Title

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Journal

Advances in Nutrition, 15(6)

ISSN

2161-8313

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Publication Date

2024-06-01

DOI

10.1016/j.advnut.2024.100241

Advances in Nutrition 15 (2024) 100241

Advances in Nutrition
AN INTERNATIONAL REVIEW JOURNAL
journal homepage: https://advances.nutrition.org/

Review

Human MicroRNAs Modulated by Diet: A Scoping Review

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A B S T R A C T

Because of their role in regulating and fine-tuning gene expression in the posttranscriptional period, microRNA (miRNA) may represent a mediating factor that connects diet and metabolic regulation. Given the vast number of miRNAs and that modulations in miRNA happen in response to a variety of stimuli, a comprehensive registry of miRNAs impacted by diet and the food items that modulate them, would have utility in the identification of miRNA complements for analysis of diet interventions and in helping to establish linkages between the specific impacts of diet components. A scoping literature search of online databases (PubMed, SCOPUS, EMBASE, and Web of Science) was performed. Only studies in human populations, those that used a diet intervention or meal challenge, and those that measured miRNA profiles in the same subject at multiple time points were included. Of the 6167 studies screened, only 25 met the study criteria and were included in the review. Seven studies examined miRNA following a meal challenge, whereas 18 investigated miRNA following a sustained diet intervention. The results demonstrated that miRNA are modulated following a variety of diet interventions and that intensity of miRNA response is greater in metabolically healthy subjects. Heterogeneity in the intensity and length of the diet intervention, the study populations being observed, and the methodology through which target miRNA are identified contribute to a lack of comparability across studies. The findings of this review highlight the need for more study of miRNA responsiveness to intake and provide recommendations for future research.

Keywords: microRNAs, nutriepigenomics, diet, precision nutrition, food

Statement of Significance

This scoping review summarizes the literature related to microRNAs, a class of important epigenomic regulators, which are responsive to diet in human subjects. This review highlights challenges and makes recommendations in identifying miRNAs that are consistently responsive to diet as well as highlighting the importance of thorough reporting of methodology for the purpose of replication and the establishment of reliable response markers.

Introduction

MicroRNA (miRNA) are near ubiquitous regulators of metabolic processes. First described in 1993, miRNA are short nucleobases (~21 to 23 nucleotides in length), which engage in posttranscriptional regulation of gene expression [1,2]. MiRNA can pair perfectly or imperfectly with its mRNA complement, leading to degradation of the mRNA complement, inhibition of mRNA translation, or sequestration of the mRNA from the translational complex, which generally results in decreased protein expression [3,4]. MiRNA regulation is complex, as individual miRNA may complement multiple genes [5–7] and specific genes may be regulated by multiple miRNAs [8]. It is estimated that >60% of coding genes within the human genome have been conserved by selective pressure to pair to miRNA [9]. Most miRNAs are encoded within the intronic section of a gene and transcribed by RNA polymerase II [10]. MiRNAs are expressed within all tissue types and can also be extracted from cell-free biofluids such as plasma and serum. MiRNAs are expressed in response to a variety of stimuli, including hypoxia [11–13], stress [14,15], and exercise [16]. Nutrients have also been shown to influence miRNA expression across a range of laboratory models, whether because of nutrient supplementation or an induced deficiency of specific nutrients [17,18].

MiRNAs have been shown to be dysregulated in disease states, including cardiovascular disease, diabetes, and cancer

Abbreviations: miRNA, microRNA; PBMC, peripheral blood mononuclear cell.

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https://doi.org/10.1016/j.advnut.2024.100241
Received 28 February 2024; Received in revised form 4 May 2024; Accepted 8 May 2024; Available online 10 May 2024

[19–24]. Because of the observed dysregulation and their recoverability from plasma or serum samples, miRNAs have been examined as biomarkers across a variety of disease pathologies [25–28]. Unfortunately, progress toward establishing miRNAs as clinical biomarkers has been slow, owing in no small part to heterogeneous methodologies that result in low reproducibility [29–31].

Beyond clinical biomarkers, miRNAs have potential to be biomarkers of effectiveness in nutrition research. However, for this potential to be realized, it is necessary to identify which miRNAs are responsive to diet interventions and to interrogate sources of variability in results. As such, this review surveys the existing literature to identify miRNAs, which may be modulated following consumption of a food item of interest in human subjects with a focus on additional sources of heterogeneity that have not been previously covered in recent reviews.

Methods

This review was conducted in accordance with the PRISMA 2020 guidelines [32]. The primary research question to be addressed was "Which microRNA change in response to diet interventions, both in the immediate postprandial period and in levels over time?" The study protocol was prospectively registered in PROSPERO (CRD42022276782). The literature search, data extraction, and risk of bias assessment was performed by 1 researcher (GMC) with oversight by another (FMS).

Search strategy and study selection

A systematic literature search was undertaken in September 2022, and a gap search was completed in April 2024. The search was conducted in the MEDLINE-PubMed, Scopus, Web of Science, and EMBASE databases. The search strategy used is detailed in Supplemental Methods. All identified studies were pooled into Covidence software (Veritas Health Information, 2022) with duplicate articles removed. Study titles and abstracts were examined, with studies that did not address miRNA changes as an outcome of a diet intervention in humans excluded. Next, full texts of the remaining studies were analyzed to determine whether they met the eligibility criteria of the review.

Study selection: inclusion and exclusion criteria

Studies were included that used pre–post measurements of miRNA expression to measure changes in miRNA profile following a dietary intervention within human subjects.

Studies were excluded for the following reasons: *1*) if interventions were performed in model organisms or cell culture; *2*) if miRNAs were not measured across multiple time points within the same subject; *3*) if miRNA modulations were induced by an intervention other than food (including diet supplements or extracts); *4*) if changes in miRNA profiles could not be solely attributed to the diet intervention; and *5*) if the altered miRNAs were identified within the study as exogenously produced.

Data extraction

The following data were extracted from the included studies: *1*) name of the first author and year of publication; *2*) study design; *3*) sample size and population; *4*) dietary intervention (food and amount); *5*) duration of intervention; *6*) compartment measured; *7*) measurement method; *8*) miRNAs downregulated; *9*) miRNAs upregulated; and *10*) miRNAs without significant changes.

Results

Study selection

The search protocols identified 6167 articles, including 831 duplicates retrieved across multiple searches that were removed. Abstracts from the remaining 5336 articles were screened for possible relevance to the search criteria, and 5169 articles were excluded for relevance at this stage. Full-text assessment was undertaken for the remaining 167 studies. A total of 25 studies were included for data extraction. Figure 1 provides the PRISMA diagram for the visualization of the search process and number of studies examined at each stage.

