Fatty acids, epigenetic mechanisms and chronic diseases: a systematic review

K. González-Becerra¹, O. Ramos-Lopez²,3, E. Barrón-Cabrera¹, J. I. Riezu-Boj²,4, F. I. Milagro²,4,5, E. Martínez-López¹,6* and J. A. Martínez²,4,5,7

Abstract

Background: Chronic illnesses like obesity, type 2 diabetes (T2D) and cardiovascular diseases, are worldwide major causes of morbidity and mortality. These pathological conditions involve interactions between environmental, genetic, and epigenetic factors. Recent advances in nutriepigenomics are contributing to clarify the role of some nutritional factors, including dietary fatty acids in gene expression regulation. This systematic review assesses currently available information concerning the role of the different fatty acids on epigenetic mechanisms that affect the development of chronic diseases or induce protective effects on metabolic alterations.

Methods: A targeted search was conducted in the PubMed/Medline databases using the keywords “fatty acids and epigenetic”. The data were analyzed according to the PRISMA-P guidelines.

Results: Consumption fatty acids like n-3 PUFA: EPA and DHA, and MUFA: oleic and palmitoleic acid was associated with an improvement of metabolic alterations. On the other hand, fatty acids that have been associated with the presence or development of obesity, T2D, pro-inflammatory profile, atherosclerosis and IR were n-6 PUFA, saturated fatty acids (stearic and palmitic), and trans fatty acids (elaidic), have been also linked with epigenetic changes.

Conclusions: Fatty acids can regulate gene expression by modifying epigenetic mechanisms and consequently result in positive or negative impacts on metabolic outcomes.

Keywords: DNA methylation, Obesity, Epigenetic, N-3 fatty acids, Butyrate, Insulin resistance, Metabolic alterations

Introduction

Nutriepigenomics is an emerging scientific area that studies the relationships between nutrition and the epigenetic. In recent years, several studies have focused on the description of different dietary components that can contribute to modify epigenetic processes and consequently, modulate gene expression and metabolic responses. These epigenetic modifications may be associated with the susceptibility to develop non-communicable chronic diseases (NCCD), such as obesity, lipid disorders, insulin resistance (IR), cardiovascular diseases (CVD), type 2 diabetes (T2D), and some types of cancer [1].

Epigenetics is defined as the study of heritable changes in DNA and histones without concomitant alterations in the nucleotide sequence [2, 3]. These modifications can affect gene expression and the phenotype in response to environmental stimuli [2, 4]. The main epigenetic mechanisms include DNA methylation, histone modifications, and non-coding RNAs such as microRNAs (miRNAs), among others [5].

Epigenetic changes are plastic genomic processes that are influenced by endogenous and exogenous factors, and these modifications could be potentially propagated from one generation to the next [6]. Thus, it might be possible to reprogram epigenetic modifications that are associated with an increased disease risk through nutritional or lifestyle changes. In this context, a number of nutritional factors involved in epigenetic modifications have been reported, including methyl donors, amino acids, vitamins and minerals, polyphenols, and other phytochemicals, and fatty acids (FA) [7].

* Correspondence: erikamtz27@yahoo.com.mx
¹Institute of Traslational Nutrigenetics and Nutrigenomics, Health Sciences University Center, University of Guadalajara, Guadalajara, Jalisco, Mexico
²Department of Molecular Biology in Medicine, Health Sciences University Center, University of Guadalajara, Sierra Mojada 950, 44340 Guadalajara, Jalisco, Mexico
Full list of author information is available at the end of the article

© The Author(s). 2019 Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.
Regarding FA, some studies have demonstrated the effects of n-3 and n-6 polyunsaturated acids (PUFA) on DNA methylation, including specific responses of eicosapentaenoic acid (EPA), docosahexaenoic acid, (DHA), [8] and arachidonic acid (AA) [9]. However, the mechanisms underlying the effects of different types of FA on epigenetic landmarks, are still not completely known. The most extensively studied FA is butyric acid, a short-chain fatty acid produced in the anaerobic colonic fermentation that can act as an inhibitor of histone deacetylases (HDAC) and has been associated with histone deacetylation [10].

In the last years, the profile of FA intake has dramatically changed from diets with high monounsaturated (MUFA) and polyunsaturated fatty acid (PUFA) content, to a Westernized dietary pattern characterized by a high content in saturated fatty acids (SFA) and trans fatty acids (TFA) and poor in n-3 PUFA [11]. This nutritional transition is associated with the rising prevalence of NCCD, which have been recently associated with aberrant epigenetic changes and are now major cause of death worldwide [12].

