Review

Meat Consumption and Gut Microbiota: a Scoping Review of Literature and Systematic Review of Randomized Controlled Trials in Adults

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A B S T R A C T

Emerging research indicates the importance of gut microbiota in mediating the relationship between meat intake and human health outcomes. We aimed to assess the state of available scientific literature on meat intake and gut microbiota in humans (PROSPERO, International Prospective Register of Systematic Reviews, CRD42020135649). We first conducted a scoping review to identify observational and interventional studies on this topic. Searches were performed for English language articles using PubMed, Cochrane Library, Scopus, and CINAHL (Cumulated Index to Nursing and Allied Health Literature) databases from inception to August 2021 and using keywords related to meat (inclusive of mammalian, avian, and aquatic subtypes) and gut microbiota. Of 14,680 records, 85 eligible articles were included in the scoping review, comprising 57 observational and 28 interventional studies. One prospective observational study and 13 randomized controlled trials (RCTs) were identified in adults without diagnosed disease. We included the 13 RCTs, comprising 18 comparisons, in the systematic review to assess the effects of higher and lower intakes of total meat and meat subtypes on the gut microbiota composition. The bacterial composition was differentially affected by consuming diets with and without meat or with varied meat subtypes. For example, higher meat intake tended to decrease population sizes of genera *Anerostipes* and *Faecalibacterium*, but it increased the population size of *Roseburia* across studies. However, the magnitude and directionality of most microbial responses varied, with inconsistent patterns of responses across studies. The data were insufficient for comparison within or between meat subtypes. The paucity of research, especially among meat subtypes, and heterogeneity of findings underscore the need for more well-designed prospective studies and full-feeding RCTs to address the relationships between and effects of consuming total meat and meat subtypes on gut microbiota, respectively.

Keywords: red meat, poultry, fish, seafood, animal-based protein sources, dietary pattern

Statement of Significance

This scoping and systematic review summarizes the current state of knowledge on meat intake and gut microbiota, and identifies gaps and priorities for future research.

Introduction

Meat is an integral part of most individuals' dietary patterns, which affects their health. Since the 1960s, the total amount of meat consumed has increased by 40% among Americans and by 100% globally [1]. The meat types consumed by Americans (as of 2017) include 51% red meat, 42% poultry, and 7% fish and shellfish [2]. Historically, meat-related research has focused on the nutrients in meat and their influence on traditional health indices (e.g., cardiometabolic diseases and risk factors). This body of literature presents inconsistent and controversial health impacts of meat intake. Importantly, accumulating research indicates that the influence of diet on human health may be mediated, in part, by the gut microbiota. Knowing how meat

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Abbreviations used: AMSA, American Meat Science Association; RCT, randomized controlled trial; TMAO, trimethylamine-*N*-oxide.

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intake influences gut microbiota can provide novel insights into understanding the impact of meat intake on human health outcomes. However, how the gut microbiota is impacted by meat intake is not well-studied.

Notably, "meat" is not a single food, but is defined by the American Meat Science Association (AMSA) as including mammalian, avian, aquatic, and other sources of flesh and related tissue foods [3]. However, the term "meat" is used inconsistently among and between observational and interventional studies and in regulatory, scientific, or public settings [4]. For example, the 2015–2020 Dietary Guidelines for Americans identifies meats as mammalian sources, including "beef, goat, lamb, pork, and game meat (e.g., bison, moose, elk, and deer)," separate from other muscle food categories such as poultry and seafood [5]. The varied uses of the term "meat" add to the inconsistency and controversy of research evidence on meat intake and health outcomes [6]. Our review addresses the inconsistency by adhering to the AMSA definition of meat by including mammalian, avian, and aquatic sources (i.e., red meat, white meat, and fish/seafood).

Over the past decade, there has been an exponential increase in the number of studies on human gut microbiota with fast-advancing sampling and sequencing technologies. In contrast, few systematic reviews have synthesized meat consumption and gut microbiota–related outcomes in humans. A rigorous, unbiased, systematic assessment of research literature is needed to evaluate the current evidence on the effects of consuming mammalian, avian, and aquatic meats on the gut microbiota. Although another systematic review included research using animal models [7], findings in the gut microbiota from animal models (murine in particular) may have limited transferability into humans because of the differences in gut and microbial physiologies and metabolisms [8, 9]. Therefore, this review aimed to assess the influence of consuming total meat and meat subtypes on the gut microbiota in humans. Given the large body of microbial literature, a scoping review was conducted to identify the types and extent of available research evidence, followed by a systematic review to chronicle and synthesize evidence from relevant studies.

Methods

Research question

Our research question comprised 2 parts: *1)* What are the current state of knowledge and gaps in the literature on meat intake and human gut microbiota? *2)* What are the effects of meat consumption on the gut microbiota in healthy human adults? To assess the state of knowledge, we conducted a scoping review to chronicle available literature without regard to reporting results. Based on the findings from the scoping review, we conducted a systematic review using suitable literature to assess the influence of meat intake on the gut microbiota. The systematic review presents the results and assesses the quality of the included articles.

The primary outcomes of the systematic review included changes or differences in the gut microbiota composition at the community (alpha and beta diversity metrics) and taxonomic levels (bacterial abundances). The primary outcomes were compared between the groups of participants who consumed diets with higher and lower amounts of meats or no meat. A priori subgroup analyses included comparisons *1)* between vegetarian and vegan diets; *2)* among subtypes of meats (e.g., red meat, white meat, and fish/seafood; processed or unprocessed), *3)* between different meat subtypes and nonmeat, and *4)* between higher and lower intakes of total meat and meat subtypes.

Inclusion and exclusion criteria

This systematic review was registered in the PROSPERO registry (https://www.crd.york.ac.uk/PROSPERO/) before the formal screening of search results commenced (CRD42020135649). The conduct of this review follows the PRISMA [10] and the PRISMA extension for scoping reviews [11] guidelines.

The Population, Investigated Condition, Comparison, Outcome, and Study Type criteria defining our research questions for the scoping review and systematic review are presented in Supplemental Tables S1 and S2, respectively. Relevant articles that met all of the following criteria were included in the scoping review (Supplemental Table S1): *1)* is a peer-reviewed primary research article; *2)* is published in English; *3)* includes human population; *4)* has a comparison between higher and lower dietary intakes of meat (in whole food form), with or without control of overall diets; and *5)* includes outcomes on the gut microbiota composition. Articles were excluded if they did not meet any one of the listed inclusion criteria. Review articles and gray literature were excluded. Articles from the scoping review that met all of the additional criteria were included in the systematic review (Supplemental Table S2): *1)* is a randomized controlled trial (RCT) and *2)* includes human adults without diagnosed disease and with stable health status (e.g., not pregnant). Because of the selection process, reference lists of included articles from the scoping or systematic reviews were not searched.

Search strategy

The initial search was conducted in 4 scientific databases, including PubMed, Cochrane Library, Scopus, and CINAHL (EBSCO, Cumulated Index to Nursing and Allied Health Literature), on January 14, 2020. An updated search was conducted on August 17, 2021, in all databases (e.g., with entry dates from 14 January, 2020, to 17 August, 2021, in PubMed). A complete list of search strategies developed by a research librarian (JBR) is included (**Supplemental Document 1**). Briefly, keywords and alternative terms for meat, gut microbiota, and gut microbial metabolites were used in combinations to identify relevant articles in each database. Definitions of total meat and meat subtypes used in this review are listed in Table 1 [3, 5]. Searches were restricted to articles published in English from inception to August 2021. Trial registries were searched through results generated from the Cochrane Library.

Article screening and data extraction

Records of identified articles were uploaded to the Rayyan systematic review management tool (Rayyan Systems Inc, https://www.rayyan.ai/) for screening. After removing duplicates (*n* = 10,543), articles from the initial search (*n* = 10,297) were screened independently by pairs of investigators (YW, CNU, REB, and CMC) and crosschecked to reach an agreement through 2

stages: *1)* potential eligibility assessment based on publication titles and abstracts and *2)* confirmation of eligibility based on full-text assessment of qualified abstracts. To increase the efficiency of the process, results from the updated search (from 14 January, 2020, to date) were first screened by 1 investigator to exclude clearly irrelevant records (e.g., studies not in human populations; secondary research; and non–peer-reviewed gray literature, such as reports, government documents, and white papers). A second investigator screened the full texts of the remaining results for eligibility. Information was extracted and crosschecked by pairs of investigators (YW, CNU, REB, and CMC) from each of the included articles. The extracted information primarily included article publication details (title, author, and year), study design, dietary interventions (meat consumption), gut microbial composition, and key gut microbial metabolites and cardiometabolic disease risk factors, if reported. The authors of these articles were not contacted as the purpose of the review was to assess the current state of literature based on published findings and additional information was not needed. During the screening and extraction processes, disagreements between pairs of investigators were discussed and resolved by a third investigator.

Risk of bias assessment

The risk of bias of articles in the systematic review was assessed independently and crosschecked by 2 investigators (YW and CNU) using the Cochrane Risk of Bias Assessment Tool 2 [12]. The Cochrane tool assesses each article based on 5 major domains tailored for crossover and parallel RCTs. The 5 major domains that were considered were as follows: *1)* the study randomization process, and for crossover RCT, the period and carryover effects; *2)* effects of assignment to intervention; *3)* missing outcome data; *4)* outcome measurement; and *5)* selection of results reporting. An overall judgment of low, some concerns, or high risk of bias was given for each article.

Results

The search and screening process identified 85 and 13 articles suitable for the scoping and systematic reviews, respectively (Figure 1).

Scoping review

Table 2 presents the basic characteristics of the 85 studies included in the scoping review (13–97). In all observational studies, comparisons of higher and lower meat intakes were based on various dietary patterns, instead of being meat-specific, which further limits the potential for causal inference between meat intake and gut microbiota. Overall, there was insufficient evidence from eligible prospective cohort studies for a systematic review of total meat intake and gut microbiota. Therefore, we proceeded with the 13 eligible RCTs to assess the causal relationships between total meat and meat subtype intakes and gut microbiota in healthy adults with stable health status.

Systematic review

The 13 RCTs generated 18 comparisons (Table 3), including 12 primary comparisons on higher and lower total meat intakes based on data from 10 RCTs [73, 74, 84–91] and 6 secondary

comparisons among meat subtypes based on data from 5 RCTs [71, 85, 87, 92, 93]. Adults with stable health status have relatively more stable gut microbiota composition with less influence from growth and confounding disease conditions [98]. As a result, the 13 RCTs in healthy adults included 8 crossover [71, 73, 74, 84–88] and 5 parallel RCTs [89–93].