Study and participant characteristics

Seven of the studies included examined miRNA changes across the immediate postprandial period following administration of a dietary challenge [33–39]. Studies that investigated changes in the postprandial period are summarized in Table 1. The remaining 18 studies studied changes in expression of miRNA in response to sustained interventions [40–57]. These studies are presented in Table 2.

Of the 25 included studies, 8 used a crossover design where participants were exposed to 2 or more diet interventions and measured pretest and posttest for each intervention, whereas in the remaining 17 studies, each participant was assigned to a single intervention.

The included studies measured miRNA across multiple tissues and fluids: plasma [34,38–40,42,44,50,51,54], serum [37,43,49,55], peripheral blood mononuclear cells (PBMCs) [33,36,42,52,56,57], exosomes [46–48], HDL [41], saliva [54], mucosal biopsy [45], and semen [53]. Although sequencing was used on a subset of participants in several studies, the most common analysis platform was qRT-PCR, used by 21 studies.

Diet and miRNA

Acute Consumption

The 7 studies that examined miRNAs in the postprandial period used a variety of interventions. Three studies used a singular food, whereas the other 4 used a mixed meal. These studies were generally small, enrolling between 9 and 40 subjects. Each study measured subjects from a fasted baseline and the observation period ranged from 2 to 6 h, with 3 studies collecting samples at multiple time points throughout the observation period—Daimiel et al. [34]: 1, 2, 4, and 6 h postprandial; Quintanilha et al. [38]: 1, 3, and 5 h postprandial; and Ramzan et al. [39]: 2 and 4 h postprandial.

The included studies used a variety of methods to identify miRNAs for analysis. Four studies used a prepared oligonucleotide bead array or microarrays before quantification using qRT-PCR [33,36–38], whereas the other 3 identified miRNAs of interest based on literature searches, predictive algorithms, or pilot studies before performing qRT-PCR [34,35,39].

Food challenge. Consumption of olive oil produced significant modulations in postprandial miRNA profiles in metabolically healthy individuals, but this response was blunted in individuals

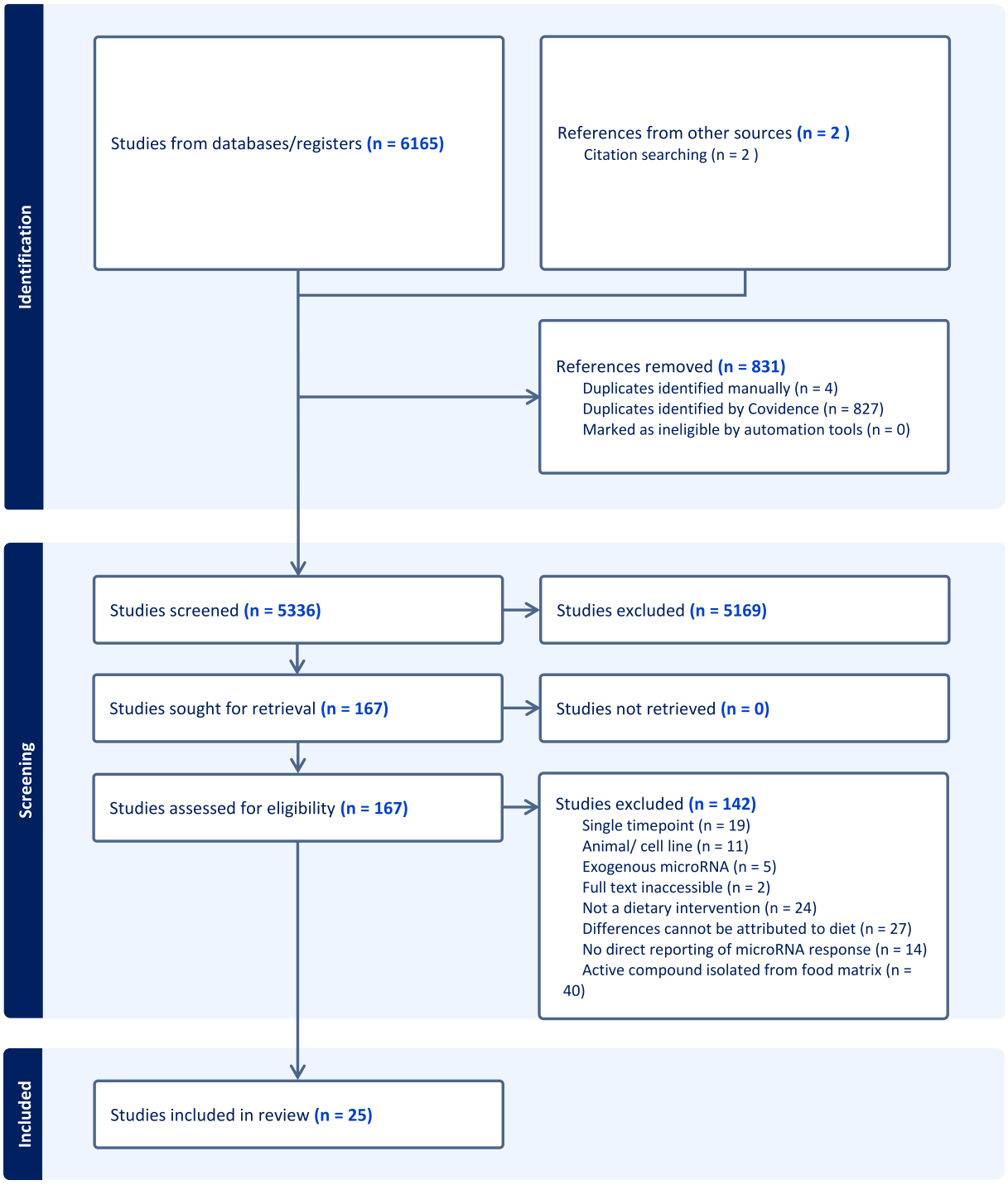

FIGURE 1. PRISMA flow diagram of search strategy and article selection process.

who had been diagnosed with metabolic syndrome [33]. Another study examining the postprandial effects of olive oil demonstrated that the postprandial response to extra virgin olive oil varied with varying concentrations of polyphenols [34]. No common miRNAs were identified as modulated between the 2 studies. An oral glucose tolerance test in children with insulin resistance compared with that in insulin-sensitive controls showed that both groups had significant modulations to miRNA profiles 2 h after consuming a glucose beverage and that metabolic health significantly impacted how miRNAs were regulated [37].

Meal challenge. A high-fat mixed meal identified 1 miRNA that was significantly downregulated 4 h postprandially [35]. Ingestion of a sweetened cream beverage led to increased expression of 9 miRNAs and decreased expression of an addition 9 miRNAs at 2 h postprandially [36].