It is well known that obesity, CVD, IR, T2D, cancer and other NCCD involving multifactorial and genetic interactions [13]. In this context, the study of pathophysiological, genetic and epigenetic processes could help to design new integrative strategies for the prevention and treatment of these conditions [14]. Therefore, the objective of the present review is to describe the role of dietary FA in the modulation of epigenetic landmarks in relation to the development of NCCD, and their ability to reverse the epigenetic landscape.

Methods
This systematic review has been developed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P) guidelines [15]. Literature search was performed using PubMed/ Medline databases and just English papers were considered. According to PRISMA-P procedures, the key words “FA and epigenetics” (including SFA, MUFA and PUFA) and the period of publication “2010–2017” were used as filters. At this stage, a total of 620 articles were identified. A flow diagram showing the selection process is depicted (Fig. 1).

Eligibility criteria
First inclusion criteria were articles analyzing the effects of FA on epigenetics mechanisms. In this section, 438 articles were removed because do not include interactions between epigenetics and FA. In a second step, articles not focused on the effect of metabolic alterations through epigenetic mechanisms in response to FA intake or supplementation were also excluded (n = 63).

Subsequently, articles showing inconsistent results, did not fulfill quality criteria or using valproic acid (considered a drug), were eliminated (n = 71). Lastly, articles that did not specify the type of FA intervention were also excluded (n = 17). The final analysis included 31 articles; however, seven additional articles obtained from reference lists were also incorporated in this review (Fig. 1).

Data extraction, data elements
Relevant information from all 38 papers was analyzed using a standardized data extraction template where two co-authors were specifically involved. Data about the type of FA used for treatment, the study model, the underlying epigenetic mechanism as well as the main results related to metabolic outcomes, were reported, more details are shown in Additional file 1.

Quality assessment
Study quality was evaluated according to Jadad scale for clinical trials and it was considering randomization, blinding and withdrawals and dropouts. The selection criteria of the articles had to meet at least 3 criteria to be included. In this review, two authors evaluated the quality of papers and to resolve some disagreements all the author make a consensus procedure to define if the article full fill the criteria for be included in the systematic review.

Data analysis
The acquired information was organized based on the type of FA and experimental model analyzed. The data were sorted according to fatty acids subtypes; firstly, unsaturated fatty acids were described (PUFA: n-3, n-6 and MUFA: oleic) (Table 1). Then, saturated and trans fatty acids were sorted in a second category (Table 2). Butyrate was independently analyzed from other FA because it is a product of anaerobic colon fermentation (Table 3). Finally, articles including more than one type of FA were grouped together (Table 4).

Results
Unsaturated fatty acids

Human studies

N-3 PUFA In the last years, many investigations have focused on the effects of n-3 PUFA in the prevention and treatment of different metabolic alterations. Thus, Tremblay and collaborators investigated the effect of n-3 PUFA supplementation in overweight and obese subjects on epigenetic modifications [16]. They found that after a 6-month supplementation 308 CpG sites (231 genes) had different methylation pattern, of which 286 CpG sites were hypermethylated representing 93% of the
changes after the supplementation and 22 were hypo-methylated (just 7%), using ingenuity pathway analysis system it was reported these epigenetic changes were related to pathways associated with inflammatory and immune responses, lipid metabolism, T2D, and cardiovascular signaling [16].

Another study in obese subjects under an energy-restricted diet supplemented with n-3 PUFA-rich fish oil conducted by do Amaral and collaborators found that the methylation levels of PDK4 (Pyruvate Dehydrogenase Kinase 4) CpG sites −222 and −50 and FADS1 CpG −25 −22 −20 were increased in the group supplemented with fish oil. Furthermore, n-3 PUFA supplementation was accompanied by improved weight loss, which was associated with changes in the methylation pattern of one specific CpG site in CD36, a gene that encodes a membrane glycoprotein that plays a relevant role in lipid metabolism and may be implicated in obesity-related complications like glucose intolerance and T2D [19].

On the other hand, Aslibekyan et al. investigated the effect of n-3 PUFA intake in a population of Yupik natives, considering that this population had a higher intake of fish-derived n-3 PUFA [17]. For this study, the population was categorized in higher and lower deciles of a nitrogen stable isotope ratio (δ15N), which is a biomarker of n-3 PUFA intake and thus, n-3 PUFA plasma content. The authors found 27 differentially methylated CpG sites at biologically relevant regions that reached epigenome-wide significance and highlighted that DNA methylation may reduce FAS (apoptosis antigen 1) expression and, consequently, regulate lipid metabolism through the apoptotic pathway. Also, the methylation pattern of AHRR (Aryl-Hydrocarbon Receptor Repressor), a gene that is involved in oxidative stress, was affected by the n-3 PUFA intake, which was accompanied by a positive impact on glucose tolerance and insulin sensitivity [17].

