three voted for a weak recommendation to reduce red meat consumption.

271 *Recommendation for processed meat*

272 For adults 18 years of age or older, we suggest continuing current processed  
273 meat consumption (weak recommendation, low certainty evidence). Again, eleven of  
274 fourteen panel members voted for a continuation of current processed meat  
275 consumption, and three voted for a weak recommendation to reduce processed meat  
276 consumption.

277 *Summary evidence for harms and benefits for unprocessed red meat*

278 For our review of randomized trials on harms and benefits (12 unique trials  
279 enrolling 54 thousand participants), we found low to very low certainty evidence that  
280 diets lower in unprocessed red meat may have little or no effect on the risk for major  
281 cardiometabolic outcomes and cancer mortality and incidence (15). Dose-response  
282 meta-analysis results from 23 cohorts studies with 1.4 million participants provided low  
283 to very low certainty evidence that decreasing unprocessed red meat intake may result  
284 in a very small reduction in the risk for major cardiovascular outcomes (cardiovascular  
285 disease, stroke, myocardial infarction) and type 2 diabetes (range 1 fewer to 6 fewer  
286 events per 1000 with a 3 serving/week decrease), with no statistically significant  
287 differences in 2 additional outcomes (all-cause mortality, cardiovascular mortality) (16).  
288 Dose-response meta-analysis results from 17 cohorts with 2.2 million participants  
289 provided low certainty evidence that decreasing unprocessed red meat intake may

290 result in a very small reduction of overall lifetime cancer mortality (7 fewer events per  
291 1000 with a 3 serving/week decrease), with no statistically significant differences for 8  
292 additional cancers observed (prostate cancer mortality, and the incidence of overall,  
293 breast, colorectal, esophageal, gastric, pancreatic and prostate cancer) (13). Similar to  
294 studies directly addressing red meat, cohort studies assessing dietary patterns (70  
295 cohort studies with just over 6 million participants) provided mostly uncertain evidence  
296 for the risk of adverse cardiometabolic and cancer outcomes. Although statistically  
297 significant, low to very low certainty evidence indicates that adherence to dietary  
298 patterns lower in red or processed meat is associated with a very small absolute risk  
299 reduction in 9 major cardiometabolic and cancer outcomes (range 1 fewer to 18 fewer  
300 events per 1000), with no statistically significant differences for 21 additional outcomes  
301 observed (14). See **Appendix 1** for the GRADE summary of finding tables.

302 We summarize the benefits of eating meat below in a section on values and  
303 preferences: in short, omnivores enjoy eating meat, and consider meat an essential  
304 component of a healthy diet. There is also evidence of possible health benefits of  
305 omnivorous versus vegetarian diets on outcomes such as muscle development and  
306 anemia (34, 35), but we did not systematically review this literature.

#### 307 *Evidence summary for harms and benefits for processed meat*

308 No randomized trials directly assessed processed meat for our target outcomes.  
309 With respect to cohorts addressing adverse cardiometabolic outcomes (10 cohort  
310 studies with 778 thousand participants providing dose-response meta-analysis), we  
311 found low to very low certainty evidence that a decreased intake of processed meat was  
312 associated with a very small reduced risk for major morbid cardiometabolic outcomes  
313 including all-cause mortality, cardiovascular mortality, stroke, myocardial infarction, and  
314 type 2 diabetes (range 1 fewer to 12 fewer events per 1000 with a 3 serving/week  
315 decrease), with no statistically significant difference in 1 additional outcome  
316 (cardiovascular disease) (16). For cohort studies addressing adverse cancer outcomes  
317 (31 cohorts with 3.5 million participants providing data for our dose-response analysis),  
318 we also found low to very low certainty evidence that a decreased intake of processed  
319 meat was associated with a very small absolute risk reduction in overall lifetime cancer