The characteristics of the 13 RCTs in the systematic review are summarized in Table 3 (with details presented in Supplemental Tables S3 and **S4**), including *1)* author, publication year, and country of study; *2)* study length; *3)* comparison groups; *4)* type of study meat; *5)* study diets; *6)* use of prebiotics, probiotics, or antibiotics; *7)* cointervention; *8)* sample size estimation; *9)* participant characteristics; *10)* fecal sample collection timepoint, collection methods, and storage; *11)* microbiota composition processing and analysis methods; and *12)* study's funding source and potential conflict of interest. The experimental designs of RCTs are provided in Table 3 and Supplemental Tables S3A and S4 and are summarized in the footnote of Supplemental Table S3A. Microbiome analysis methods used in RCTs are described in Supplemental Table S3B, including a summary in the footnote.

Type of study meat

Studies used either food substitution with total meat and meat subtypes or dietary patterns to compare higher and lower intakes of total meat and meat subtypes (Table 3). The primary comparisons include 12 comparisons from 10 studies [73, 74, 84–91] to compare higher and lower total meat intakes. Among the primary comparisons, 7 comparisons from 5 studies [74, 85, 87, 89, 91] were performed between a diet with meat (red meat, white meat, or mixed meat subtypes) and a diet without meat (vegan or vegetarian) (Table 3, meat compared with nonmeat). The other 5 comparisons from 5 studies either substituted meat (red meat or mixed meat subtypes) with plant-based foods [73,

TABLE 1
Terminology of meat subtypes.

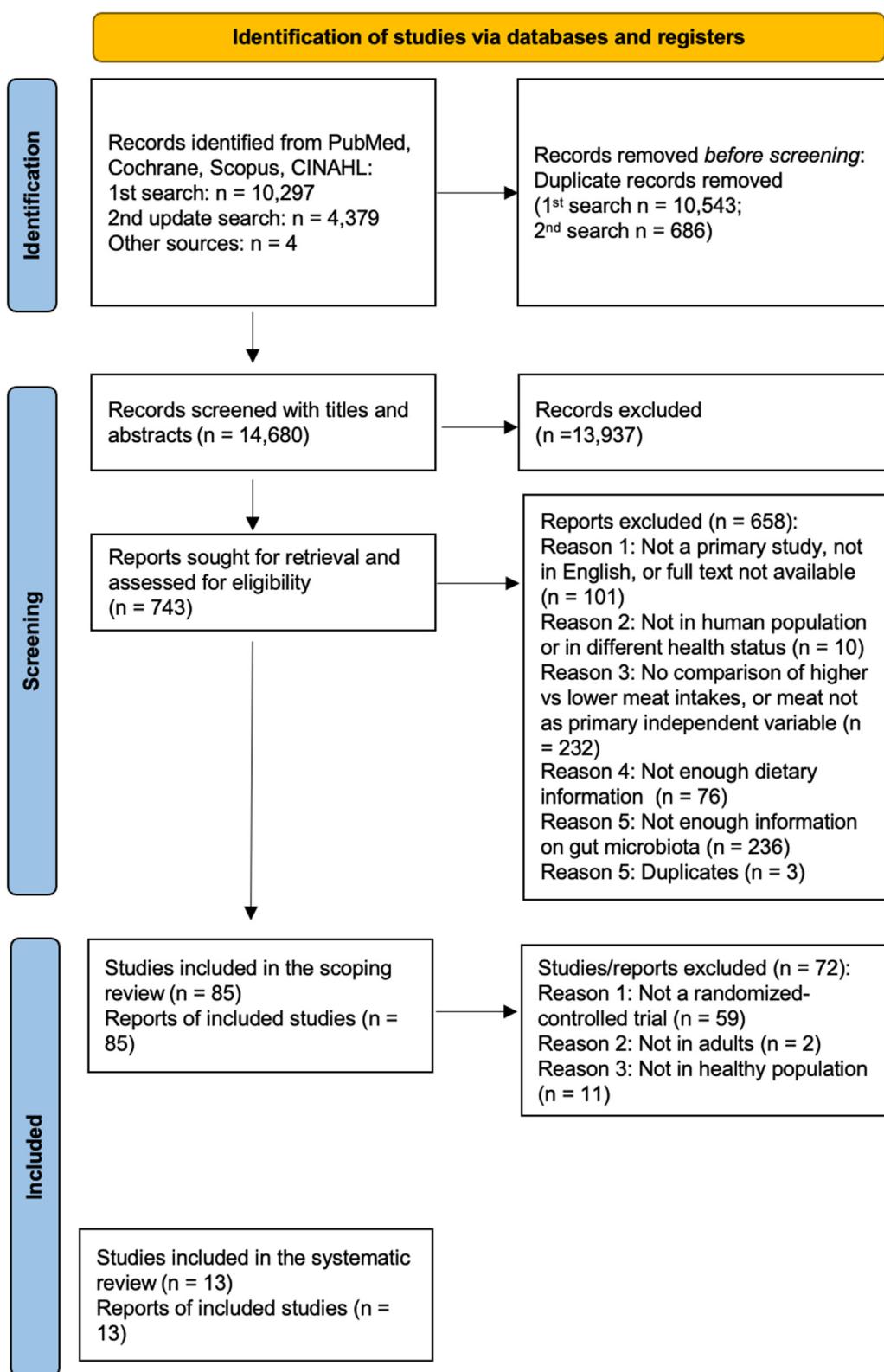| Meat subtypes	Definitions
Meat	"Skeletal muscle and its associated tissues derived from mammalian, avian, reptilian, amphibian, and aquatic species harvested for human consumption," including "edible offal consisting of organs and non-skeletal muscle tissues" [3].
Red meat	"All forms of beef, pork, lamb, veal, goat, and nonbird game (e.g., venison, bison, and elk)" [5].
White meat/poultry	"Domestic avian species that includes chickens, turkeys, geese, ducks, guinea, squab and in some cases ratites (ostrich, emu, rhea)" [3].
Fish/seafood	"Any form of animal sea life regarded as food by humans," which predominantly includes fish (e.g., "salmon, tilapia, and catfish") and shellfish (i.e., "various species of mollusks, crustaceans, and echinoderms") [3].
Unprocessed meat	Meats with "minimal processing," which includes "any process where raw, uncooked meat products have not been significantly altered compositionally and contain no added ingredients, but may have been reduced in size by fabrication, mincing, grinding, and/or a meat recovery system" [3].
Processed meat	Meat that is "preserved by smoking, curing, salting, and/or the addition of chemical preservatives" [5]. For the purpose of this review, salting during home cooking or table use is not considered processing.

Identification of studies via databases and registers

Identification

Records identified from PubMed, Cochrane, Scopus, CINAHL:
1st search: n = 10,297
2nd update search: n = 4,379
Other sources: n = 4

→ Records removed *before screening*:
Duplicate records removed
(1st search n = 10,543;
2nd search n = 686)

Screening

Records screened with titles and abstracts (n = 14,680)

→ Records excluded
(n =13,937)

Reports sought for retrieval and assessed for eligibility
(n = 743)

→ Reports excluded (n = 658):
Reason 1: Not a primary study, not in English, or full text not available (n = 101)
Reason 2: Not in human population or in different health status (n = 10)
Reason 3: No comparison of higher vs lower meat intakes, or meat not as primary independent variable (n = 232)
Reason 4: Not enough dietary information (n = 76)
Reason 5: Not enough information on gut microbiota (n = 236)
Reason 5: Duplicates (n = 3)

Included

Studies included in the scoping review (n = 85)
Reports of included studies (n = 85)

→ Studies/reports excluded (n = 72):
Reason 1: Not a randomized-controlled trial (n = 59)
Reason 2: Not in adults (n = 2)
Reason 3: Not in healthy population (n = 11)

Studies included in the systematic review (n = 13)
Reports of included studies (n = 13)

FIGURE 1. PRISMA flow diagram of the search and screening process.

84, 86, 88] or increased the amount of meat intake without dietary substitution [90], with uncontrolled or minimally controlled habitual diet (Table 3, higher compared with lower meat within omnivorous habitual/basal diets).

Five comparisons from 4 studies [71, 87, 92, 93] were included as secondary comparisons (Table 3, meat subtypes). These comparisons substituted meat with other meat subtypes with or without changes to overall dietary patterns. Specifically,

TABLE 2

Summary of the articles in the scoping review[1].

Study type/Health status	Total number of studies	Age			Study design		
Observational study	Total	≥18 y	<18 y	NR	Cross-sectional cohort	Prospective cohort	Other (retrospective, case-control)
All	57 [13–69]	47 [13–40, 48, 49, 51, 54–59, 61–69]	7 [41–47]	3 [50, 52, 53]	47 [13–27, 29–40, 43–53, 55–58, 60, 63, 67–69]	6 [28, 41, 42, 59, 61, 62]	4 [54, 64–66]
Healthy	39 [13–47, 63, 67–69]	32 [13–40, 63, 67–69]	7 [41–47]	0	36 [13–27, 29–40, 43–47, 63, 67–69]	3 [28, 41, 42]	0
With condition/disease[2]	10 [54–59, 61, 64–66]	10 [54–59, 61, 64–66]	0	0	4 [55–58]	2 [59, 61]	4 [54, 64–66]
NR health status	8 [48–53, 60, 62]	5 [48, 49, 51, 60, 62]	0	3 [50, 52, 53]	7 [48–53, 60]	1 [62]	0
Interventional study	Total	≥18 y	<18 y	NR	Crossover RCT	Parallel RCT	Other (incomplete randomization)[4]
All	28 [70–97]	26 [70–93, 96, 95]	2 [94, 95]	0	12 [70, 71, 73, 74, 79, 82, 84–88, 96]	13 [76–78, 80, 81, 83, 89–95]	3 [72, 75, 97]
Healthy	17 [71–74, 84–95, 97]	15 [71–74, 84–93, 97]	2 [94, 95]	0	8 [71, 73, 74, 84–88]	7 [89–95]	2 [72, 97]
With condition/disease[2]	10 [70, 75–83][3]	10 [70, 75–83]	0	0	3 [70, 79, 82]	6 [76–78, 80, 81, 83]	1 [75]
NR health status	1 [96]	1 [96]	0	0	1 [96]	0	0

[1] Age categories were divided based on reported subject inclusion, subject age range, and group mean age of each study. The age category "<18" also includes studies that recruited subjects aged both <18 and >18 y. The number of studies is reported in each cell, with references of studies included in square brackets.