In addition, Arpón et al. studied the effect of Mediterranean Diet (MedDiet) complemented with extra virgin olive oil (EVOO) or nuts on DNA methylation within PREDIMED (PREvención con Dieta MEDiterránea) study. They compared the two diets MedDiet + EVOO and MedDiet + nuts with a low-fat control group during five-year follow-up and found that MedDiet + nuts...
| FA | Dose | Study model | Epigenetic mechanisms | Epigenetic signature | Metabolic outcomes | Reference |
|---|---|---|---|---|---|---|
| **HUMAN** | | | | | | |
| PUFA n-3 supplementation | 3 g n-3 6-weeks | 36 overweight and obese subjects | DNA methylation | 286 CpG (99%) 22 CpG (7%) | Improvement of inflammatory and immune responses, lipid metabolism, cardiovascular signaling, and diabetes pathways, reduction of plasma triglyceride and glucose levels, improved total cholesterol/HDL-cholesterol ratio. | [16] |
| n-3 intake | 93 subjects were in the lowest 3 deciles of PUFA intake and 92 were in the top 3 deciles | 185 Yupik/ Alaskan native subjects | DNA methylation | 21 CpG 6 CpG | Improvement of lipid metabolism, insulin sensitivity, glucose tolerance and oxidative stress. | [17] |
| n-3 supplementation | MedDiet+ OOEV or MedDiet+ nuts | 12 subjects of each study group | DNA methylation | With MedDiet + nuts CPT1B/CHKB- CPT1B With MedDiet + OOEV GNASAS GNAS | Benefits in health associated with changes in genes related to intermediate metabolism, diabetes, and anti-inflammatory state. | [18] |
| n-3 supplementation | 6 capsules/ per day n-3 8-weeks | 7 overweight and obese women 5 control group | DNA methylation | CPT1B, PDK4 and FADS1, PDK4 (− 229−227) CD36 FFAR3 CpG (− 18, + 33, and + 77) FFAR3 CpG (− 53 and − 202) | Lipid metabolism, improvement of glucose tolerance and diabetes. | [19] |
| n-6 intake | 40 normal-weight women | DNA methylation | TNF CpG13 and CpG19 (+ 207 + 317pb) | Associated with truncal fat, lipid alterations, TNF-α pathway and inflammation process. | [20] |
| **Transgenerational** | | | | | | |
| DHA supplementation | 400 mg of DHA/day gestation week 18−22 to parturition. | 131 pregnant women | DNA methylation | IGF2 P3 IGF2 DMR H19 DMR | Favors expression of genes involved in growth and development. Decreases the risk to develop obesity (BMI) in infants. | [21] |
| DHA supplementation | 800 mg DHA/day 20 weeks gestation to parturition. | 517 pregnant women | DNA methylation | 21 DMR | Favors appetite regulation and immune response in infants. | [22] |
| **ANIMAL MODELS** | | | | | | |
| n-3 supplementation | n-3 1 g/Kg body weight every day for 12 weeks | 30 Rats | DNA methylation | % 5mC | Anti-colorectal cancer effect. | [23] |
| n-3 supplementation | 34.9% weight as fat, 60% kcal was fish oil for 14 weeks | 12 Rats | DNA methylation, Histone methylation and acetylation | NE on methylation Histone H3 | Ameliorates leptin resistance, decreases accumulation of adipose tissue, regulating food intake and energy expenditure. | [24] |
| n-3 supplementation | EPA and DHA 0.5% Gromega, pregnant pigs (150 days) and their offspring (lactation 21 days and nursery 56 days) | 5 Pigs | DNA methylation and miRNAs | Chromosome 4 DMR Intragenic region chromosome 4 and 12 | Improvement of immune response, inflammation, glucose uptake, apoptosis, endoplasmic reticulum stress, insulin resistance, lipid metabolism and oxidative stress. | [25] |
Table 1 Effects of unsaturated fatty acids on metabolic outcomes through epigenetic mechanisms (Continued)