320 mortality, prostate cancer mortality, and the incidence of esophageal, colorectal, and  
321 breast cancer (range 1 fewer to 8 fewer events per 1000 with a 3 serving/week  
322 decrease), with no statistically significant differences in incidence or mortality for 12  
323 additional cancers (colorectal, gastric, pancreatic mortality; overall, endometrial, gastric,  
324 hepatic, small intestinal, oral, ovarian, pancreatic, prostate cancer incidence)(13). For  
325 cohort studies assessing dietary patterns (70 cohort studies with over 6 million  
326 participants), although statistically significant, we found low to very low certainty  
327 evidence that adherence to dietary patterns lower in red or processed meat was  
328 associated with a very small absolute risk reduction in 9 major cardiometabolic and  
329 cancer outcomes (range 1 fewer to 18 fewer events per 1000), with no statistically  
330 significant differences for 21 additional outcomes observed (14). Again, we assessed the  
331 risk of adverse cardiometabolic outcomes based on an average of 10.8 years follow-up,  
332 and adverse cancer outcomes over a lifetime.

333 In our assessment of etiologic causal inferences on unprocessed red meat and  
334 processed meat and adverse health outcomes, we found that the absolute effect  
335 estimates for red meat and processed meat intake (13, 16) were smaller than those  
336 from dietary pattern estimates (14), indicating that meat consumption is unlikely to be a  
337 causal factor of adverse health outcomes (**Table 2**). We anticipated that, if unprocessed  
338 red meat or processed meat was indeed a causal factor in raising the risk of adverse  
339 outcomes, the observed association between unprocessed red and processed meat and  
340 adverse outcomes would be greater in studies directly addressing the lowest versus  
341 highest intake of unprocessed red or processed meat versus studies in which meat was  
342 only one component of a dietary pattern (7, 22). Using our findings, in our assessment  
343 of the certainty of evidence, we did not rate up for dose-response, given the potential  
344 for residual confounding (36). See **Appendix 1** for the GRADE summary of finding tables.

#### 345 *Evidence summary of health-related values and preferences for meat*

346 Our systematic review on health-related values and preferences yielded 54  
347 articles from Australia, Canada, Europe and the United States, including 41 quantitative  
348 and 13 qualitative studies (17). Omnivores reported enjoying eating meat, consider  
349 meat an essential component of a healthy diet and often felt they had limited culinary

350 skills to prepare satisfactory meals without meat. Participants tended to be unwilling to  
351 change their meat consumption. The certainty of evidence was low for “reasons for  
352 meat consumption”, and low for “willingness to reduce meat consumption” in the face  
353 of undesirable health effects due to issues of risk of bias (e.g. unvalidated surveys),  
354 imprecision (small number of participants in qualitative studies), and indirectness  
355 (failure to specifically ask about the health benefits that would motivate a reduction in  
356 meat consumption) (**Table 3**).

### 357 *Rationale for recommendations for red meat and processed meat*

358         The rationale for our recommendation to continue rather than reduce  
359 unprocessed red meat or processed meat consumption is based on: 1) low to very low  
360 certainty evidence for potential adverse health outcomes associated with meat  
361 consumption (13-16), supported by the similar effect estimates for red meat and  
362 processed meat consumption from dietary pattern studies as from studies directly  
363 addressing red meat and processed meat intake (13, 14, 16), 2) a very small absolute  
364 risk reduction based on a realistic decrease of 3 servings of red or processed per week,  
365 3) if the very small exposure effect is true, given peoples’ attachment to their meat  
366 based diet (17), the associated risk reduction is not likely to provide sufficient  
367 motivation to reduce red meat or processed meat in fully informed individuals, 4) the  
368 weak, rather than strong recommendation is based on the large variability in peoples’  
369 values and preferences related to meat (17), 5) the panel’s exclusive focus on health  
370 outcomes associated with meat, and our decision not to consider animal welfare and  
371 environmental issues. Taken together, these observations warrant a weak  
372 recommendation to continue current levels of red meat and processed meat  
373 consumption.

### 374 *Other considerations*

375         The panel judged that though for some people in some circumstances, issues of  
376 cost, acceptability, feasibility and equity may be relevant, these issues were not major  
377 considerations in making their judgements. Considerations of animal welfare, and  
378 particularly of environmental impact will certainly be important to some individuals; the  
379 latter might be of particular importance from a societal perspective (37-41). The panel,

380 at outset, decided that issues of animal welfare, and potential environmental  
381 impact were outside the scope of this guideline.