[2] With condition/disease: Ten observational studies had cohorts with certain diseases or health conditions [54–59, 61, 64–66], including reactive hypoglycemia [54], cirrhosis [55], type 2 diabetes [58], metabolic syndrome [61], colorectal cancer [64], intestinal diseases (colon carcinoma, inflammatory bowel disease [56], Crohn's disease or ulcerative colitis, irritable bowel syndrome [56, 65, 66]), or pregnancy [57, 59]. Among interventional studies, 10 studies were in cohorts with the following diseases or health conditions: Crohn's disease [75], type 2 diabetes [76, 77], multiple sclerosis [78], chronic kidney disease [79], obesity with insulin resistance [80] or metabolic syndrome [81], chronic gastrointestinal disease [70], ischemic heart disease [82], or pregnancy [83].

[3] One study [70] included all healthy subjects, except for 1 subject with chronic gastrointestinal disease.

[4] One study [75] had all participants receive the same intervention (pre vs. post), thus the study was not categorized as crossover or parallel RCT; 2 studies [72, 97] included partial randomization, in which the intervention group was compared with a nonrandomly assigned comparison group. NR, not reported; RCT, randomized controlled trial.

TABLE 3
Characteristics and gut microbiota outcomes of included comparisons by subgroups[1].

Study (year)	Comparison diet 1	Comparison diet 2	Study type	Diet length	Dietary control	Alpha diversity	Phylum	Class	Order	Family	Genus	Species	Other	Major differences in gut microbiota outcomes	Effects? ($p<0.05$)
						Primary comparisons: meat vs. nonmeat									
Lang et al. 2018 [87]	Red meat[2,3]	Nonmeat[2,3]	CO, Yes	4 wk	F	N	N	NR	NR	NR	Y	—	—	3 OTUs differed when high and low amounts of saturated fat were combined	Yes
	White meat[2,3]		CO, Yes	4 wk	F	N	N	NR	NR	NR	Y	—	—	1 OTU differed when high and low amounts of saturated fat were combined	Yes
van Faassen et al. 1987 [85]	Western omnivorous[2]	Vegetarian[2]	CO, NS	20 d	F	—	—	N	—	N	N	—	N[12]	No difference	No
		Vegan[2]	CO, NS	20 d	F	—	—	N	—	N	Y	—	N[12]	Omnivorous diet ↑ counts of genus Lactobacilli	Yes[14]
Kohnert et al. 2021 [91]	Omnivorous[4,5]	Vegan[4,5]	PL	4 wk	C	N[4]	NR	NR	NR	NR	Y[4,5]	Y[4,5]	—	Differences in several genera and species (Table 4)	Yes
Kahleova et al. 2020 [89]	Habitual omnivorous[4,5]	Vegan[4,5]	PL	16 wk	C	Y	Y[4]	N	N	Y[4]	Y[4]	Y[4,5]	—	Differences in alpha diversity and bacterial abundance (Table 4)	Yes
Pagliai et al. 2020 [74]	Mediterranean[4,5]	Vegetarian[4,5]	CO[10], No	12 wk	C	Y[5]	N[4,5]	Y[4]	Y[4]	Y[4,5]	Y[4,5]	—	—	Differences in alpha diversity and bacterial abundance from phylum to genus levels (Table 4)	Yes
Total % of significant out of measured (%) – meat vs. nonmeat						40	25	25	50	50	86	100	N/A	N/A	86
Proportion of significant out of measured (counts) – meat vs. nonmeat						2/5	1/4	1/4	1/2	2/4	6/7	2/2	N/A	N/A	6/7
					Primary comparisons: higher vs. lower meat within omnivorous habitual/basal diets										
Hess et al. 2018 [84]	Red meat[2]	Mushroom[2]	CO, Yes	10 d	P2	—	Y	NR	NR	NR	Y	—	—	Red meat ↓ phylum Bacteroidetes and ↑ phylum Firmicutes	Yes
Foerster et al. 2014 [86]	Red meat[5]	Whole grain[5]	CO, Yes	3 wk	P2	—	—	—	—	—	—	Y	Y[13]	Whole grain ↑ DGGE band number and species Collinsella aerofaciens; red meat ↓ species Clostridium sp	Yes

TABLE 3 (continued)

Study (year)	Comparison diet 1	Comparison diet 2	Study type	Diet length	Dietary control	Alpha diversity	Phylum	Class	Order	Family	Genus	Species	Other	Major differences in gut microbiota outcomes	Effects? (p<0.05)
Crimarco et al. 2020 [88]	Animal-based meat[2,6]	Plant-based meat[2,6]	CO, No	8 wk	P1	—	NR	NR	NR	NR	Y[6]	Y[6]	—	Differences in bacterial abundance (Table 4)	Yes
McKenna et al. 2021 [90]	Higher red meat[2,4,7]	Lower red meat[2,4,7]	PL[11]	10 wk	P2	N	NR	NR	Y[2,4]	Y[2,4]	Y[2,4]			Differences in bacterial abundance (Table 4)	Yes
Windey et al. 2012 [73]	Higher meat[2,8]	Lower meat[2,8]	CO, No	2 wk	C	—	—	—	—	—	—	—	N13	No difference in DGGE band numbers	No
Total % of significant out of measured (%) – higher vs. lower meat						0	100	0	100	100	—	100	N/A	N/A	80
Proportion of significant out of measured (counts) – higher vs. lower meat						0/1	1/1	0	1/1	1/1	3/3	2/2	N/A	N/A	4/5
Total % of significant out of measured (%) – primary comparisons						33	40	25	67	60	90	100	N/A	N/A	83
Proportion of significant out of measured (counts) – primary comparisons						2/6	2/5	1/4	2/3	3/5	9/10	4/4	N/A	N/A	10/12
Secondary comparisons: meat subtypes															
Lang et al. 2018 [87]	Red meat[2,3]	White meat[2,3]	CO, Yes	4 wk	F	N	N	NR	NR	NR	Y	—	—	Several OTUs differed at low or high amounts of saturated fat, but no difference when both amounts were combined.	Yes
Schmedes et al. 2019 [71]	Lean seafood[4,5]	Non-seafood meat[4,5]	CO, Yes	4 wk	P1	—	N	NR	NR	NR	Y	—	—	Non-seafood diet ↓ genus group Clostridium cluster IV	Yes
Bratlie et al. 2021 [93]	Cod2	Nonfish habitual Meat[2]	PL	8 wk	P2	—	NR	NR	Y	NR	NR	NR	—	Cod/Salmon ↓ order-level bacterial counts of Bacteroidales, Clostridiales, and Selenomonadales	Yes
	Salmon[2]		PL	8 wk	P2	—	NR	NR	Y	NR	NR	NR	—		Yes
Meslier et al. 2020 [92]	Mediterranean (higher fish)[2,4,9]	Habitual omnivorous (higher nonfish meat)[2,4,9]	PL	8 wk	P1	—	NR	NR	NR	NR	NR	Y[2,4]	—	Differences in beta diversity and several species (Table 4)	Yes
Total % of significant out of measured (%) – secondary comparisons						0	0	0	100	0	100	100	N/A	N/A	100
Proportion of significant out of measured (counts) – secondary comparisons						0/1	0/2	0	2/2	0	2/2	1/1	N/A	N/A	5/5
Secondary comparison: vegetarian vs. vegan															
van Faassen et al. 1987 [85]	Vegetarian[2]	Vegan[2]	CO, NS	20 d	F	—	—	N	—	N	Y	—	N12	Vegetarian diet ↑ counts of genus Enterococci and Lactobacilli	Yes

(continued on next page)

TABLE 3 (*continued*)

Study (year)	Comparison diet 1	Comparison diet 2	Study type	Diet length	Dietary control	Alpha diversity	Phylum	Class	Order	Family	Genus	Species	Other	Major differences in gut microbiota outcomes	Effects? ($p<0.05$)
Total % of significant out of measured (%) – all comparisons						29	29	20	80	50	92	100	N/A	N/A	89
Proportion of significant out of measured (counts) - all comparisons						2/7	2/7	1/5	4/5	3/6	12/13	5/5	N/A	N/A	16/18
Secondary comparison not available: unprocessed vs. processed meat															

[1] All vegetarian diets are lacto-ovo vegetarian that included dairy and eggs. Vegan diet did not contain any animal-based products. Meat, if not specified, refers to mixed meat subtypes. Category "Study type" includes CO and PL RCTs, as well as the washout period for crossover RCTs (Yes for existence, No for no washout, and NS for not specified or not reported). Category "Length" is the length of intervention of each study arm (d, day; wk, week). Category "Dietary control" includes full control (F) that provided all study foods; partial control that provided some but not all study foods, either with dietary guidance on basal diet (P1) or with uncontrolled habitual diet (P2) and counseling only (C) that did not provide any study foods except for dietary guidance. Categories "Alpha diversity" through "Other": bacterial abundance at taxonomic levels such as phylum, class, order, family, genus, and species, or in other forms of measurement (e.g., OTU, operational taxonomic unit). Y, significant changes or differences were observed; N, no significant change or difference was observed; NR, outcomes were evaluable using methods reported by the study authors, but no data were reported at the specific taxonomic level; Em dash (-), outcomes and data likely were not measured based on study description, and thus were not reported for the selected comparisons; N/A, not applicable. Results were considered significant only when the authors of the included studies reported the statistical significance of the outcome measures. Category "Effects": overall effects of diet on gut microbiota. Summary of Table 3: Among the primary comparisons, 83% of the comparisons showed significant effects of meat intake on the gut microbiota (Figure 2B). Although global bacterial composition measured using alpha diversity metrics was reported in 50% of primary comparisons, only 33% of them showed significant effects of meat intake on the gut microbiota composition. In contrast, among 83% of primary comparisons that reported bacterial abundances at the genus level, 90% of them showed significant effects. Only 4 of the 12 primary comparisons reported outcomes at the species level, but all 4 comparisons suggested significant effects. A similar hierarchical pattern of findings was observed among the secondary comparisons. Two of 2 comparisons (100%) at the genus level and 1 of 1 comparison at the species level showed significant effects, but zero of 1 comparison showed effects for alpha diversity metrics (Figure 2C).

[2] Difference in post-intervention values between groups.

[3] Each diet was consumed with high vs. low amounts of saturated fat.

[4] Within-group pre–post changes.

[5] Difference in between-group changes.

[6] Pre- and post-intervention samples combined.