| FA       | Dose                  | Study model                                      | Epigenetic mechanisms | Epigenetic signature               | Metabolic outcomes                                                                 | Reference |
|----------|-----------------------|-------------------------------------------------|-----------------------|------------------------------------|-------------------------------------------------------------------------------------|-----------|
| **IN VITRO MODELS** |                       |                                                  |                       |                                    |                                                                                     |           |
| n-6 AA   | 1 µM, 10 µM and 100 µM| Human THP-1 monocytes                           | DNA methylation       | Dose-dependent DNA methylation     | + Associated with atherosclerosis, diabetes, inflammatory profile, obesity and cancer | [26]      |
|          |                       |                                                  |                       | A 10.5% increase in 5mC content at 100 mM compared to 1 µM dose |                                                                                     |           |
| AA       | 3 µM                  | Human umbilical vein endothelial cells (HUVECs) and endothelial progenitors (EPCs) | DNA methylation       | Promoter region of genes KDR and Notch4 | – Associated with changes in expression of genes implicated in carcinogenesis and angiogenesis. | [9]       |
| **MUFA** |                       |                                                  |                       |                                    |                                                                                     |           |
| Oleic acid | 1 µM, 10 µM and 100 µM| In vitro human THP-1 monocytes                  | DNA methylation       | Global hypomethylation at 100 µM compared to the 1 µM dose | Anti-inflammatory effects.                                                          | [26]      |
| Oleic acid | 1–200 µM range       | 20 pregnancy mice and THP-1 cells                | DNA methylation       | 1–50 µM but in 5 µM weaker response peaking | Improvement of proinflammatory profile and adipogenesis                           | [27]      |

**FA**: Fatty acids, **PUFA**: Polyunsaturated fatty acids, **n-3**: Linolenic acid, **DHA**: Docosahexaenoic acid, **EPA**: Eicosapentaenoic acid, **AA**: Arachidonic acid, **MUFA**: Monounsaturated fatty acid, **TNF**: Tumor necrosis factor

**DMR**: Differentially methylated regions

**NE**: No-effect on DNA methylation

+ hypermethylated

- hypomethylated

++ Hyperacetylation
| Table 2 Effects of saturated and trans FA on metabolic outcomes through epigenetic mechanisms |
|---------------------------------------------|-----------------|---------------------------------------------|---------------------------------------------|---------------------------------------------|
| FA                                          | Dose            | Study model                                  | Epigenetic mechanism                         | Epigenetic signature                       |
|---------------------------------------------|-----------------|---------------------------------------------|---------------------------------------------|---------------------------------------------|
| HUMANS                                      |                 |                                             |                                             |                                             |
| Trans FA                                    |                 |                                             |                                             |                                             |
| Industrial TFA                              | 10.2 g/2500 kcal, 3.7% of daily energy | 9 healthy men                               | miRNAs                                      | 5 miRNAs in purified HDLs                  |
|                                             |                 |                                             |                                             | 13 HDL-carried miRNAs to the plasmatic miRNA pool |
|                                             |                 |                                             |                                             | ↑ Related to carcinogenesis, FA biosynthesis and alteration in FA metabolism | [28] |
| ANIMAL MODELS                                |                 |                                             |                                             |                                             |
| Transgenerational                           |                 |                                             |                                             |                                             |
| Elaidic acid                                |                 |                                             | DNA methylation                             | 1–50 μM 5.2% increase in 5mC up to 200 μM  |
|                                             |                 |                                             |                                             | + Favors the accumulation of adipose tissue, obesity, and hepatic steatosis | [27] |
| IN VITRO MODELS                              |                 |                                             |                                             |                                             |
| SFA                                         |                 |                                             |                                             |                                             |
| Palmitic acid                               | 750 μM palmitate| In vitro urinary human podocyte cell line and male Sprague-Dawley rats | Histone methylation and acetylation         | H3K27me3 and H3K36me2 on promoter region of FOXO1 |
|                                             |                 |                                             |                                             | ↓ Related to insulin resistance and decrease of glucose tolerance, favors gluconeogenesis | [29] |
| Palmitic acid                               | 1 mM palmitate  | In vitro human pancreatic islets            | DNA methylation                             | 4561 sites increased DNA methylation (2753 unique genes and 1429 intergenic sites) |
|                                             |                 |                                             |                                             | 129 sites decreased DNA methylation (99 unique genes, and 30 intergenic sites) |
|                                             |                 |                                             |                                             | + Associated with insulin resistance, lipotoxicity, T2D, glycolysis, gluconeogenesis, dysregulation in FA metabolism related to obesity | [30] |
| Palmitate                                   | 0.4 mmol/l palmitate | Pancreatic beta cell line and diabetic rats | DNA methylation                             | No changes in DNA methylation              |
|                                             |                 |                                             |                                             | No change in DNA methylation of \( \text{Ins1} \) promoter under normal or high glucose conditions | [31] |
| Oleo-palmitate                              | 250 μM olate-palmitate ratio 1:1 | Human skeletal muscle cells from severely obese women | DNA methylation                             | PPARδ (sites - 71 and 61 bp)               |
|                                             |                 |                                             |                                             | + Changes in methylation of \( \text{PPARD} \), increases FA uptake and oxidation, favors abnormal accumulation of lipids in oxidative tissues | [32] |
| Stearate and palmitate                      | 3.75 mM, Stearate-palmitate ratio 4:1 | Raw264.7 macrophage cell line               | DNA methylation                             | PPARg promoter                             |
|                                             |                 |                                             |                                             | + Promote metabolic disorders and inflammation, increase insulin resistance and obesity | [33] |