Long-term consumption

Within the 18 studies investigating the effects of a sustained dietary intervention over time, 11 examined the addition of a single food to a baseline diet. In the remaining 7, investigators assigned subjects to more extensive dietary changes. These

TABLE 1
Seven studies examining modulation of microRNAs (miRNAs) through diet interventions in the acute postprandial period.

Food	Study ID	Amount	Time	Population	Study design	Measurement method	Compartment	Downregulated miRs	Upregulated miRs	miRs not significantly changed
Olive oil	D'Amore et al. [33]	50 mL	4 h	$n = 12$	Parallel feeding challenge	Oligonucleotide bead array, validated by qRT-PCR	PBMC	miR-146b-5p, miR-19a-3p, miR-181b-5p, miR-107, miR-769-5p, miR-192-5p	miR-23b-3p, miR-519b-3p	
				$n = 12$ with newly diagnosed metabolic syndrome				miR-19a-3p		miR-146b-5p, miR-181b-5p, miR-107, miR-769-5p, miR-192-5p, miR-23b-3p, miR-519b-3p
Low-polyphenol extra virgin olive oil	Daimiel et al. [34]	30 mL	1, 2, 4, 6 h	$n = 12$	Randomized crossover	Targeted qRT-PCR (based on literature search and predictive algorithms)	Plasma	At 1 h: let-7e-5p, miR-328a-3p	At 1 h: miR-20a-5p At 2 h: miR-20a-5p At 4 h: miR-17-5p	
Medium-polyphenol extra virgin olive oil		30 mL	1, 2, 4, 6 h						At 6 h: miR-17-5p, miR-192-5p	Let-7e-5p, miR-328a-3p, miR-20a-5p
High-polyphenol extra virgin olive oil		30 mL	1, 2, 4, 6 h					Let-7e-5p, miR-10a-5p, miR-21a-5p, miR-26b-5p		
High-fat meal with ursodeoxycholic acid or lactose control	Kračmerová et al. [35]	6151 kJ (47.4% lipid)	4 h	$n = 10$	Randomized crossover	qRT-PCR	$CD14^+$ cells	miR-181a		miR-146a
High-SFA meal	Lopez et al. [36]	30 g sucrose/m^2 + 50 g cow milk cream/m^2 of body surface area; mean kilocalories, ~800	2 h	$n = 9$	Single-arm pre–post	miRNA array validated by qRT-PCR	PBMC	miR-613, miR-629-3p, miR-24-2-5p, miR-555, miR-148a-5p, miR-621, miR-875-3p, miR-513c-5p, miR-1226	miR-653, miR-19b-1-5p, miR-363-5p, miR-885-3p, miR-339-3p, miR-938, miR-148b-5p, miR-593-5p, miR-200b-5p	
Glucose beverage	Masotti et al. [37]	1.75 g of glucose/kg body weight (≤75 g)	2 h	$n = 12$	Parallel feeding challenge	Panel	Serum			
				Normoglycemic controls ($n = 6$)				miR-27a-3p, miR-142-3p, miR-374a-5p, miR-26a-5p, miR-409-3p, miR-26a-5p, miR-409-3p, miR-28-5p, miR-584-5p, miR-200c-3p, miR-382-5p, miR-32-5p, miR-18a-5p, miR-339-3p,	miR-2110, miR-20b-5p, miR-605, miR-128, miR-501-3p, miR-485-3p, miR-320b, miR-95, let-7b-5p, miR-34a-5p, miR-423-5p, miR-22-3p, miR-222-3p, miR-93-5p,	

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TABLE 1 (*continued*)

Food	Study ID	Amount	Time	Population	Study design	Measurement method	Compartment	Downregulated miRs	Upregulated miRs	miRs not significantly changed
								miR-376a-3p, miR-19a-3p, miR-30d-5p, miR-151a-3p, miR-21-5p, miR-660-5p, miR-30c-5p	miR-143-3p, miR-99a-5p, miR-652-3p, miR-341-3p, miR-125b-5p, miR-146a-5p	
				Insulin resistant ($n = 6$)				miR-142-3p, miR-339-5p, miR-374b-5p, miR-27b-3p, let-7f-5p, miR-27a-3p, miR-301a-3p, miR-409-3p, miR-495-3p, miR-141-3p, miR-30b-5p, miR-374a-5p, miR-424-5p, miR-26a-5p, miR-26b-5p, miR-328, miR-30c-5p, miR-28-5p, miR-148b-3p, miR-151a-3p, miR-30d-5p, miR-21-5p, let-7d-3p, miR-148a-3p, miR-101-3p, miR-126-3p	miR-346, miR-190a, miR-30e-3p, let-7b-5p, miR-500a-5p, miR-200c-3p, miR-320b, miR-122-5p, miR-486-5p, miR-133b, miR-95, miR-1, miR-34a-5p, miR-501-3p, miR-532-5p, miR-423-5p, miR-140-3p, miR-93-5p, miR-378a-3p, miR-222-3p	
High-saturated fat meal	Quintanilha et al. [38]	Test meal: croissants, cheese, butter, and chocolate wafer—1067 kcal (54% fat, 37% CHO, 9% protein)	1, 3, 5 h	$n = 11$	Single-arm pre–post	Panel	Plasma	1 h: miR-10b-5p, miR-1260a, miR-342-3p, miR-150-5p, miR-92b-3p, miR-548c-5p, miR-34a-3p, miR-29a-5p, miR-181c-5p, miR-136-3p 3 h: miR-205-5p, miR-16-1-3p, miR-29a-3p, miR-505-3p 5 h: miR-1260a, miR-92b-3p, miR-205-5p, miR-545-3p, miR-885-5p, miR-454-3p	1 h: miR-200b-3p, miR-200c-3p, miR-143-3p, miR-145-5p, miR-2110, miR-33b-5p, miR-195-5p, miR-143-5p 3 h: miR-200b-3p, miR-143-3p, miR-145-5p, miR-375, miR-379-5p, miR-191-5p, miR-410-3p, miR-376b-3p 5 h: miR-200c-3p, miR-145-5p, miR-143-5p, miR-136-3p, miR-375, miR-95-3p, miR-18a-5p, miR-486-3p	

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TABLE 1 (*continued*)

Food	Study ID	Amount	Time	Population	Study design	Measurement method	Compartment	Downregulated miRs	Upregulated miRs	miRs not significantly changed
High-carbohydrate meal	Ramzan et al. [39]	Test meal: 2500 kJ; 50% carbohydrate, 20% fat, 27% protein	2, 4 h	$n = 40$ Healthy weight insulin sensitive, $n = 20$ Overweight insulin resistant, $n = 20$	Single-arm pre–post	10 preselected miRNA based on pilot study, quantified by qPCR	Plasma	4 h: miR-17-5p, miR-15a-5p	4 h: miR-21-3p	miR-126-3p. miR 16-5p, miR-222-3p miR-126-3p, miR-17-5p, miR-21-3p, miR-15a-5p, miR-16-5p, miR-222-3p

Abbreviations: PBMC, peripheral blood mononuclear cell.

studies included 5–166 participants, who were observed over periods ranging from 2 wk to 1 y. All studies examined participants following an overnight fast.