[7] Comparisons were made among baseline vs. 1-wk intervention vs. post-intervention within and between the groups.

[8] Samples were collected during the diet intervention period without a clearly specified timepoint.

[9] Comparisons were made among baseline vs. 4-wk intervention vs. 8-wk intervention within and between the groups.

[10] Cointervention with energy restriction.

[11] Cointervention with resistance training.

[12] Counts of total aerobes and anaerobes.

[13] Denaturing gradient gel electrophoresis (DGGE) bandclass counts.

[14] Results from this study were obtained via the cultivation-dependent method, which could potentially miss capturing significant gut microbial outcomes compared with more advanced techniques.

Table 4

Gut microbiota outcomes reported in studies[1].

Study author, year	n	Comparison diet 1	Comparison diet 2	Alpha diversity	Beta diversity	Phylum	Class	Order	Family	Genus	Species	Other/notes	Significant effects on gut microbiota?
van Faassen et al. 1987 [85]	12	Post-omnivorous	Post-vegan	—	—	—	Clostridia:↔	—	Enterobacteriaceae:↔	Anaerobes: Bifidobacteria (count):↔ Bacteroides (count):↔ Aerobes: Enterococci (count):↔ Lactobacilli (count):↑	—	Mean counts of bacteria: Total anaerobes:↔ Total aerobes:↔	Yes
	12	Post-omnivorous	Post-vegetarian	—	—	—	Clostridia:↔	—	Enterobacteriaceae:↔	Anaerobes: Bifidobacteria (count):↔ Bacteroides (count):↔ Aerobes: Enterococci (count):↔ Lactobacilli (count):↔	—	Mean counts of bacteria: Total anaerobes:↔ Total aerobes:↔	No
	12	Post-vegetarian	Post-vegan	—	—	—	Clostridia:↔	—	Enterobacteriaceae:↔	Anaerobes: Bifidobacteria (count):↔ Bacteroides (count):↔ Aerobes: Enterococci (count):↑ Lactobacilli (count):↑	—	Mean counts of bacteria: Total anaerobes:↔ Total aerobes:↔	Yes
Windey 2012 et al. [73]	20	Higher meat	Lower meat	—	—	—	—	—	—	—	—	Among 64 bandclasses, no difference was detected in the allocation of bandclass between diets.	No
Foerster et al. 2014 [86]	20	Post-red meat	Pre-red meat	—	—	—	—	—	—	—	Clostridium sp.:↓	Band appearance of bacteria: ↔ band diversity (total number of bands) ↑ 5 bands appearance ↓ 3 bands appearance	Yes
	20	Post-whole grain	Pre-whole grain	—	—	—	—	—	—	—	Collinsella aerofaciens:↑	Band appearance of bacteria: ↑ band diversity (total number of bands) ↑ 5 bands appearance ↓ 3 bands appearance	
Lang et al. 2018 [87]	109	By protein sources (1) Red meat (2) White meat (3) Non-meat	By amounts of saturated fat (1) High saturated fat (2) Low saturated fat	Shannon diversity index:↔ among protein sources or between high vs low amounts of saturated fat	↔ unweighted UniFrac distance: no clustering by diet	F/B ratio (log2):↔ by diet or saturated fat	NR	NR	NR	2 reported genera (Caprococcus and Ruminococcus) differed by protein sources, but pairwise comparisons between protein sources were not reported. 57 genera differed by saturated fat amounts.	—	19 OTUs responded to protein source at both high and low saturated fat amounts (protein-sensitive, but not specific to protein sources). Differentially abundant OTUs: [high and low amounts of saturated fat combined] 3 between red meat vs non-meat, 1 between white meat vs non-meat, 0 between red meat vs white meat; [low saturated fat] 115, 125, 130 OTUs, respectively; [high saturated fat] 203, 198, 240 OTUs, respectively.	Yes
Hess et al. 2018 [84]	32	Post-Red meat (5d average)	Post-Mushroom (5d average)	—	—	Bacteroidetes:↓ Firmicutes:↑	NR	NR	NR	Bacteroides:↓ Parabacteroides:↓ Coprococcus:↓ Anaerostipes:↓ Sutterella:↓ Dorea:↑	—	Taxa (phylum and genus) with at least 0.05% relative abundance were reported. Relative abundances were log-transformed and controlled for false discovery rate with p<0.004.	Yes
Schmedes et al. 2018 [71]	19	Post-lean seafood	Pre-lean seafood	—	—	Firmicutes:↔ Bacteroidetes:↔ F/B ratio:↔	—	—	—	Clostridium cluster IV:↔	—	The following results were described and not reported in details: the dataset included "42 bacterial OTU groups at the genera level, 8 bacterial level, 2 bacterial OTU groups at the order level, 1 bacterial OTU group at the class level, and 1 bacterial OTU group at the domain level".	Yes
	19	Post-non-seafood	Pre-non-seafood	—	—	Firmicutes:↔ (p=0.1) Bacteroidetes:↔ (p=0.1) F/B ratio:↔ (p=0.1)	NR	NR	NR	Clostridium cluster IV:↓ (greater reduction than lean-seafood group)	—		
Pagliai et al. 2020 [74]	23	Post-Mediterranean diet	Pre-Mediterranean diet	Richness; inverse Simpson's, Gini-Simpson's, Shannon's indices; evenness, dominance: Phylum-level:↔ Class-level:↔ Family-level:↔ Genus-level:↔	(1) Weighted Unifrac (PCoA) (2) Bray-Curtis dissimilarity metrics (3) Principle component analysis (PCA) & co-inertia analysis (CIA): No clearly separated clustering by diet.	F/B ratio:↔ F/P ratio:↔ Other phyla:↔	Betaproteobacteria:↓ (p=0.05)	Burkholderiales:↓ (p=0.05)	Alcaligenaceae:↓ (p=0.05)	Enterorhabdus:↑ Lachnoclostridium:↑ Parabacteroides:↓ Parasutterella:↓ (p=0.05)	—	—	Yes
	23	Post-vegetarian diet	Pre-vegetarian diet	Richness; inverse Simpson's, Gini-Simpson's, Shannon's indices; evenness, dominance: Phylum-level:↔ Class-level:↔ Order-level:↔ Family-level:↔ Genus-level:↔	LEfSe tool: no discriminating characteristics by diet. PERMANOVA: no difference in microbiota composition by diet at any taxonomic level.	F/B ratio:↔ F/P ratio:↔ Euryarchaeota:↑ (abundance median increased from 0 to 1) Other phyla:↔	Methanobacteria:↑ (abundance median increased from 0 to 1)	Methanobacteriales:↑ (abundance median increased from 0 to 1)	Clostridiaceae_1:↓ Methanobacteriaceae:↑ (abundance median increased from 0 to 1)	Anaerostipes:↓;↓ Clostridium_sensu_stricto_1:↓ Methanobrevibacter:↑ (abundance median increased from 0 to 1) Odoribacter:↓ Streptococcus:↑ Tyzzerella; ↓ abundance median=0, interquartile range ↑	—	—	Yes

Table 4 (*continued*)

Study author, year	n	Comparison diet 1	Comparison diet 2	Alpha diversity	Beta diversity	Phylum	Class	Order	Family	Genus	Species	Other/notes	Significant effects on gut microbiota?
	23	Post-Post change of Mediterranean diet	Pre-Post change of vegetarian diet	Order-level richness: median=1, interquartile range↑ Genus-level richness↓ All other parameters:↔		F/B ratio:↔ F/P ratio:↔ Other phyla:↔	—	—	*Clostridiaceae_1*:↑	*Anaerotignes*:↓ *Clostridium_sensu_strato_1*:↑ *Enterorhabdus*:↑ *Slackia*: abundance median=0, interquartile range↑ *Veillonella*:↑	—	—	
Crimarco et al. 2020 [88]	36	Animal diet	Plant diet	—	Bray-Curtis dissimilarity:↔	NR	NR	NR	NR	Volcano plot of taxa with between-group difference in abundance: *Lachnospiraceae sp*: mixed *Ruminococcus sp*:↑ *Roseburia sp*:↓	Volcano plot of taxa with between-group difference in abundance: *H. parainfluenzae*:↓	—	Yes
Kahleova et al. 2020 [89]	36	Post-animal	Pre-animal	—	—	—	—	—	—	—	—	—	
	36	Post-plant	Pre-plant	—	—	—	—	—	—	—	—	—	
	84	Post-omnivorous	Pre-omnivorous	Abundance-weighted phylogenetic diversity measure:↑	—	—:↑	—	—	—	*Methanobrevibacter* (read counts and %):↑ *Bilophila* (read counts):↑	*Bacteroides fragilis* (read counts and %):↓	—	Yes
	84	Post-vegan	Pre-vegan	Abundance-weighted phylogenetic diversity measure: ↔	—	Bacteroidetes (read counts):↑ Proteobacteria (%):↓	—	—	—	*Bifidobacterium* (read counts):↑ *Anaerostipes* (read counts):↑	*Faecalibacterium prausnitzii* (read counts&%):↑ *Bacteroides fragilis* (read counts and %):↓	—	
	168	Post-pre change in vegan	Post-pre change in omnivorous	Abundance-weighted phylogenetic diversity measure:↑	—	↔:↑	—	—	—	↔	*Faecalibacterium prausnitzii* (%):↓ *Bacteroides fragilis* (read counts and %):↑	—	
Meslier et al. 2020 [92]	62	Post-Mediterranean diet (wk4)	Post-omnivorous diet (wk4)	—	Separate diversity (N-integrative supervised analysis) Dissimilarity by adherence to MedD diet 0-4wk	NR	NR	NR	NR	NR	77 species differed at week 4, primarily: ↓ species: *Ruthenibacterium lactatiformans, Flavonifractor plautii, Parabacteroides merdae, Ruminococcus torques, Ruminococcus Gnaus, Streptococcus thermophilus, Streptococcus thermophilus* ↑ species: 5 members of *Faecalibacterium prausnitzii* and 7 members of taxa *Roseburia* and *Lachnospiraceae*	—	Yes
	62	Post-Mediterranean diet (wk8)	Post-omnivorous diet (wk8)	—							44 species differed at week 8. Information on detailed species was not extracted.	—	
	32	Post-omnivorous diet (wk4/wk8)	Pre-omnivorous diet	—							14 species differed at week 4 compared to baseline, 19 differed at week 8 compared to week 4. Information on detailed species was not extracted.	—	
	30	Post- Mediterranean diet (wk4/wk8)	Pre- Mediterranean diet	—							69 species differed at week 4 compared to baseline, 17 differed at week 8 compared to week 4. Information on detailed species was not extracted.	—	
Kohnert et al. 2021 [91]	53	Post-pre change in omnivorous	Post-pre change in vegan	NR	Bray-Curtis dissimilarity: no clustering	NR	NR	NR	NR	↑ genera: *Bacteroides, Clostridium, Faecalibacterium, Roseburia* ↓ genera: *Bacteroides, Blautia, Dialister, Faecalibacterium, Ruminococcus*	Differences in species were observed at ASV level. Information on detailed species was not extracted.	Unweighted UniFrac distances showed two separate clusters, but not clearly between two diets.	Yes
	27	Post-omnivorous	Pre-omnivorous	Chao1, Shannon, Inverse Simpson, Fisher's index:↔	Bray-Curtis dissimilarity: no clustering	NR	NR	NR	NR	↑ genera: *Alistipes, Bacteroides, Blautia, Clostridium, Faecalibacterium* (unspecified species), *Megamonas, Roseburia, Ruminococcus* ↓ genera: *Bacteroides, Bifidobacterium, Blautia, Dialister, Faecalibacterium, Gemminger, Phascolarctobacterium, Prevotella, Ruminococcus, Sutterella*		—	Yes
	26	Post-vegan	Pre-vegan	Chao1, Shannon, Inverse Simpson, Fisher's index:↔	Bray-Curtis dissimilarity: no clustering	NR	NR	NR	NR	↑ genera: *Alistipes, Bacteroides, Blautia, Coprococcus, Dialister, Dorea, Faecalibacterium* (unspecified species)*, Phascolarctobacterium, Ruminococcus* ↓ genera: *Akkermansia, Bacteroides, Bifidobacterium, Clostridium, Coprococcus, Faecalibacterium, Roseburia, Ruminococcus*		—	Yes
McKenna et al. 2021 [90]	28	wk1-higher red meat (high)	Pre-high	Faith's phylogenetic diversity and Shannon: ↔	Unweighted UniFrac: significant between-group difference Weighted UniFrac:↔ DEICODE metrics:↔	NR	NR	Betaproteobacteriales:↑	—	↑ genera: *Akkermansia,* unclassified genus of family *Eggerthellaceae, Ruminococcaceae UCG-010, Megasphaera, Veillonella* ↑ genera: *Catenibacterium*	—	—	Yes