FA Fatty acids, TFA Trans fatty acids, THP-1 Human monocytic cell line, HDL High density lipoprotein
↑ Increase
↓ Decrease
+ hypermethylated
- hypomethylated
| SCFA                     | Dose                        | Study model                                      | Epigenetic mechanism               | Epigenetic signature                | Metabolic outcomes                                                                                     | Reference |
|-------------------------|-----------------------------|--------------------------------------------------|-------------------------------------|-------------------------------------|--------------------------------------------------------------------------------------------------------|-----------|
| Sodium butyrate         | 500 mg/kg/day               | Juvenile diabetic rats                            | Histone acetylation                | Decreased HDAC activity             | ↓ Decreases plasma glucose, HbA1c, and beta-cell apoptosis. Favors insulin sensitivity and glucose homeostasis | [34]      |
| Sodium butyrate         | 5% NaB (wt/wt)              | C57BL/6J mice                                    | Histone modifications              | Modify chromatin structure and repositioning of the −1 nucleosome | Modifies gene expression to have anti-obesity and anti-diabetic effects, improves insulin sensitivity. | [35]      |
| Butyrate                | 1.5 g/kg feed for 21 days   | 308 chickens                                     | Histone acetylation                | Hepatic histone H2A at lysine 5     | ++ Improves body weight, regulation of cell function.                                                  | [36]      |
| Sodium butyrate         | 1% butyrate sodium          | Offspring of Sprague Dawley rats                 | Histone acetylation                | Increase of acH3K27 in Pparg gene   | ↑ Maternal butyrate supplementation during gestation and lactation leads to insulin resistance and accumulation of ectopic lipids, risk Aod development T2D. | [37]      |
|                        |                             |                                                  |                                     | Increase of acH3K9 and acH3K27 on the promoters of C/EBPβ and FAS genes |                                                                                                        |           |
| Butyric acid            | 3 mM of butyrate            | Chinese hamster ovary cells                      | DNA methylation                    | Around 8113 and 8616 DMR            | - Cell cycle, apoptosis, signaling, protein transport and RNA processing.                               | [38]      |
|                        | 10 mM of butyrate           | Bovine cells                                     | Histone modification               | Around 5589 and 6524 DMR           | + Activation of genes related to growth, proliferation, energy metabolism, cell growth and division, cell cycle, apoptosis and differentiation. | [39]      |
| Sodium butyrate         | 10 mM of NaB               | HeLa 57A and HEK293 cells                        | Histone acetylation                | Histone H3 and H4                  | ++ NF-κB activation in response to TNF-α, increased proinflammatory response and immune responses, cell proliferation and differentiation. | [40]      |
| Sodium butyrate         | 0.5 mM, 1 mM, 2.5 mM and 5  | Two human prostate cancer cell lines              | Histone acetylation                | Lysine 8 and Lysine 12 of Histone H4| ++ Suppression of tumor growth in prostate cancer.                                                      | [41]      |
| Sodium butyrate         | Mn of NaB                   | AGS, KatoII, MKN28, MKN45, MKN74, NCI-N87, SNU-1, | Histone acetylation                | Demethylation and histone modification at the promoter of SFRP1/2 | − Demise proliferation of human gastric cancer cells (protective effect against cancer).              | [42]      |
| Sodium butyrate         | 2 μM of NaB                 | SNU-16, and NCI-N87                             | Histone acetylation                | H3Lys9, H3Lys9, H3Lys12 di-methylation| ++ Atheroprotective and antiatherogenic effect, altering G1-specific cell cycle proteins through its chromatin remodeling activity to arrest VSMCs proliferation. | [43]      |
| Sodium butyrate         | 5 mM of butyrate            | Rat vascular smooth muscle cells (VSMCs) isolated from thoracic aortas | modification of histone H3 by acetylation, phosphorylation and methylation | HL3Ly9, HL3Ly9, HL3Ly9 di-methylation |                                                                                                        |           |
| Combination of butyrate + DHA | 5 mM NaB + 50 μM of DHA     | In vitro human colon cancer cells                | DNA methylation histone acetylation| Reduced methylation of proapoptotic (BCL2, BCL11, CIDEB, DAPK1, LTB, and TNFRSF5) genes | − Induction of proapoptotic genes related to cancer.                                                   | [44]      |

SCFA: Short chain fatty acids, FA: Fatty acids, HDAC: Histone deacetylases, HbA1c: Glycated hemoglobin, T2D: Type 2 Diabetes, NFκB: Nuclear factor kappa B