The included studies used a variety of techniques to select miRNA for investigation. Two studies analyzed miRNA using a prepared oligonucleotide bead array [46] or microarrays [52] within all collected samples, whereas 2 used a microarray within a subsample of the intervention group [56,57]. Four studies used microarrays to identify miRNA of interest that were then quantified using qRT-PCR [42,49,50,53]. The remaining 10 studies examined miRNA of interest that had been generated from previous experiments or literature searches through qRT-PCR [40,41,43–45,47,48,51,54,55].

Food intervention. Studies supplementing nuts make up the largest proportion of articles in the review. In 1 large study following 1 y of walnut supplementation, only 1 miRNA was significantly changed by the intervention [43]. A second study found that 2 miRNAs were upregulated in exosomes following 1 y of walnut supplementation [47]. An 8-wk intervention supplementing mixed nuts (15 g almonds and 15 g walnuts) also resulted in the decreased expression of 4 miRNAs and the increased expression of 7 miRNAs [50]. Another study found that daily pistachio consumption over the course of 4 mo significantly upregulated expression of 4 miRNAs [44]. Other interventions testing Brazil nut intake over 2 mo found that expression of 2 circulating miRNA were increased in the experimental arm; however, only 1 of these miRNAs was significant when comparing solely among participants with metabolic syndrome [51].

Only 5 studies included in this review examined food other than nuts. MiRNA profiles were differentially modulated in response to daily consumption of 500 mL of beer or nonalcoholic beer [40]. Lean red meat was demonstrated to induce increased expression of several miRNAs in the rectal mucosa [45]. Daily consumption of blood orange juice differentially modulated miRNAs in plasma and PBMCs, whereas grapefruit juice consumption led to modulations in miRNA and gene expression in PBMCs [42]. Consumption of freeze-dried blueberries resulted in modulation of 3 miRNAs in PBMCs [56].

Diet intervention. Interventions using dietary patterns or diets with modifications to specific categories of foods have been used to examine miRNA response. A diet designed to reduce glycemic load also modulated miRNA profiles 4 mo after starting the diet intervention [49]. HDL-carried miRNA were not differentially modulated by either of 2 transfat-enriched diets, although correlations between HDL miRNAs and blood lipid concentrations did vary [41]. An 8-wk Mediterranean diet intervention that used 2 different methods of analysis identified 28 miRNAs that were differentially expressed across both methods of analysis in a cohort of breast cancer survivors [46]. A year-long Mediterranean diet intervention identified 11 miRNAs modulated in those following a low-fat diet, 8 miRNAs that were modulated in those following a Mediterranean diet supplemented with extra virgin olive oil, and 21 miRNAs that were modulated while following a Mediterranean diet supplemented with mixed nuts [48].

miRNA and mRNA or protein targets

Of the 25 studies in the review, 7 analyzed observed changes in 40 miRNA profiles relative to gene expression or clinical

TABLE 2
Eighteen studies examining modulation of microRNAs (miRNAs) after prolonged dietary intervention.

Food	Study ID	Amount	Duration	Population	Study design	Measurement method	Compartment	Downregulated miRs	Upregulated miRs	miRs not significantly changed
Blood orange juice	Capetini et al. [42]	500 mL	4 wk	$n = 20$	Single-arm pre–post	RT-qPCR	Plasma		miR-144-3p	miR-107, miR-150-5p, miR-30e-5p, miR-106b-5p, miR-15a-5p, miR-101-3p
							PBMC	let-7f-5p, miR-126-3p	miR-424-5p, miR-144-3p, miR-130b-3p	miR-27a-3p, miR-142-3p, miR-17-5p, let-7d-5p
Beer	Daimiel et al. [40]	500 mL	14 d	$n = 7$	Crossover	Custom array	Plasma		miR-145a-5p	miR-155-5p, miR-328-3p, miR-320a-3p, miR-92a-5p
							Macrophage			miR-145a-5p, miR-17-5p, miR-20a-5p, miR-26b-5p, miR-223-3p
Nonalcoholic beer		500 mL	14 d	$n = 7$	Crossover	Custom array	Plasma	miR-320a-3p, miR-92a-5p		miR-155-5p, miR-328-3p
							Macrophage	miR-17-5p		miR-145a-5p, miR-17-5p, miR-20a-5p, miR-26b-5p, miR-223-3p
Commercially available shortening	Desgagné et al. [41]	3.7% daily energy	4 wk	$n = 9$	Randomized crossover	qRT-PCR	HDL			HDL-miR-223-3p, HDL-miR-135a-3p
Transfat-enriched butter										HDL-miR-223-3p, HDL-miR-135a-3p
Walnuts	Gil-Zamorano et al. [43]	15% daily energy (~30–60 g/d)	1 y	$n = 166$	Randomized controlled parallel	Screening of subset of participants with LDL-C reduction at 1 y using panel	Serum		miR-551a	miR-224-3p, miR-181c-3p, miR-1271-5p, miR-30d-3p, miR-493-3p, miR-589-3p, miR-1227-3p, miR-181c-5p, miR-130b-5p, miR-542-5p, miR-340-3p, miR-192-5p, miR-330-3p
Pistachios	Hernández-Alonso et al. [44]	57 g/d	4 mo	$n = 49$	Randomized crossover	7 predefined miRNA qRT-PCR	Plasma		miR-15a-5p, miR-21-5p, miR-29b-3p, miR-126-3p	miR-192-5p, miR-223-3p, miR-375
Lean red meat	Humphreys et al. [45]	300 g/d	4 wk	$n = 23$	Randomized crossover	8 predefined miRNA; qRT-PCR	Rectal mucosa		miR-19a-3p, miR-19b-3p, miR-21-5p	miR-17-5p, miR-18a-5p, miR-20a-5p, miR-92a-3p, miR17-92 cluster, miR-16-5p

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TABLE 2 (*continued*)