Table 4 (*continued*)

Study author, year	n	Comparison diet 1	Comparison diet 2	Alpha diversity	Beta diversity	Phylum	Class	Order	Family	Genus	Species	Other/notes	Significant effects on gut microbiota?
	28	Post-high	wk1-high					—	—	↓ genera: *Catenibacterium* ↑ genera: *Akkermansia*, unclassified genus of family *Eggerthellaceae*, *Veillonella*	—	—	
	28	Post-high	Pre-high					Betaproteobacteriales:↑	—	*Megasphaera:↓*	—	—	
	22	wk1-Lower red meat (MOD)	Pre-MOD	Faith's phylogenetic diversity and Shannon: ↔	Unweighted UniFrac: significant between-group difference Weighted UniFrac:↔ DEICODE metrics:↔	NR	NR	Mollicutes RF39:↓	*Lachnospiraceae:↑*	↓ genera: *Streptococcus* ↑ genera: *Coprococcus 2, Holdemanella, Acidaminococcus*	—	—	
	22	Post-MOD	wk1-MOD					Mollicutes RF39:↑	—	↓ genera: *Acidaminococcus, Holdemanella, Catenibacterium* ↑ genera: *Veillonella*	—	—	
	22	Post-MOD	Pre-MOD					—	*Lachnospiraceae:↑*	↓ genera: *Blautia, Catenibacterium* ↑ genera: *Coprococcus 2*	—	—	
	50	Post-MOD	Post-high	Faith's phylogenetic diversity and Shannon: ↔	Unweighted UniFrac: significant between-group difference Weighted UniFrac:↔	NR	NR	—	*Ruminococcaceae:↓*	↓ genera: *Holdemanella], Acidaminococcus* ↑ genera: *Megasphaera, metagenome*	—	—	
	50	wk1-MOD	wk1-high		DEICODE metrics:↔			Mollicutes RF39:↓	—	↑ genera: *Ruminiclostridium 5, Oscillibacter, Megasphaera, metagenome, Lactobacillus, Veillonella*, uncultured genus of family *Eggerthellaceae*	—	—	
	50	Pre-MOD	Pre-high					Betaproteobacteriales:↑	*Enterobacteriaceae:↑*	↓ genera: *[Eubacterium] eligens group, Ruminococcaceae UCG-013, Coprococcus 2, Holdemanella, Acidaminococcus, Slackia*, uncultured genus of family *Eggerthellaceae* ↑ genera: *Streptococcus, Catenibacterium, metagenome, Dielma*	—	—	
Bratlie et al. 2021 [93]	9 13 11	Post-cod Post-salmon Post-control	Pre-cod Pre-salmon Pre-control	—	No clear separation between diets pre-intervention. Trend of separation between diets post-intervention, especially between post-salmon and post-control.	NR	NR	Post-Cod & Post-Salmon compared to Post-Control (bacterial counts): Bacteroidales:↓ Clostridiales:↓ Selenomonadales:↓	NR	NR	NR	—	Yes

[1] Higher abundance (↑), lower abundance (↓), or comparable abundances (↔). NR, data measured but not reported; OTU, operational taxonomic unit; ASV, amplicon sequence variant.

3 comparisons from 2 studies [71, 93] substituted fish or seafood with non-seafood meat; 1 comparison [92] compared Mediterranean diet with higher fish-meat intake to a habitual omnivorous diet with higher non–fish-meat intake. Only 1 comparison [87] was between red and white meat. We also documented 1 comparison [85] of vegetarian and vegan diets based on data from RCTs, but this comparison was not used because it was not covered in our *a priori* search strategies.

Summary of study outcomes on gut microbiota

Overall, the effects of consuming meat on the gut microbiota were more frequently detected at the lower taxonomic levels (genus and species) than at the higher taxonomic levels (phylum and class) or in overall community diversity (e.g., Shannon's and inverse Simpson's indices; Table 3). Significant changes or differences in the gut microbiota composition were reported at the genus (12 of 13 comparisons) and species (5 of 5 comparisons, Figure 2A) levels. In contrast, significant effects on gut microbiota composition were reported for alpha diversity in only 2 of 7 comparisons (Figure 2A). The percentages of primary and secondary comparisons showing study-reported significant effects of meat intake on the gut microbiota are presented in Figure 2 and Table 3, with a summary in the footnote of Table 3.

The types and directionality of bacterial taxa responses varied (Table 3, Table 4). Complementing the summary provided in Table 3, Table 4 presents the types and directionality of bacterial differences per taxonomic level for all studies. Although most comparisons did not show any significant effects of higher intake of total meat and meat subtypes on the phyla Bacteroidota (formerly Bacteroidetes [99]), Bacillota (formerly Firmicutes [99]), and Pseudomonadota (formerly Proteobacteria [99]), seemingly consistent directions of changes or differences in members of the phylum Bacteroidota were observed in 2 primary comparisons [84, 89]. After consuming red meat or mushroom in an otherwise uncontrolled diet for 10 d, abundances of bacteroidota and bacillota were lower and higher, respectively [84]. Consuming a controlled vegan diet or a habitual omnivorous diet for 16 wk did not influence the observed increase in bacteroidota over time [89].

There was limited consistency in bacterial taxa responses at the lower taxonomic levels when effects were detected. At the genus level, which was the most frequently reported taxonomic level by the included studies, 28 genera were reported to be affected by meat intake, with only 4 of these genera observed more than once (*Bacteroides*, *Anaerostipes*, *Ruminococcus*, and *Roseburia*; Table 5). Higher meat consumption, including presumably self-chosen omnivorous diets before vegan or vegetarian diets, appeared to reduce *Anaerostipes* abundance as reported in 3 studies [74, 84, 89]. The abundance of *Bacteroides* was reduced in 1 study [84] after consuming red meat compared with mushroom but not different as reported in 2 other studies [85, 91]. Similarly, the abundance of *Roseburia* was increased by higher meat intake in 2 studies [88, 91] but reduced in another study [92]. Although 3 studies [87, 88, 91] reported meat-related changes or differences in *Ruminococcus* abundance, the results were not clearly reported or were inconsistent for a comparison between higher and lower meat intakes. At the species level, *Faecalibacterium prausnitzii* was reported in 2 studies [89, 92] to have a lower abundance with higher meat intake (Table 5).

Subgroup analysis for heterogeneity exploration

To investigate potential contributors to the heterogeneity in reported outcomes, our *a priori* subgroup analyses included the following: *1)* lacto-ovo vegetarian diet compared with the vegan diet; *2)* comparisons between meat subtypes, including *i)* unprocessed compared with processed meat and *ii)* red meat compared with white meat compared with fish/seafood; *3)* meat compared with nonmeat (plant-based foods or vegetarian/vegan diet), including *i)* red meat compared with nonmeat, *ii)* white meat compared with nonmeat, and *iii)* fish/seafood compared with nonmeat; and *4)* higher and lower meat intakes (mixed meat subtypes). We also included additional subgroup analyses based on the type and length of studies, type of study diets, and levels of dietary control. The categorization of studies based on the listed subgroups is presented in Table 3.

Insufficient comparisons were available to compare specific meat subtypes, with only 1 comparison [87] available between red meat and white meat and 3 comparisons [71, 93] between mixed seafood subtypes and mixed non-seafood meat subtypes. No comparison was available between unprocessed and processed meat, red meat and fish/seafood, or white meat and fish/seafood. Among the 12 primary comparisons on higher and lower meat intakes, comparisons were between red meat (4 comparisons [84, 86, 87, 90]), white meat (1 comparison [87]), or mixed meat subtypes (7 comparisons [73, 74, 85, 88, 89, 91]) and plant-based foods or diets (Table 3). Although 4 comparisons [84, 86, 87, 90] used red meat and 3 [84, 86, 87] of them compared red meat with plant-based foods (e.g., mushroom and whole grains), only 1 of them [87] controlled basal dietary intake besides the intervention foods.