++ hyperacetylation
↓ Decrease
+ hypermethylated
- hypomethylated

González-Becerra et al. Lipids in Health and Disease (2019) 18:178
## Table 4: Comparison of different types of FA influences on epigenetic mechanisms

| FA                        | Dose                                                                 | Study model                                                                 | Epigenetic mechanism          | Epigenetic signature                                                                 | Metabolic effect                                                                                                                                                                                                 | Reference |
|---------------------------|----------------------------------------------------------------------|-----------------------------------------------------------------------------|--------------------------------|---------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| **HUMANS**                |                                                                      |                                                                             |                                |                                                                                                                                                                                                 |                                                                                                                                                                                                             |           |
| Excessive SFA             | Palmitic acid intake (+ 750 kcal/d)                                  | High-caloric muffins that contained refined palm oil or refined sunflower oil for 7 wk | DNA methylation                | PUFA n-6 + SFA modify 4933 CpG sites (4795 hypermethylated and 138 hypomethylated) Expression changes in 1117 transcripts (776 up, 241 down regulated) 26 pathways up-regulated 3 pathways down-regulated | SFA and PUFA n-6 diets modify methylation patterns of genes related to adipose tissue accumulation, obesity, pathways related to cancer, cell cycle, FA uptake, transport, and lipid metabolism                                      | [45]      |
| Excessive PUFA n-6 intake | (+ 750 kcal/d)                                                      |                                                                             |                                |                                                                                                                                                                                                 |                                                                                                                                                                                                             |           |
|                           |                                                                    |                                                                             |                                |                                                                                                                                                                                                 |                                                                                                                                                                                                             |           |
| Lower PUFA/SFA ratio and  | A higher unsaturated: saturated ratio considered ‘healthier’, and a lower unsaturated: saturated ratio considered ‘unhealthier’ |                                                                             |                                |                                                                                                                                                                                                 | A lower PUFA/SFA ratio was associated with adipogenesis and mechanisms regulated by PPARα, regulation of energy intake, inflammatory processes and obesity; a lower MUFA+PUFA vs SFA ratio was related to pathways linked to NF-κB (inflammation process) | [46]      |
| lower PUFA+MUFA/SFA ratio |                                                                    |                                                                             |                                |                                                                                                                                                                                                 |                                                                                                                                                                                                             |           |
| Fish oil (FO) and Sunflower oil (SO) | 3.8 g/day of fish oil (FO) or sunflower oil (SO) for 9 months |                                                                             |                                |                                                                                                                                                                                                 | FO supplementation was associated with higher amounts of n-3, EPA, and DHA and lower levels of n-6 and AA in RBC, improved arterial pressure and a tendency to lower levels of IL-6                                                                                           | [47]      |
| PUFA (EPA)                | MUFA (palmitoleic acid) SFA (palmitic acid)                           |                                                                             |                                |                                                                                                                                                                                                 | SFA were associated with obesity (BMI), lipid metabolism, and glucose disbalance, whereas PUFA (EPA) were related to normal weight, and MUFA with insulin sensitivity                                                        | [48]      |
| ANIMAL AND IN VITRO MODELS |                                                                      |                                                                             |                                |                                                                                                                                                                                                 |                                                                                                                                                                                                             |           |
| PUFA Linoleic acid        | (olive oil)                                                          |                                                                             | DNA methylation                | Lower methylation levels of Vegfb promoter in rats that were fed with coconut oil vs olive and sunflower oil | SFA was related to higher levels of Vegfb, involved in insulin resistance, lipid distribution and lipid metabolism in type 2 diabetes vs MUFA and PUFA                                                                 | [50]      |
|                           | MUFA Oleic acid (sunflower oil)                                      |                                                                             |                                |                                                                                                                                                                                                 |                                                                                                                                                                                                             |           |
|                           | SFA Palmitic acid (coconut oil)                                      |                                                                             |                                |                                                                                                                                                                                                 |                                                                                                                                                                                                             |           |
| PUFA Linoleic acid        | n-6 (sunflower oil)                                                  |                                                                             | DNA methylation                | Hypomethylation in Tnf promoter in SFA vs PUFA and MUFA | SFA was related with inflammation (TNF-α elevation), adiposity and obesity, whereas PUFA and MUFA did not induce changes in TNF-α                                                                               | [49]      |
|                           | (olive oil)                                                          |                                                                             |                                |                                                                                                                                                                                                 |                                                                                                                                                                                                             |           |
|                           | SFA Palmitic acid (coconut oil)                                      |                                                                             |                                |                                                                                                                                                                                                 |                                                                                                                                                                                                             |           |
| Fish oil (FO)             | Fish oil (FO) n-3 PUFA                                              |                                                                             |                                |                                                                                                                                                                                                 | SFA was related with fat accumulation in liver, dysregulation of vascular tone vs n-3 PUFA. Epigenetic regulation of Fads2 may contribute to the regulation of PUFA synthesis                                                                            | [51]      |
|                           | (n-3 PUFA)                                                          |                                                                             |                                |                                                                                                                                                                                                 |                                                                                                                                                                                                             |           |