Food	Study ID	Amount	Duration	Population	Study design	Measurement method	Compartment	Downregulated miRs	Upregulated miRs	miRs not significantly changed
Grapefruit juice	Krga et al. [57]	340 mL/d	6 mo	$n = 48$ (miRNA measured in subgroup $n = 12$)	Randomized crossover	Microarray	PBMC	miR-361-5p, miR-125a-5p, miR-758-5p, miR-329-3p	miR-623, miR-629-5p	
Mediterranean diet	Kwon et al. [46]		8 wk	$n = 16$	Randomized parallel trial	NanoString human miRNA panel	Extracellular vesicles isolated from plasma	Let-7a-5p, miR-1253, miR-3144-3p, miR-532-3p	miR-122-5p, miR-144-3p, miR-216a-5p, miR-217, miR-324-3p, miR-324-5p, miR-329-3p, miR-378d, miR-379-5p, miR-384, miR-429, miR-483-5p, miR-491-3p, miR-495-3p, miR-496, miR-504-5p, miR-512-3p, miR-515-3p, miR-517b-3p, miR518c-3p, miR-518d-3p, miR-519c-3p, miR-758-5p	
Walnuts	Lopez et al. [36]	15% of total energy (~30–60 g/d) Control group: Usual diet w/walnut restriction	1 y	$n = 101$	Randomized parallel trial	Pooled samples screened using panel and validated using qRT-PCR	Exosomes		miR-29b-3p,miR-32-5p	miR-15a-5p, miR-15b-5p, miR-106b-5p, miR-107, miR-144-3p, miR-148a-3p, miR-151a-3p, miR-424-5p
Mediterranean diet + extra virgin olive oil	Mantilla-Escalante et al. [48]		1 y	$n = 44$	Randomized parallel trial	qRT-PCR	Exosomes isolated from plasma	miR-21-5p, miR-107, miR-103a-3p, miR-151a-3p, miR-22-3p	miR-215-5p, miR-34b-5p, miR-222-3p	miR-10a-5p, miR-210-3p, miR-29c-3p, miR-106a-5p, miR-20b-5p, miR-20a-5p, miR-1224-5p, miR-1246, miR-17-5p, miR-23a-3p, miR-320b, miR-193b-3p, miR-125a-3p, miR-28-5p

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TABLE 2 (*continued*)

Food	Study ID	Amount	Duration	Population	Study design	Measurement method	Compartment	Downregulated miRs	Upregulated miRs	miRs not significantly changed
Mediterranean diet + nuts				$n = 44$					miR-215-5p, miR-10a-5p, miR-21-5p, miR-210-3p, miR-34b-5p, miR-29c-3p, miR-106a-5p, miR-107, miR-20b-5p, miR-20a-5p, miR-103a-3p, miR-1224-5p, miR-151a-3p, miR-1246, miR-17-5p, miR-23a-3p, miR-222-3p, miR-320b, miR-193b-3p, miR-22-3p, miR-28-5p	miR-125a-3p
Low-fat diet group				$n = 49$				miR-210-3p	miR-34b-5p, miR-107, miR-103a-3p, miR-1224-5p, miR-1246, miR-222-3p, miR-320b, miR-193b-3p, miR-22-3p, miR-125a-3p	miR-215-5p, miR-10a-5p, miR-21-5p, miR-29c-3p, miR-106a-5p, miR-20b-5p, miR-20a-5p, miR-151a-3p, miR-17-5p, miR-23a-3p, miR-28-5p
Reduced glycemic load diet	McCann et al. [49]	Diet reduced glycemic load by 15%	4 mo	$n = 34$	Single-group assignment intervention	Illumina Human v2 MiRNA Expression BeadChips, with some miRNA confirmed with qRT-PCR	Serum	miR-130a, miR-663b, miR-1179, miR-944, miR-338-3p, miR-1182, miR-623	Let-7b, miR-521, miR-1281, miR-205, miR-942, miR-10b, miR-1224-3p, miR-218-2, miR-550, miR-664, miR-424	
Mixed nuts	Ortega et al. [50]	30 g/d walnuts + almonds (15 g each)	8 wk	$n = 38$	Single-group assignment intervention	TaqMan Array human miRNA cards for discovery, validation by qRT-PCR	Plasma	miR-328, miR-330-3p, miR-221, and miR-125a-5p	miR-192, miR-486-5p, miR-19b, miR-106a, miR-130b, miR-18a, and miR-769-5p	
Brazil nuts	Reis et al. [51]	1 Brazil nut/d	2 mo	$n = 29$	Randomized clinical trial	miRNAs with significant expression levels in plasma from unpublished pilot data ($n = 25$)	Plasma		miR-454-3p, miR-584-5p	miR-193a-5p, miR-10b-5p, miR-7-5p, miR-205-5p, miR-200b-3p, miR-486-3p, miR-342-3p, miR-30a-5p, miR-200c-3p, miR-2110, miR-18a-5p, miR-375, miR-33b-5p, miR-143-3p, miR-188-5p, miR-150-5p, miR-548c-

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TABLE 2 (*continued*)

Food	Study ID	Amount	Duration	Population	Study design	Measurement method	Compartment	Downregulated miRs	Upregulated miRs	miRs not significantly changed
										5p, miR-29a-3p, miR-191-5p, miR-505-3p, miR-145-5p
				Subgroup: participants with MetS, $n = 10$				miR-548c-5p		miR-193a-5p, miR-10b-5p, miR-7-5p, miR-205-5p, miR-200b-3p, miR-486-3p, miR-342-3p, miR-30a-5p, miR-200c-3p, miR-2110, miR-18a-5p, miR-375, miR-33b-5p, miR-143-3p, miR-188-5p, miR-150-5p, miR-548c-5p, miR-29a-3p, miR-191-5p, miR-505-3p, miR-145-5p, miR-454-3p
Blueberries	Rodriguez-Mateos et al. [56]	11 g of freeze-dried wild blueberries, twice daily	28 d	$n = 40$ (miRNA measured in subgroup $n = 10$)	Randomized controlled trial	Microarray	PBMC	miR-126-5p, miR-30c-5p	miR-181c-3p	
Ketogenic diet	Ruiz-Herrero et al. [52]		6 mo	$n = 8$	Single-group assignment intervention	Gene chip array	PBMC	miR-3978, miR-6726-3p, miR-130a-3p, miR-4758, miR-6745, miR-532, miR-185-5p	miR-4538, miR-602, miR-330-5p, miR-4673	
Mixed nuts	Salas-Huetos et al. [53]	60 g mixed nuts/d (30 g walnuts, 15 g almonds, 15 g hazelnuts)	14 wk	$n = 49$	Randomized controlled clinical trial	Initial screening by low-density arrays for subcohort ($n = 10$) to create a custom array, which was used to analyze full sample	Semen	miR-34b-3p		miR-15b-5p, miR-29c-5p, miR-26a-1-3p, miR-27a-3p, miR-222-3p, miR-517a-3p, miR-517c-3p, miR-519a-3p, miR-535-5p, miR-650, miR-1180-3p, miR-1275
Korean diet	Shin et al. [54]		2 wk	$n = 5$	Randomized controlled trial	Array				
							Plasma	miR-126-3p, miR-18a-5p, miR-19b-3p, miR-107, miR-148a-3p, miR-26b-5p, miR-374a-5p, miR-26a		