The effects of meat consumption on the gut microbiota were observed in studies utilizing various experimental design features (Figure 3). The proportions of outcomes showing and not showing effects of meat consumption on the gut microbiota are comparable between the crossover and parallel RCTs (Figure 3A) or between studies with meat-specific diets and those with dietary patterns (Figure 3C). At least 67% of comparisons across different study lengths and levels of dietary control consistently showed some effects (Figure 3B, D). The direction of changes and specific differences in the gut microbiota composition for each comparison showed limited consistency across studies (Table 4).

Risk of bias assessments

Crossover and parallel RCTs were assessed separately for the intention-to-treat effects on the gut microbiota with selected experimental and comparator groups. Among the 13 studies, none was rated low risk, 11 were rated with some concerns, and 2 were rated high risk of bias (Table 6) [71, 73, 74, 84–93]. The risk of bias is mainly generated from *1)* period and carryover effects, *2)* deviations from the intended interventions (effect of assignment to intervention), and *3)* selection of the reported results. The 2 studies [73, 74] rated high risk of bias were crossover RCTs without washout periods between interventions, of which the one [74] with cointervention of energy restriction showed significant effects on the gut microbiota.

Discussion

The scoping review documents both observational and experimental research assessing the influence of meat consumption on
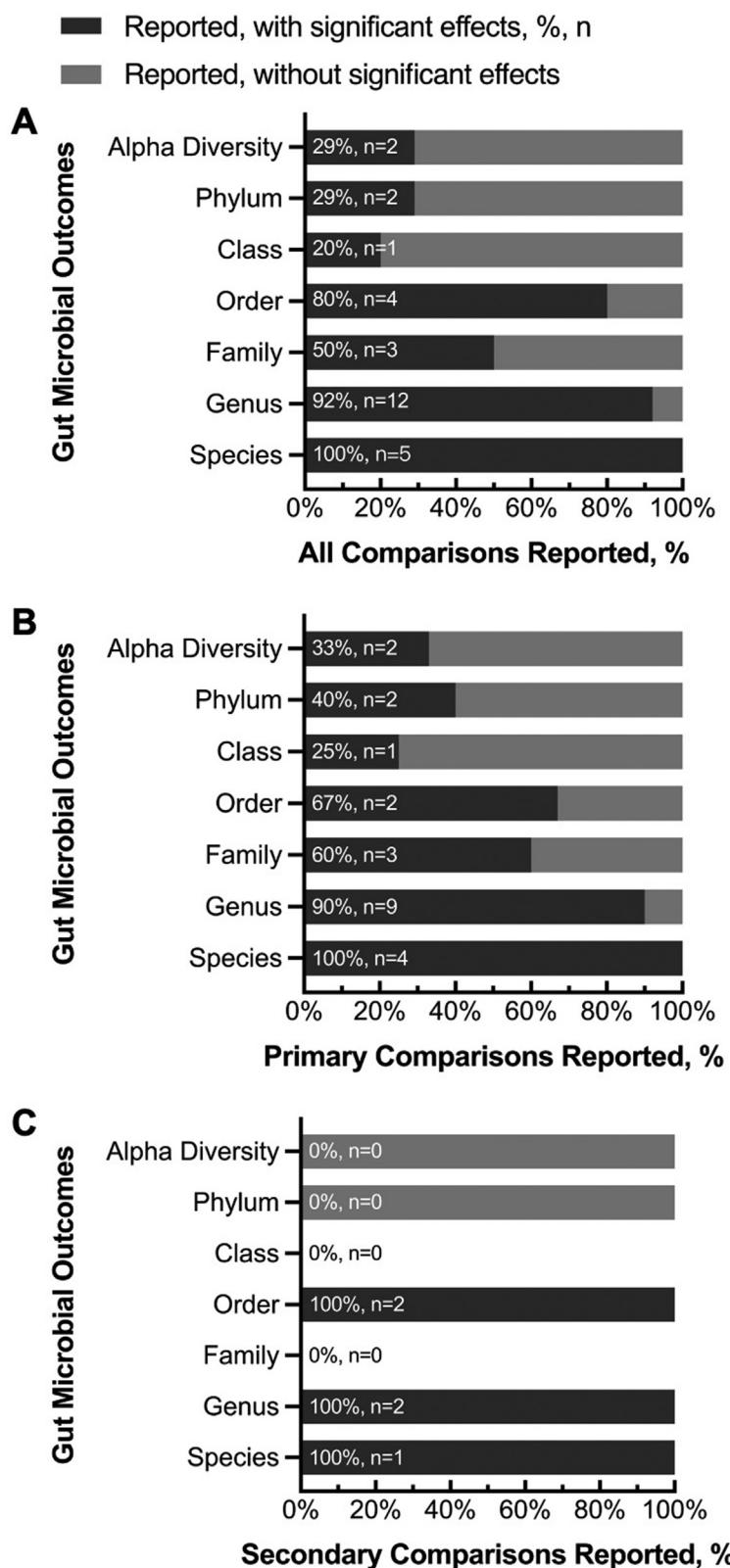
FIGURE 2. Percentages of (A) all, (B) primary, and (C) secondary comparisons that reported gut microbial outcomes at the specified levels, with (darker gray) or without (lighter gray) significant effects of diet on gut microbiota. The effects refer to whether significant changes or differences in microbiota composition were reported by authors of the included studies. The percentages and numbers of studies showing any significant effects out of the total number of studies that reported the specific outcome were denoted in percentages and *n*.

the gut microbiota. Most observational research used cross-sectional designs. The paucity of meticulously designed prospective cohort studies precluded systematically assessing associations between meat intake and gut microbiota. Experimental research, primarily conducted with apparently healthy adults and using RCTs with crossover or parallel intervention designs, suggests that changes and differences in gut microbiota composition due to meat consumption are more detectable at lower taxonomic levels (e.g., genus and species) than higher taxonomic or community levels. Caution is warranted against drawing firm conclusions

TABLE 5

Genera and species that were affected by meat intake as reported by at least 2 studies.

Bacteria	Study	Higher meat intake	Lower meat intake	Higher vs lower[1]
Genera				
Bacteroides	van Faassen et al. 1987 [85]	Post-omnivorous	Post-vegan	↔
		Post-omnivorous	Post-vegetarian	↔
		Post-vegetarian	Post-vegan	↔
	Hess et al. 2018 [84]	Post-red meat	Post-mushroom	↓
	Kohnert et al. 2021 [91]	Post-pre-omnivorous	Post-pre, post-, or pre-vegan	↔[2]
Anaerostipes	Hess et al. 2018 [84]	Post-red meat	Post-mushroom	↓
	Kahleova et al. 2020 [89]	Pre-vegan	Post-vegan	↓
	Pagliai et al. 2020 [74]	Post-pre-Mediterranean	Post-pre-vegetarian	↓
		Pre-vegetarian	Post-vegetarian	↓
Ruminococcus	Lang et al. 2018 [87]	Red/white meat	Nonmeat	Differed[3]
	Crimarco et al. 2020 [88]	Animal-based diet	Plant-based diet	↑
	Kohnert et al. 2021 [91]	Post-pre-omnivorous	Post-pre-vegan	↓[2]
		Post-omnivorous	Pre-omnivorous	↔[2]
		Pre-vegan	Post-vegan	↔[2]
Roseburia	Crimarco et al. 2020 [88]	Animal-based diet	Plant-based diet	↑
	Meslier et al. 2020 [92]	Post-omnivorous (higher nonfish meat)	Post-Mediterranean diet (higher fish)	↓
	Kohnert et al. 2021 [91]	Post-pre-omnivorous	Post-pre-vegan	↑
		Post-omnivorous	Pre-omnivorous	↑
		Pre-vegan	Post-vegan	↑
Species				
Faecalibacterium prausnitzii	Kahleova et al. 2020 [89]	Post-pre-omnivorous	Post-pre-vegan	↓
		Pre-vegan	Post-vegan	↓
	Meslier et al. 2020 [92]	Post-omnivorous (higher nonfish meat)	Post-Mediterranean diet (higher fish)	↓

[1] Higher abundance (↑), Lower abundance (↓), or comparable abundances (↔) in the higher meat intake group compared to the lower meat intake group.

[2] Amplicon sequence variant of the genus or species was reported as both enriched and depleted in the comparison by the study author.

[3] Authors reported that the abundance of the genus differed among the red meat, white meat, and non-meat groups, but did not report the pairwise difference between groups.

regarding the effects of meat intake on gut microbiota due to inconsistencies among the levels of dietary control, sources of meat, and specificity of bacterial composition.

Current state of knowledge (scoping review)

To our knowledge, our scoping and systematic review is among the first systematic reviews pertinent to meat intake and gut microbiota in humans. Our scoping review provides a comprehensive overview of the current state of knowledge and clearly identifies where research gaps exist. Compared with interventional studies, the number of observational studies more than doubled, whereas the health status and ages of participants in these studies were not always clearly described. Most observational research did not focus on meat intake but more broadly on dietary patterns with or without meat. Importantly, there is a paucity of prospective cohorts especially in healthy humans and RCTs, in particular crossover RCTs, in children and adolescents. In addition, the degree of meat processing (including the use of meat extenders) and cooking methods were not well documented by most studies. Given that most Americans and the global population consume meat, the influence of consuming total meat and specific meat subtypes on the gut microbiota composition across different age groups requires investigation.

Limitations and gaps in the current literature (systematic review)

Our systematic review included 13 RCTs in healthy adults with stable health status to assess the effects of meat intake on the gut microbiota. Initially, we planned to include both prospective cohort and RCT studies in healthy human adults with stable health status in our systematic review. However, only 1 eligible prospective cohort [25] was identified, which was insufficient for a systematic review. The findings from our systematic review implicate that the consumption of total meat and meat subtypes affects the gut microbiota composition, but the directionality and interpretation of these changes should be cautiously discussed, considering the inconsistencies across studies.