## 382 **Discussion**

### 383 *Summary*

384 We developed recommendations for unprocessed red meat and processed meat  
385 following the NutriRECS guideline development process that adheres to the Institute of  
386 Medicine and GRADE working group standards. Based on four systematic reviews  
387 assessing the harms and benefits associated with red meat and processed meat  
388 consumption, and one systematic review assessing people's health-related values and  
389 preferences on meat consumption, we suggest that individuals continue their current  
390 consumption of both unprocessed red meat and processed meat (both weak  
391 recommendations, low certainty evidence).

392 Our weak recommendation that people continue their current meat  
393 consumption highlights both the uncertainty associated with possible harmful effects,  
394 and very small magnitude of effect, even if the best estimates represent true causation,  
395 which we believe to be implausible. Despite our findings from our assessment of intake  
396 studies versus dietary pattern studies that suggest that unprocessed red meat and  
397 processed meat are unlikely to be causal factors for adverse health outcomes (13, 14,  
398 16), this does not preclude the possibility that meat has a very small causal effect. Taken  
399 together with other potential casual factors (e.g. preservatives such as sodium, nitrates  
400 and nitrites) (42) among dietary patterns with very small effects, this may explain the  
401 larger reductions among dietary patterns high in red meat and processed meat (14). The  
402 guideline panel's assessment was based on the available evidence regarding values and  
403 preferences suggesting that the majority of individuals, when faced with a very small  
404 and uncertain absolute risk reduction in cardiometabolic and cancer outcomes would  
405 choose to continue their current meat consumption. People considering decreasing  
406 their meat consumption should be aware of this evidence.

### 407 *Strengths*

408 We conducted five separate rigorous systematic reviews addressing both  
409 evidence from randomized trials and observational studies regarding the impact of

410 unprocessed red meat and processed meat on cardiovascular and cancer outcomes (13-  
411 16), and community values and preferences regarding red meat and processed meat  
412 consumption (17). Using the GRADE approach, our reviews explicitly addressed the  
413 uncertainty of the underlying evidence. We have presented results focusing on absolute  
414 estimates of effects associated with realistic decreases in meat consumption of three  
415 servings per week (See **Appendix 1**), and these estimates informed our  
416 recommendations. Our panel included nutrition content experts, methodologists, health  
417 care practitioners, and members of the public, and we minimized conflicts of interest  
418 through pre-screening panel members for financial, intellectual and personal conflicts of  
419 interest; providing a full account of potential competing interests (panel member  
420 conflict of interest forms available upon request).

#### 421 *Limitations*

422 Our guideline is limited in that we considered issues of animal welfare and  
423 potential environmental impact outside the scope of our recommendations. These  
424 guidelines may therefore be of limited relevance to individuals for whom these issues  
425 are of major importance. Related to this, we took an individual rather than a societal  
426 perspective. Decision makers considering broader environmental issues may reasonably  
427 consider evidence regarding the possible contribution of meat consumption to global  
428 warming, and suggest policies limiting meat consumption on that basis.

429 Regarding the uncertainty of the evidence - randomized trials were limited by  
430 the small differences in meat consumption between the intervention and control  
431 groups, while observational studies were limited in the accuracy of dietary  
432 measurement and possible residual confounding related both to aspects of diet other  
433 than red meat and processed meat and non-dietary confounders – making decisions  
434 regarding meat consumption particularly value and preference dependent. With respect  
435 to our review on dietary patterns, studies did not typically report data separately for red  
436 and processed meat. Moreover, although all dietary patterns discriminated between  
437 participants with low and high red and processed meat intake, other food and nutrient  
438 characteristics of dietary patterns varied widely across studies (14). Evidence was also  
439 limited in that we found information insufficient to conduct planned subgroup analyses

440 regarding the method of meat preparation (e.g. grilling vs. boiling) based on possible  
441 carcinogenic compounds from grilling such as polycyclic aromatic hydrocarbons (PAHs)  
442 and heterocyclic amines (HCAs) (43). Finally, our panel was not unanimous in its  
443 recommendation: three of 14 panel members favoured a weak recommendation in  
444 favour of decreasing red meat consumption.