(*continued on next page*)

TABLE 2 (*continued*)

Food	Study ID	Amount	Duration	Population	Study design	Measurement method	Compartment	Downregulated miRs	Upregulated miRs	miRs not significantly changed
							Saliva	miR-92-3p, miR-17-3p, miR-25b-3p, miR-122a-5p, miR-193a-5p		
Grapes	Tutino et al. [55]	5 g/kg of body weight per day	21 d	$n = 21$	Randomized controlled trial	qRT-PCR; panel	Serum	miR-181a-5p, miR-30e-5p, miR-30d-5p, miR-335-5p, miR-222-3p, miR-15a-5p, miR-421, miR-339-5p, miR-378a-3p, let-7f-5p, miR-29b-3p, miR-106b-3p, miR-324-5p, miR-1260a, miR-365a-3p, miR-155-5p, miR-335-3p, miR-200c-3p	miR-208a-3p, miR-33a-5p	

Abbreviations: MetS, metabolic syndrome; PBMC, peripheral blood mononuclear cell.

measures of metabolic function [34,37,43,44,50–52]. Reported significant associations between miRNA expression and relevant outcomes are summarized in Table 3. Only 2 miRNAs—miR-21-5p and miR-192-5p—had modulations that were significantly associated with gene expression or clinical measures across multiple studies.

Discussion

This review examined 25 human intervention trials that examined changes in miRNA profiles in response to diet challenges or a long-term intervention. Among the 7 studies that were conducted as an acute dietary challenge, only 2 studies examined comparable foods and did not identify any common miRNA modulated through the intervention. However, consistent with the effort to identify clinically viable miRNA biomarkers for disease, there is considerable heterogeneity between studies, even among those which used similar intervention foods. There are many different factors that may explain some of the observed variability between studies, including the composition of the test food or meal, intensity or duration of the intervention, population in which the intervention was tested, tissue from which miRNAs were isolated, the postprandial timing of sample collection, and method used to select miRNAs for analysis.

Several studies included tested similar foods within the same population, such as high-polyphenol and low-polyphenol extra virgin olive oil [33,34], nonalcoholic beer compared with typical beer [40], and commercially available and *trans*-fat–enriched shortening [41]. Each study determined that differences in nutrient composition resulted in differential miRNA expression within subjects. Future studies examining the impacts of a food or diet intervention on miRNAs should include a nutrient analysis of the food, including relevant phytochemicals. More research is also needed to establish dose-response thresholds in miRNA response to diet components and to parse whether miRNA responses are a function of typical metabolic processes or related to alternate excretion pathways.

Interventions providing nuts or olive oil are the most numerous found within this review, but there are differences in many of these studies in terms of the amount and type of nuts provided, as well as the duration of the intervention period. Investigators provided both a variety of different types of nuts, including pistachios [44], Brazil nuts [51], walnuts [43,47], or mixed nuts [50], as well as different amounts provided, ranging from a single nut per day [51] to $\leq$60 g/d [43,47,53]. Intervention lengths ranges from 8 wk [50,53] to a year [43,47]. Only Gil-Zamorano et al. [43] and Lopez et al. [36] investigated interventions that were directly comparable in intensity and duration, both providing walnuts totaling 15% of a subjects' estimated caloric needs for a 1-y timeframe. Beyond potential variability that may have been introduced as a result of the nutrient composition of the intervention food, it is possible that the amount of food comprising the intervention, as well as the length of the intervention period, may also underlie the heterogeneity observed among the studies summarized in this review.

Several studies compared miRNA response between different groups of participants exposed to the same intervention food. D'Amore et al. [33] compared the postprandial response to 50 mL extra virgin olive oil in healthy controls and individuals with

TABLE 3
Associations between modulations of dietary-responsive miRNAs and gene targets and clinical biomarkers.

miRNA	mRNA	Biochemical markers	Intervention	Reference
miR-9-5p	NEDD4 and FGF12[1]		Ketogenic diet	Ruiz-Herrero et al. [52]
miR-328a-3p		HDL, plasma	Low-polyphenol extra virgin olive oil (at 4-h time point)	Daimiel et al. [34]
miR-20a-5p		Total cholesterol[1]	Low-polyphenol extra virgin olive oil (at 6-h time point)	Daimiel et al. [34]
miR-26b-5p		Glucose	High-polyphenol extra virgin olive oil (at 2-h time point)	Daimiel et al. [34]
miR-21-5p	IL-6[1]	oxLDL	High-polyphenol extra virgin olive oil (at 2-h time point) Pistachio	Daimiel et al. [34] Hernández-Alonso et al. [44]
miR-17-5p		Total cholesterol[1] oxLDL	Medium-polyphenol extra virgin olive oil (at 2-h time point) Low-polyphenol extra virgin olive oil (at 4-h time point)	Daimiel et al. [34] Daimiel et al. [34]
miR-93-5p	FGF12[1]		Ketogenic diet	Ruiz-Herrero et al. [52]
miR-153-3p	BSN, CACNA1C[1] and DOC2A		Ketogenic diet	Ruiz-Herrero et al. [52]
miR-185-5p	CNTN2 and BSN		Ketogenic diet	Ruiz-Herrero et al. [52]
miR-192-5p		Triglycerides Glucose and HOMA-IR VLDL and triglycerides	Medium-polyphenol extra virgin olive oil (at 6-h time point) Pistachio Almonds and walnuts	Daimiel et al. [34] Hernández-Alonso et al. [44] Ortega et al. [50]
miR-323a-3p	CACNA1C		Ketogenic diet	Ruiz-Herrero et al. [52]
miR-30b-5p		Insulin[1]	Glucose beverage (2 h postconsumption)	Masotti et al. [37]
miR-194-5p		Total cholesterol[1]	Glucose beverage (2 h postconsumption)	Masotti et al. [37]
miR-95		HOMA-IR[1], plasma glucose (30-min postprandial)[1], 30 min insulin[1], 2 h insulin	Glucose beverage (2 h postconsumption)	Masotti et al. [37]
miR-424-5p		Plasma insulin (30-min postprandial)[1]	Glucose beverage (2 h postconsumption)	Masotti et al. [37]
miR-301a-3p		HOMA-IR[1], plasma glucose (30-min postprandial)[1]	Glucose beverage (2 h postconsumption)	Masotti et al. [37]
miR-320a-3p		LDL cholesterol	Beer	Daimiel et al. [40]
miR-135a-3p		LDL cholesterol	Ruminant derived *trans*-fatty acid–enriched diet	Desgagné et al. [41]
miR-375		Glucose, insulin, and HOMA-IR	Pistachio	Hernández-Alonso et al. [44]
miR-15a	IL-6[1]		Pistachio	Hernández-Alonso et al. [44]
miR-29b	SLC2A3		Pistachio	Hernández-Alonso et al. [44]
miR-126	IL-6		Pistachio	Hernández-Alonso et al. [44]
miR-330-3p		Total cholesterol, triglycerides	Almond and walnuts	Ortega et al. [50]
miR-221		CRP	Almonds and walnuts	Ortega et al. [50]
miR-125a-5p		VLDL, triglycerides	Almonds and walnuts	Ortega et al. [50]
miR-106a		Triglycerides	Almonds and walnuts	Ortega et al. [50]
miR-130b		VLDL, CRP	Almonds and walnuts	Ortega et al. [50]
miR-505-3p		Fasting glucose	Brazil nuts	Reis et al. [51]
miR-7-5p		Fasting glucose	Brazil nuts	Reis et al. [51]
miR-188-5p		Fasting insulin	Brazil nuts	Reis et al. [51]
miR-143-3p		HOMA-IR	Brazil nuts	Reis et al. [51]
miR-29a-3p		Total cholesterol, HDL	Brazil nuts	Reis et al. [51]
miR-30a-5p		Total cholesterol	Brazil nuts	Reis et al. [51]
miR-33b-5p		Total cholesterol	Brazil nuts	Reis et al. [51]
miR-150-5p		Total cholesterol	Brazil nuts	Reis et al. [51]
miR-193a-5p		Total cholesterol	Brazil nuts	Reis et al. [51]
miR-199b-5p	CDH2[1]		Ketogenic diet	Ruiz-Herrero et al. [52]
miR-454-3p		Total cholesterol[1]	Brazil nuts	Reis et al. [51]
miR-486-3p		Total cholesterol[1]	Brazil nuts	Reis et al. [51]
miR-875-5p	NEGR1		Ketogenic diet	Ruiz-Herrero et al. [52]