To investigate potential sources of heterogeneity, our *a priori* subgroup analyses based on the sources of meat did not yield any meaningful results because of the inadequate number of comparisons per subgroup. Gathering available literature, the number of comparisons between red meat and nonmeat intakes (4 comparisons [84, 86, 87, 90]) may potentially qualify for a subgroup review. However, only 1 of these 4 comparisons fully controlled participants' basal dietary intake, and their comparator foods ranged from high-fiber plant-based foods (e.g., mushroom and whole grains) to mixed nonmeat foods or lower amounts of red meat. Comparing meat to different comparator foods was shown to result in differential cardiometabolic effects in a meta-analysis of RCTs [100]. For example, consuming red meat led to greater reductions in LDL and HDL cholesterol concentrations when fish was the comparator and to greater reductions in triglycerides when carbohydrates were the comparat but lesser reductions in triglycerides when high-quality plant-based protein foods were
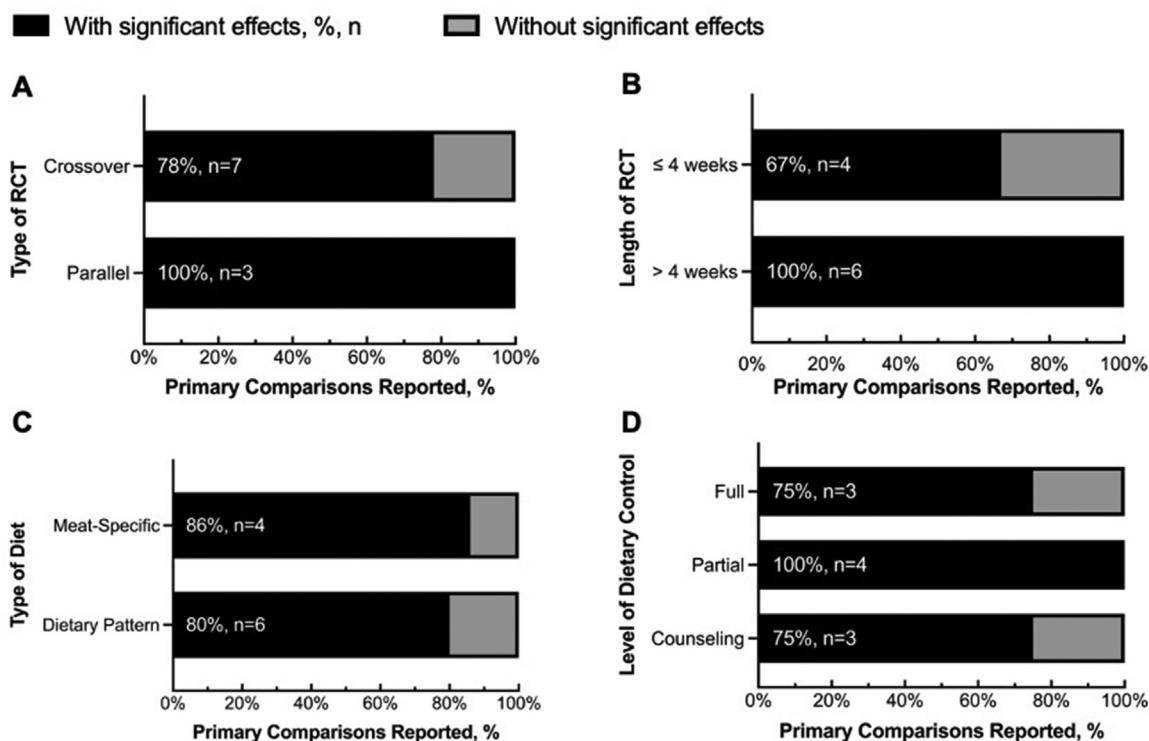
FIGURE 3. Percentages of primary comparisons that did vs. did not report significant effects of diet on gut microbiota based on the (A) type of randomized controlled trial (RCT), (B) length of RCT, (C) type of diet, and (D) level of dietary control. The partial level of dietary control (D) encompasses the studies in which partial foods were provided with or without control over basal dietary intake, as well as studies in which 1 group was controlled and 1 group followed a habitual diet. The significant effects refer to whether significant changes or differences in microbiota composition were reported by authors of the included studies. The percentages and numbers of studies showing any significant effects out of the total number of studies with the specific study characteristics were denoted in percentages and *n*.

the comparator [100]. It remains questionable how much of the dietary effects on the gut microbiota were attributable to red meat intake when the participant's dietary intake was not fully controlled and the comparator food was not specific, highlighting the importance of the "instead of what" question inherent to all nutrition science inquiries [101].

There is a particular paucity of research on the degree of meat processing. Of all red meat and poultry consumed by the US population, 55% were red meat and 45% were poultry, among which 32% of total red meat and 14% of total poultry were consumed in processed form (NHANES 2015–2018) [102]. Only ~10% of the US adults who are beef consumers choose lean and unprocessed forms [103]. Accumulating observational research indicates that consuming processed meat is associated with a higher risk for cardiometabolic diseases compared with consuming unprocessed meat [104]. However, our search did not identify any available study comparing intakes of unprocessed and processed meats. High-temperature cooking methods (e.g., grilling) also produce carcinogens from meat that may increase the risk for certain cancers (e.g., colorectal cancer) [105, 106]. However, among the 4 studies [84, 86, 87, 90] that reported using meat in unprocessed form, only 1 study [90] briefly described the cooking method (Supplemental Table S4).

Although the study designs varied among studies, our post hoc subgroup analyses based on selected study characteristics (i.e., study type, length of diet, type of diet, and level of dietary control) did not suggest any specific sources of heterogeneity.

Other subgroup analyses by demographic and anthropometric criteria may be considered but were not possible due to reasons such as unclear age cut-offs or an insufficient number of comparisons (male compared with female). The mean group ages of the study participants were between 18 and 65 y, whereas healthy older adults aged >65 y were rarely studied. Aging shifts the gut microbiota composition by reducing *Bacteroides*, which contributes to healthy aging [107]. Most studies have more female than male participants included in one or both of their intervention arms, whereas gut microbiota composition and responses can differ by sex [108, 109]. The racial diversity was inconsistently reported among studies (6 of 13 studies [71, 74, 85, 87–89]), with most participants being Caucasian. Collectively, these limitations underscore the importance of future research being inclusive of age, sex, and racial diversity.

Noteworthy, we observed a lack of *a priori* power calculation based on the microbiota outcome in almost all RCTs. Only 1 [89] of the 13 RCTs reported the estimation of sample size based on outcomes related to gut microbiota. The lack of *a priori* power calculation could be due to not only a lack of pilot data or challenge of estimating the sample size for microbiota outcomes [110] but also that the gut microbiota were secondary or exploratory outcomes. Each study's primary outcome is presented in Supplemental Table S3A (column "sample size estimation"). Although an adequate sample size is important for detecting statistical significance in outcomes of interest, the limited comparability and lack of research evidence restrict meaningful sample size estimation. Age, sex, and race are

TABLE 6
Cochrane risk of bias.

Study (year)	Domain 1a: risk of bias arising from the randomization process	Domain S: risk of bias arising from period and carryover effects	Domain 2: risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Domain 3: risk of bias due to missing outcome data	Domain 4: risk of bias in the measurement of the outcome	Domain 5: risk of bias in the selection of the reported result	Overall risk of bias[1]
Crossover RCTs							
van Faassen et al. (1987) [85]	Some concerns	Low	Low	Low	Low	Some concerns	Some concerns
Windey et al. (2012) [73]	Low	High	Some concerns	Low	Low	Some concerns	High
Foerster et al. (2014) [86]	Low	Some concerns	Low	Low	Low	Some concerns	Some concerns
Lang et al. (2018) [87]	Some concerns	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns
Hess et al. (2018) [84]	Some concerns	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns
Schmedes et al. (2019) [71]	Low	Low	Some concerns	Low	Low	Some concerns	Some concerns
Pagliai et al. (2020) [74]	Low	High	Some concerns	Low	Low	Some concerns	High
Crimarco et al. (2020) [88]	Low	Low	Low	Low	Low	Some concerns	Some concerns
Parallel RCTs							
Kahleova et al. (2020) [89]	Low	N/A	Low	Low	Low	Some concerns	Some concerns
Meslier et al. (2020) [92]	Low	N/A	Low	Low	Low	Some concerns	Some concerns
Kohnert et al. (2021) [91]	Low	N/A	Low	Low	Low	Some concerns	Some concerns
McKenna et al. (2021) [90]	Low	N/A	Low	Low	Low	Some concerns	Some concerns
Bratlie et al. (2020) [93]	Low	N/A	Some concerns	Low	Low	Some concerns	Some concerns

[1] For the description of overall risk of bias, "some concerns" refers to "the study is judged to raise some concerns in ≥1 domain for this result but not to be at high risk of bias for any domain"; "high" refers to "the study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result." N/A, not applicable; RCT, randomized controlled trial.

important participant characteristics to consider, which contribute to interpersonal variability in the gut microbiota but remain challenging to be addressed or adjusted for. One RCT [87] assessed how individual biological and anthropometric characteristics altered gut microbiota relative abundances. Genera such as *Akkermansia* and *Haemophilus* are positively and negatively associated with age, respectively; race and sex were found to influence community diversity and dozens of bacterial

taxa abundances [87]. However, individual traits were not adjusted for when assessing diet-induced effects [87]. Three studies [84, 86, 89] reported statistical adjustments of potential confounders (e.g., age, sex, BMI, and race). Studies also attempted to control for differences in individual traits by recruiting within the same race (e.g., Caucasian [71, 74, 85]) or the same sex (e.g., male [85]). However, they missed considering other potential confounders such as the use of medications (e.g., antibiotics) or supplementations (e.g., pre- or probiotics), as well as intakes of certain dietary components (e.g., fiber) with a known impact on the gut microbiota. Nevertheless, data from these RCTs can serve as preliminary pilot data for future research studying the effects of specific meat subtypes on the gut microbiota.

The analysis and reporting of data were not standardized, thereby limiting the comparability of findings among studies. For instance, 2 of the 12 primary comparisons [73, 85] did not suggest any effect of meat consumption on the gut microbiota. Yet, these 2 studies [73, 85] differ from others in both study design (i.e., no washout [73]) and molecular analysis methods (i.e., denaturing gradient gel electrophoresis [73] and cell culture [85]). Compared with more recent techniques such as 16S rRNA amplicon and shotgun sequencing, cell culture captures a small fraction of the bacterial profile, and denaturing gradient gel electrophoresis does not provide phylogenetic characterization without further analysis [111]. For community-level diversity measures, operational taxonomic unit (OTU)-based Shannon's index and Bray–Curtis dissimilarity were used most frequently for measuring alpha and beta diversity, respectively, in the RCTs (Table 4), but they tend to be less sensitive in detecting differences than phylotype-based approaches (e.g., weighted UniFrac distance) [112, 113]. The type of metrics used for alpha and beta diversity was not consistent either, which requires careful consideration based on the meaning and ecological relevance of the indices or metrics [114]. Biases in assessing the bacterial composition are introduced when different sample collection, processing, and analysis methods are chosen [115–117], whereas they were generally not justified by the study authors. In the 2 comparisons [71, 93] that compared fish/seafood with a mixture of non–fish/seafood meat subtypes, changes in bacterial abundances were detected in both studies but were reported at different taxonomic levels for different taxa. Recent findings argue against using the relative abundance of bacteria compared with absolute abundance for potentially misleading reporting [118]. Among the comparisons with significant effects, either mean change values or post-intervention values were used for between-group comparisons. In line with the aforementioned inconsistencies, all studies were rated as having some concerns for or high risk of bias. Although it was impractical to completely blind subjects regarding the type of diet in RCTs studying the effects of meat intake at the whole food level, in 3 crossover RCTs without a washout period between 2 diet interventions [73, 74, 88], the effects of the first diet on the following diet were not adequately assessed or discussed in 2 studies [73, 74]. The lack of washout period and repeated measures for baseline assessments and comparisons before each intervention leads to a high risk of bias from period and carryover effects in these 2 studies [73, 74]. Future studies on diet and gut microbiota should follow standardized protocols that are comparable with those reported in the previous studies, with justified and comprehensive reporting to improve research reproducibility [119].