González-Becerra et al. Lipids in Health and Disease (2019) 18:178

Page 8 of 18
| FA              | Dose                                           | Study model                        | Epigenetic mechanism | Epigenetic signature                                                                 | Metabolic effect                                                                                       | Reference |
|----------------|-----------------------------------------------|------------------------------------|----------------------|--------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|-----------|
| Olive oil (OO) | 80–90 mg/day from conception to day 12 of gestation | Pregnant rats and their offspring | miRNAs               | Pregnant rats fed SO and FO diets showed a significant lower expression of miR-449c-5p, miR-134-5p, miR-188, miR-32, miR130a, miR-144-3p, miR-431, miR-142-5p, miR-33, miR-340-5p, miR-301a, miR-30a, miR-106b, and miR-136-5p, as compared with OO, LO, and PO diets in liver and adipose tissue. | Adipose tissue mass was lower in the FO group compared with other groups, except with LO group. Decreased expression of miRNAs related to insulin and glucose metabolism compared with PO and OO No differences in miRNA expression between FO and LO | [52]      |
| Fish oil (FO)  |                                               |                                    |                      |                                                                                      |                                                                                                     |           |
| Linseed oil (LO)|                                               |                                    |                      |                                                                                      |                                                                                                     |           |
| Palm oil (PO)  |                                               |                                    |                      |                                                                                      |                                                                                                     |           |
favors a hypermethylation of cg01081346 in CPT1B/CHKB-CPT1B genes (Carnitine palmitoyltransferase 1B/Choline kinase-like, Carnitine palmitoyltransferase 1B) and MedDiet + EVOO induce hypomethylation in cg17071192 in GNAS/GNASAS genes GNAS/GNASAS (Guanine Nucleotide Binding Protein, G Protein), however both diets were associated with intermediate metabolism as well as improve genes involved in diabetes and inflammation pathways [18].

**Transgenerational studies** Several investigations have reported the effects of n-3 PUFA supplementation (DHA) in the maternal diet on epigenetic changes in the offspring [21, 22]. Thus, Lee and collaborators demonstrated that DHA supplementation in pregnant women demonstrated higher methylation levels of IGF2/H19 in their offspring versus control group, a gene that is crucial for the correct fetal growth, development, and metabolism of the infants and this effect was dependent on the maternal BMI before pregnancy. Furthermore, IGF2/H19 DMR methylation changes have also been associated with paternal obesity or the risk of overweight, diabetes or some types of cancer in early life [21].

On the other hand, Van Dijk et al. found in a large randomized controlled trial that DHA supplementation during pregnancy did not significantly affect the global methylation pattern, although they identified 21 differentially methylated regions (DMRs) at birth (this difference was sex-dependent) in genes implicated in diverse functions including lipid exchange between membranes (EVT3), appetite regulation (CCK), and immune function (RAETIL and LTB) among others [22].

**N-6 PUFA** A trial by Hermsdorff et al. showed that AA intake (an n-6 PUFA) was related with higher values of truncal fat, BMI, and waist circumference in women [20]. Moreover, they found a negative correlation between the methylation of TNF and the levels of this proinflammatory cytokine. In particular, the hypermethylation of two CpGs of this gene (+ 207 and + 317pb) was associated with the under expression of the gene, and the result of a linear regression model suggest this methylation levels of TNFa promoter were associated with n-6 PUFA intake, suggesting a complex nutriepigenomic interaction that could exacerbate the proinflammatory state [20].

**Animal models**

**N-3 PUFA** In a study to explore whether n-3 PUFA affects DNA methylation levels in colorectal cancer, rats were fed with n-3 PUFA during tumor induction [23]. The main results showed that the tumor incidence in rats fed the n-3 PUFA-enriched diet was lower than in the non-treated group, demonstrating that the anti-tumorigenic effect of n-3 PUFA was mediated by an increase of DNA methylation [23]. On the other hand, Shen et al. observed that n-3 PUFA could modulate histone modifications by inhibiting enzymes that catalyze or alter the availability of substrates that are required for enzymatic reactions. A significantly lower activity of DNMT1 (DNA methyltransferase 1) and MBD2 (Methyl-CpG-binding domain protein 2) enzymes was observed in mice fed the n-3 PUFA-enriched diet. This outcome was accompanied by an increase in H3 acetylation, lower binding levels of HDAC1, HDAC2, HDAC6 and higher levels of methyl-H3K4 and -H3K9. Hence, the authors concluded that the regulation of leptin expression by n-3 PUFAs is mediated by epigenetic factors, such as MBD2 and histone modifications. Furthermore, n-3 PUFA supplementation in high fat-fed rodents decrease leptin mRNA expression, ameliorate leptin resistance, and decreased the differentiation and proliferation of adipocytes and their storage capacity [24].