Abbreviation: CRP, C-reactive protein.
[1] Signifies inverse association.

newly diagnosed metabolic syndrome, concluding that miRNA expression in the postprandial period was blunted in individuals with metabolic syndrome [33]. This is congruent with the findings of Masotti et al. [37] who reported different patterns of miRNA response to a glucose beverage between insulin-resistant and insulin-sensitive individuals, as well as Ramzan et al. [39] who demonstrated that a high-carbohydrate meal also yielded differences in miRNA expression between insulin-resistant and insulin-sensitive individuals. Among studies that provided a long-term intervention, only Reis et al. [51] reported a subgroup analysis, showing that women with metabolic syndrome within their intervention group had differential miRNA expression patterns than the group as a whole. In each study, individuals with metabolic dysfunction displayed less responsiveness in their miRNA profiles than their metabolically healthy comparators. The observed differences highlighted in this review point to the need to better understand the mechanisms of action and downstream impacts of dietary interventions in individuals with metabolic risk—are such interventions bringing metabolic responses more in line with normal metabolism or are observed improvements in biochemical indicators occurring through compensatory pathways? Until the answers to these questions are better understood, it must be acknowledged that differences in metabolic health between subjects likely limits the ability to extrapolate miRNA responsiveness to diet across groups of different health status.

The observation that miRNA profiles may be less responsive in subjects with metabolic dysfunction has biological and clinical implications. Dysregulation of metabolic flexibility, or the ability to adapt to changes in metabolic demand, is associated with many conditions that negatively impact health span and lifespan [58]. First, it is important to recognize that dysregulation in cellular processes may be the underlying cause of disease development [59]. Single nucleotide polymorphisms impacting miRNA production and function have been observed [60–62]. Additionally, metabolic conditions may lead to alterations in cell signaling and transcriptional activation. Glucotoxicity in β cells leads to alterations in gene expression [63] and is likely a key underlying process of β-cell exhaustion in response to metabolic stress. Inflammation, which is a component of many chronic disease, inhibits several key cell processes including nutrient sensing [64] and may also relate to blunted responses in cell signaling or gene expression. Dietary components, from macronutrients to polyphenolic bioactives, modulate multiple levels of metabolic regulation, including miRNA evidence described in this review. Molecular mechanisms of metabolic flexibility need to be viewed within an integrated system, and as such, the use of multilevel omics provide the ability to interrogate responses to nutritional inputs. Future research to better unravel metabolic flexibility and miRNA responsiveness in a variety of health conditions should include a comparator group of healthy individuals.

An advantage of measuring miRNA is their presence in a variety of tissues. However, miRNA responsiveness may vary by tissue as demonstrated by the findings of Daimiel et al. [40], who measured both plasma and macrophage miRNAs and found that expression patterns did not conform across the 2 tissues. This raises the possibility that some of the inconsistencies in results between studies may be reflective of true differences in miRNA presence between different tissues. Although comparisons between plasma and serum miRNA collection were not made within the studies included in this review, previous research has examined differences in miRNA measured across serum or plasma [65,66], which revealed contradictory findings. Wang et al. [65] found concentrations of miRNA to be higher in serum, whereas McDonald et al. [66] observed higher concentrations in plasma. Despite the increased abundance found in serum, Wang et al. [65] concludes that plasma may be more suitable for analysis, given that the coagulation process may lead to the release of miRNAs from platelets and white blood cells. These results suggest that caution must be taken when selecting target miRNA from studies across different tissue types. The most nutritionally relevant tissue type for examining miRNA is an important consideration in study design and may vary based on the hypothesis being investigated in addition to practical considerations in obtaining samples. Therefore, more comparisons of miRNA across different tissues within individual subjects may be useful in elucidating the relevant expression across different sources of samples.

Additional heterogeneity arises from the methods used to identify candidate miRNAs for consideration. Studies within this review used a variety of methods to identify which miRNA to analyze: miRNA targets previously identified in the literature; miRNAs identified based on identification within a pilot study, or miRNAs from analysis of a subsample of the study undergoing analysis. Targeted analyses evaluate only a few specific miRNAs for hypothesis testing, whereas untargeted approaches allow exploration of dietary effects on multiple miRNA, potentially revealing undetermined responses and discovery of new relationships. Analysis of global miRNA changes also facilitates bioinformatic approaches such as use of online tools to predict associated cellular functions and network analyses and multilevel omic analyses to integrate different levels of nutrigenomic regulation. A more comprehensive understanding of the impact of diet on molecular mechanisms of action can lead to greater insights into the development of precision nutrition recommendations. The current landscape of dietary miRNA data is not yet adequate to describe their role in health and disease nor to characterize phenotypic variability in response. As a whole, this discussion lays out some of the challenges in examining the literature to identify candidate miRNAs, given that food composition, tissue analyzed, and length of intervention are potential sources of variability in using data generated in existing trials.