The connections behind changes in the gut microbiota and host health outcomes warrant further research. Ten [71, 74, 86–93] of the 13 RCTs measured clinical health outcomes besides gut microbiota, and 9 [71, 74, 86, 87, 89–93] of the 10 studies conducted correlation analyses to explore potential concurrence. Among the genera and species reported to be affected by meat intake (Table 5), *Anaerostipes* was shown to be positively associated with LDL cholesterol and total cholesterol [74]. However, the functions and clinical relevance of bacteria and their metabolites remain largely unclear. Bacteria with no expression of metabolic activities may not be as clinically relevant as those producing clinically relevant metabolites, but the metabolic activities of bacteria can also be altered by the environment (e.g., diet) [118]. Identified correlations between gut microbiota and health outcomes should be further validated with functional analyses, which, however, requires expensive molecular and analysis methods with higher resolution (e.g., metagenomics and multiomic approaches) [118], and is currently limited by the availability of functional databases [120].

Potential mechanisms of meat–microbiota interactions

The effects of meat intake on the gut microbiota and host health are complex. Mechanistically, meat may influence gut microbiota by providing abundant nutrients (e.g., protein, fat, choline, and iron) available after host digestion and absorption for further metabolism, influencing the host health directly through bacterial components (e.g., LPS entering the systemic circulation) or indirectly through generating metabolites. Although these nutrients are not unique to meat, it is unclear how the matrix (e.g., combination of dietary components) and processing (e.g., cooking and addition of dietary emulsifiers) of meat may influence the health effects of consumption on gut microbiota [121]. Potential health-impacting gut microbiota–derived metabolites include secondary bile acids (e.g., deoxycholic and lithocholic acids) [122], SCFAs and branched-chained fatty acids [122], and trimethylamine and trimethylamine-*N*-oxide (TMAO) [123], as well as ammonia, hydrogen sulfide, polyamine, and indolic and phenolic compounds [124]. However, inconsistencies in the effects of meat intake on these metabolites (e.g., secondary bile acids [85, 92, 93], SCFAs and branched-chained fatty acids [71, 73, 74, 84, 86, 92, 93], and TMAO [71, 88, 92]) were observed in RCTs included in this review. Assessments of purported plausible mechanisms to explain the effects of meat intakes on the gut microbiota and host health outcomes are beyond the scope and focus of this review.

The effects of meat intake on the gut microbiota are further complexed by interactions with and the effects of nonmeat components within a dietary pattern [125–127]. Purported confounding dietary factors may include different fiber intakes [128] between higher and lower meat intake groups [84, 89, 91, 92], saturated fat with overriding effects on gut microbiota independent of meat subtypes or protein sources [87], or components (e.g., 3,3-dimethyl-1-butanol in olive oil) [129, 130] of a healthy dietary pattern that counteracts certain effects of meat intake.

Therefore, it is important to specify meat subtypes and control the overall dietary intake (including acutely co-consumed foods and broader dietary patterns) when studying meat and gut microbiota and to interpret changes in the gut microbiota considering their functional impacts.

Strengths and limitations

Our scoping and systematic reviews provide a comprehensive summary and overview of the current scientific literature on meat intake and gut microbiota in humans. By focusing on RCTs in the systematic review, we provided informative guidance on features of study design and reporting of results for conducting the human gut microbiota study with dietary interventions. However, our review focuses on summarizing and synthesizing research evidence for gut microbial changes related to meat intake and not on mechanisms. Although we observed the effects of dietary modifications on the gut microbiota, the biological significance of these effects is limited by associations but not causal relationships to health indices. The findings of results were determined by authors of the studies, which are prone to the bias of results' reporting. Furthermore, adequate data are not available for quantitative analysis of outcome measures, but a quantitative assessment and meta-analysis of the gut microbiota outcomes remain implausible.

Conclusions

The prominence of meat consumed in the United States and globally underscores the importance of knowing how it relates to and affects the human gut microbiota as an important diet-health mediator. The main intentions of this research were to provide a scoping review and a systematic review to inform meat industry stakeholders, nutrition and health researchers, and policymakers about the current state of literature and directions for future research. The main findings from this review are as follows: *1)* a limited number of RCTs (particularly in older adults) and prospective cohort studies have been conducted to understand the relationships between meat intake and gut microbiota in healthy adults; *2)* inconsistencies among studies were observed for the types of bacteria affected and the magnitude and directionality of bacterial responses; *3)* the experimental designs and reporting of results were inconsistent among studies, highlighting the need for well-designed, full-feed RCTs; *4)* the current evidence is not adequate for studying the heterogeneity of results based on meat subtypes, the degree of processing (including degree of meat extension), or method of cooking; and *5)* the directionality and health implications of changes or differences in the gut microbiota warrant future research. Our findings will hopefully shed light on areas that have not been well explored and spur new research.

Recommendations for Future Research

Based on the findings from our scoping review and systematic review, future research may consider the following 3 high-priority recommendations:

1) Full-feeding RCTs are warranted to assess the effects of consuming specific meat subtypes, with specified degrees of meat processing and dietary patterns, on the gut microbiota in humans.

Rationale

Our findings indicate a paucity of research assessing meat subtypes with full-feeding dietary interventions. Our review identified only 1 study in white meat [87], 2 studies in fish/-seafood [71, 93], and 4 studies in red meat [84, 86, 87, 90]. None of the studies assessed how the degree of meat processing (e.g., unprocessed or processed meat) or methods of cooking (e.g., baking or grilling) affects the gut microbiota. We identified and excluded 1 RCT [131] comparing the effects of processed meat and nitrate-added drinking water on the gut microbiota because it did not provide a comparison between higher and lower meat intakes and no changes in gut microbiota abundance were reported; it is also unlikely that nitrate by itself transits to the colon [132]. Although the level of dietary control (i.e., full-feed, partial-feed, and dietary counseling) did not seem to influence whether any diet-induced effects can be observed in the gut microbiota, when meat was consumed within different dietary patterns or minimally controlled habitual diets, it was implausible to assess meat-specific effects. There also seems to be a trend of more studies showing dietary effects on the gut microbiota when the diet intervention was >4 wk. However, the selection of 4 wk to categorize and group studies was based on the observations of included study durations and not on an established definition of short- and long-term studies. Further, the 2 studies that showed "no effects" either used a cultivation-based method that is prone to miss capturing statistically significant findings in the gut microbiota [85] or did not include a washout period between 2 interventions to avoid any carryover effects [73]. Thus, the recommended length of intervention should be determined based on the expected time needed for both microbial and nonmicrobial outcomes of interest to respond to a diet intervention. Studies should also be powered based on the gut microbiota outcomes of interest *a priori*. Additional suggestions are presented elsewhere [119]. Nevertheless, data from these RCTs can be used for sample size estimation based on gut microbiota outcomes in future studies.

2) There is a need for more prospective observational studies on gut microbiota with total meat and meat subtypes as *a priori* independent variables among adults without diagnosed disease. A standardized definition of total meat and meat subtypes should be used and reported.

Rationale

Only 1 prospective observational study on meat intake and gut microbiota in healthy adults was identified through our comprehensive and systematic search of available English peer-reviewed literature. Most observational studies were cross-sectional (47 of 57 studies) with a weak level of temporality (i.e., exposure happens before the outcome occurs). Meat was studied as part of a habitual dietary pattern with inconsistent groupings of meat [133], making it challenging to draw consistent conclusions on the associations between meat and gut microbiota based on observational evidence. Furthermore, most of our identified observational studies had a small sample size. However, current national databases such as the NHANES [134] or the Human Microbiome Project [135,136] provide data on either dietary intake or gut microbiota composition, but not both. Further research collecting data on both dietary intake and gut microbiota with larger cohorts is warranted.

3) Upon addressing recommendations 1 and 2, systematic reviews and meta-analyses are needed to assess the effects of meat intake on gut microbiota–derived metabolites and health outcomes (e.g., cardiometabolic risk factors), as well as the relationships between meat-induced gut microbiota compositional changes and health outcomes.

Rationale

It remains unclear how the effects of meat consumption on gut microbiota would impact the host's health. Although gut microbiota–derived metabolites and health indices other than gut microbiota were also assessed in the included RCTs, their conclusions generally only describe effect or no-effect regarding diet and gut microbiota. Six [71, 86, 88–91] of the 13 RCTs associated results in the gut microbiota with potential health implications, but only 1 [91] of them summarized their findings with directional terms (e.g., harmful or beneficial). Our systematic review documents secondary outcomes of gut microbiota–derived metabolites that were also measured and reported in the included RCTs (Supplemental Table S5). We specifically selected metabolites that are associated with health outcomes (e.g., cardiometabolic disease risk factors). We also documented whether a correlational analysis was conducted between changes in gut microbiota composition and these metabolites or cardiometabolic health outcomes (Supplemental Table S5). However, this was not the focus and intention of our current review. Systematic reviews and meta-analyses with targeted focus on dietary intake and gut microbiota are lacking. Based on our brief search on PubMed, the few systematic reviews published previously on diet and gut microbiota are mostly qualitative or have a broader scope of focus on nutrition, including diet and nutrition in general [137, 138], probiotic supplementation [139], oat intake [140], and a specific nutrient in both humans and animals [7]. None of them included any of the 13 RCTs identified and included in our systematic review. Importantly, both the current and previous reviews emphasize the need for future research to address the differences in individual responses, the influence of dietary patterns and processing and cooking methods, and health implications and mechanisms related to microbial changes.

Author disclosures

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Appendix A. Supplementary data

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