#### 445 *Comparison with other guidelines*

446 As noted in our introduction, other dietary guidelines and position statements  
447 suggest limiting consumption of red and processed meat because of the reported  
448 association with cancer (1, 2, 44-46). There are three major explanations for these  
449 discrepancies. First, other guidelines have not used the GRADE approach to rating  
450 certainty of evidence that highlight the low or very low certainty of evidence supporting  
451 the causal nature of the association between meat consumption and health outcomes.  
452 As a result, we are less convinced of meat consumption as a cause of cancer. Because of  
453 the likelihood of residual confounding (i.e. confounding that exists after adjustment for  
454 known prognostic factors) the GRADE approach we used for assessing causation  
455 considers that – in the absence of a large effect or a compelling dose-response gradient  
456 – observational studies provide only low or very low certainty evidence for causation  
457 (47, 48). Second, even if one assumes causation, other guidelines have not calculated, or  
458 if calculated have not highlighted, the very small magnitude of the absolute adverse  
459 impacts over long periods of time associated with meat consumption. Third, other  
460 guidelines have paid little or no attention to the reasons people eat meat, and the  
461 extent to which they would choose to reduce meat consumption given small and  
462 uncertain health benefits. Indeed, no prior guideline has attended with care to evidence  
463 bearing on values and preferences, and in particular has not conducted a systematic  
464 review addressing the issue.

465 Nutritional guidelines are challenging because each potential source of evidence  
466 has substantial limitations. Randomized trials are limited by sample size, duration of  
467 follow-up, and difficulties participants have adhering to prescribed diets. These  
468 limitations make showing an intervention effect very challenging. Observational studies  
469 are limited in the inevitable residual confounding (unmeasured differences in prognosis

470 that remain after adjusted analyses). These limitations in randomized trials and  
471 observational studies are evident in studies addressing meat consumption and health  
472 outcomes. Studies focusing on intermediate outcomes (e.g. cholesterol and  
473 triglycerides) suffer from additional limitations in that changes in biomarkers often fail  
474 to deliver the anticipated benefits in patient-important health outcomes. Therefore, our  
475 reviews focused only on those outcomes important to patients. Nutritional  
476 recommendations must therefore, acknowledge the low quality evidence and avoid  
477 strong “just do it” recommendations that can, as evidenced by the many low fat  
478 recommendations worldwide (49), be very misleading.

#### 479 *How to interpret the recommendations*

480 A weak recommendation indicates that the panel believed that for the majority  
481 of individuals, the desirable effects (a potential lowered risk of cancer and  
482 cardiometabolic outcomes) associated with reducing meat consumption probably do  
483 not outweigh the undesirable effects (impact on quality of life, burden associated with  
484 modifying cultural and personal meal preparation and eating habits). The weak  
485 recommendation reflects the panel’s awareness that values and preferences differ  
486 widely, and that as a result a minority of fully informed individuals will choose to reduce  
487 meat consumption.

#### 488 *Implications for future research*

489 Generating higher quality evidence regarding the impact of red meat and  
490 processed meat on health outcomes would be, were it possible, both desirable and  
491 important. It may not, however, be possible. Randomized trials will always face  
492 challenges with participants complying with diets that differ sufficiently in meat  
493 consumption, adhering to these diets for very long periods of time, and being available  
494 for follow-up over these long periods. These challenges are all the more formidable  
495 because results of observational studies may well represent the upper boundary of  
496 causal effects of meat consumption on adverse health outcomes, and the estimated  
497 effects are very small. Observational studies will continue to be limited by challenges of  
498 accurate measurement of diet, the precise and accurate measurement of known



499 confounders (50), and the likelihood of residual confounding after adjusted analyses  
500 (13, 14, 16).

501           This assessment may be excessively pessimistic; indeed, we hope that is the  
502 case. What is certain is that generating higher quality evidence regarding the  
503 magnitude of any causal effect of meat consumption on health outcomes will test the  
504 ingenuity and imagination of health science investigators.

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