Beyond the issues of comparability raised in this review, other work has demonstrated that methodology is another domain that influences observed results. Time to extraction from plasma [67], RNA extraction method [67], profiling techniques used [7, 26], choice of housekeeping gene [68], and normalization method [68] have been demonstrated to introduce variability into the analysis of miRNA data with negative implications for reproducibility.

However, uncertainty also remains in several key areas regarding the source and regulation of miRNAs. First is the extent to which the microbiome may mediate the miRNA response to a dietary intervention. Several studies have demonstrated interplay between miRNA and the host microbiome in human subjects [69–71]. Other studies have examined the possibility that exogenous ingested miRNA may be absorbed and be present in measurable quantities within human tissue [72–75].

The extent to which such exogenous miRNA directly regulate metabolic pathways in humans is unclear and somewhat controversial [76–78]. The regulation of RNA transcription is complex and, in addition to miRNA, involves multiple regulatory mechanisms such as epigenetics [79]. More research is needed to elucidate the contribution of these factors to the interplay of miRNA and metabolic regulation. Another uncertainty relates to the threshold of dietary intake, which will induce miRNA expression. This review focused on miRNA that are modulated by diet and excluded studies examining dietary supplements or extracts because of an inability to conclusively determine whether those results would be generalizable to a diet intervention. Only 3 studies in this review measured miRNA at multiple time points in the postprandial period, but each demonstrated that significant modulation of miRNA is dependent on the timing of measurement [34,39,42]. The variable timing of miRNA induction raises the possibility that other studies only examining a single time point may miss significant changes in miRNA expression. More research is needed to better elucidate the timing of miRNA responses in the postprandial period. Uncertainty persists in the relationship between the miR changes in fasted baseline produced in response to a long-term diet intervention and the immediate postprandial response following a meal challenge and which may be more relevant for health. Relatedly, although studies have demonstrated differences in responses between metabolically healthy individuals and individuals with metabolic conditions [33,37,39,51], the extent to which diet intervention "normalizes" the miRNA signatures of individuals at metabolic risk is unknown. Further, when considering the significance of modulated miRNAs, many studies rely on literature searches or bioinformatics tools to identify relevant pathways or clinical outcomes impacted by miRNA. Within this review, few studies sought to analyze associations or mediations between miRNA expression and gene expression or biochemical measures. One study that did see modulation in miRNAs and reductions in LDL cholesterol in subjects following a year-long walnut supplementation and found that those 2 observations were unrelated [43]. Although such tools undoubtedly have a role, it is also important for researchers to examine relationships between miRNA and gene expression and clinical biomarkers within experimental data. Even when restricting searches to experimentally validated mRNA complements, competitive binding or threshold effects may result in predicted targets not being activated as expected in experimental data. MiRNA have multiple complements, and although in silica tools may identify possible pathways wherein miRNA may interact, it is necessary to identify whether modulations are in miRNA expression are associated with changes in relevant biomarkers or levels of gene expression to elucidate clinically relevant differences.

Within studies that linked miRNA modulations to gene expression or clinical biomarkers, only 2 miRNAs were observed to have significant associations across multiple studies. MiR-192-5p was modulated by long-term intake of pistachio [44] and mixed nuts [50], as well as by 1 variety of extra virgin olive oil in the postprandial period [34]. The modulations of miR-192-5p were associated with triglyceride concentrations in the postprandial period [34] and with triglycerides and concentrations of VLDL cholesterol [50], as well as with glucose and HOMA-IR [44] following chronic intake. A previous review has noted the roles of miR-192-5p in multiple physiologic processes relevant to chronic disease, including coordination of energy metabolism and regulation of oxidative stress [80]. MiR-21-5p was modulated by 1 variety of olive oil in the postprandial period and associated with fluctuations in oxidized LDL cholesterol [34] and with sustained intake of pistachios, where it was associated with IL-6 expression [44]. Previous research has concluded that miR-21-5p reduces inflammation-induced injuries [81] and oxidative stress and regulates lipid content and lipid peroxidation in cell models [82]. Both miR-192-5p and miR-21-5p have regulatory roles in metabolically important physiologic processes and are responsive to dietary interventions.

There are multiple sources of heterogeneity observed among the included studies that make direct comparison between studies difficult and limits the ability to develop an index of miRNAs that are responsive to specific dietary interventions. This review also highlights potential pitfalls that should be avoided when using a literature review to select candidate miRNAs to examine in a study. Ideally, miRNA candidates would be selected based on studies that used a similar dietary intervention with a similar intensity in a similar population to measure miRNA in corresponding tissues. The use of miRNA

During study design:

1. Identify relevant biological compartments for microRNA changes and consider inclusion of more than one compartment
2. When analyzing microRNA profiles in subjects with overweight, obesity or in other metabolic disease states, include an arm of healthy individuals as a positive control
3. Weigh relative advantages and costs of global untargeted microRNA analysis versus hypothesis driven targeted microRNA
4. Dietary intervention aspects need to be well defined (food composition, dose, duration of feeding)
5. Plan for timing and number of sample collections for microRNA assessment (post-prandial period vs fasted) and use of baseline or control sample vs intervention
6. Consider statistical power

In analysis and reporting:

1. Provide comprehensive reporting of changes in microRNA profiles, including change from baseline
2. Where possible, analyze associations between microRNA and target genes, cellular pathways and/or relevant clinical outcomes

FIGURE 2. Recommendations to improve future microRNA research.

sequencing presents its own difficulties. Given the number of miRNAs that are detectable in humans, the relatively modest range of variability in expression, and the cost of sequencing limiting the number of samples analyzed, it is likely that type II errors occur with some frequency in the context of stringent *P* values used to correct for testing across multiple comparisons. As the cost of miRNA sequencing and untargeted global miRNA analyses becomes more affordable, more comprehensive miRNA data may become available. To limit these pitfalls and maximize the scientific knowledge gained, Figure 2 provides recommendations for best practices for future research.

This review highlights challenges in identifying miRNAs that are consistently responsive to diet as well as highlighting the importance of thorough reporting of methodology for the purpose of replication and the establishment of reliable biomarkers. Although miRNAs have potential to be useful biomarkers of intake or measures of effectiveness, more research is needed to establish food items or diet patterns that consistently modulate miRNAs within the same tissue in similar populations as well as in metabolically compromised populations. In identifying miRNAs that are relevant to a study question, researchers must not only consider the methods they will use to select miRNAs for analysis but also consider the most appropriate for the tissue to be examined and the study population under investigation.

Authors contributions

The authors' responsibilities were as follows – GMC, FMS: planned the research; GMC: conducted the literature search and data extraction with oversight from FMS; GMC: wrote the first draft of the manuscript with review and final edits by FMS; and both authors have read and approved the final version of the manuscript.

Conflict of interest

The authors report no conflicts of interest.

Funding

This study was funded by USDA CA-D-NTR-6316-H.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.advnut.2024.100241.

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