**Transgenerational studies** A genome-wide methylation study was conducted in pigs to determine the effect of prenatal and postnatal n-3 PUFA supplementation (throughout gestation, lactation, and post-weaning periods) on the methylation pattern of the offspring [20]. Different methylation patterns were observed when comparing the supplemented and non-supplemented groups in chromosome 4, finding a hypomethylated DMR in supplemented groups; conversely, hypermethylation was detected in two intergenic regions of chromosomes 4 and 12. The authors concluded that the genes differentially methylated in the offspring were mainly involved in pathways that were improved by the n-3 PUFA supplementation, such as apoptosis, endoplasmic reticulum stress, glucose and insulin homeostasis, immune function, inflammatory profile, glucose uptake, lipid metabolism, and oxidative stress [25]. On the other hand, another study reported that EPA was able to inhibit the expression of lipogenic genes while up-regulating genes involved in fatty acid oxidation [53].

In conclusion, the effects of PUFA depend upon the subtype of FA, (n-6 or n-3; AA and EPA-DHA, respectively), the doses, the sources, and the way of administration (in foods or as nutraceutical). In this sense, more studies are needed in humans and animal models, to uncover the epigenetic effects of PUFA in relation to their beneficial role in NCCD.

**In vitro models**

**N-6 PUFA** Silva-Martínez et al. studied the effect of AA on global DNA methylation and gene expression in cultured human THP-1 monocytes. The cell stimulation was for 24 h using different concentrations of AA (1, 10,
or 100 μM). The results showed that AA induced a dose-dependent DNA hypermethylation peak at the 100 mM dose and the AA stimulation could alter the methylation profile in a similar way that was reported with palmitic acid (saturated acid that was related with aberrant epigenetic changes). This methylation profile was associated with the alteration of pathways involved in metabolic diseases like atherosclerosis, T2D, obesity, the proinflammatory profiles, and some types of cancer [26].

Another research group employed human umbilical vein endothelial cells (HUVECs) and endothelial progenitors (EPCs) to study the effect of AA on DNA methylation and the expression of genes related to angiogenesis as a mechanism involved in the carcinogenesis process [9]. After the stimulation with AA (3 μM) for 24 h, the expression of 18 proangiogenic genes was affected. The authors concluded that the beneficial effect of AA on carcinogenesis may be due, at least in part, to changes in the expression of angiogenic genes, which may be mediated by changes in DNA methylation [9].

**MUFA** In addition to AA, Silva-Martínez et al. also evaluated the impact of oleic acid (OA) on cultured human THP-1 monocytes [26]. This study demonstrated that OA had an opposite effect than AA, inducing a global hypomethylation and consequently an expression pattern that were related with an improvement of the inflammation profile [26].

As previously described for PUFA, the epigenetic effects of MUFA depended on the subtype of FA and the doses. For example, OA, whose principal sources are vegetable oils like olive oil, can ameliorate processes related to atherosclerosis, inflammation, T2D and obesity through epigenetic modifications [26].

By other hand, palmitoleic acid is an n-7 MUFA that is biosynthesized from palmitic acid (SFA) whose principal sources are of animal origin and dairy products [54]. Thus, FA can also alter the epigenome, affecting genes associated with prevention of insulin resistance and diabetes and improved lipid and glucose metabolism [55].

**Saturated and trans fatty acids**

**Human studies**

**Trans FA** Dietary trans-fatty acids (TFA) are associated with an increased risk of metabolic diseases. Some of these effects can be mediated by epigenetic mechanisms. For example, a study in humans associated industrial TFA consumption with HDL-carried miRNA concentrations and plasmatic HDL-c levels [28]. The diet rich in industrial TFA altered the concentrations of 5 miRNA in purified HDL and also contributed to 13 HDL-carried miRNA to the plasmatic miRNA pool. These miRNAs modified through the TFA-enriched diet were associated with lipid metabolism and extracellular matrix receptor interaction, suggesting an important role of miRNAs in plasma lipid metabolism regulation [28].

**Animal models**

**Trans FA**

**Transgenerational** Flores-Sierra et al. studied the effects of elaidic acid (EA; tC18:1) on global DNA methylation in the adipose tissue of the offspring 3 months after birth, and it was associated with weight gain and adipose tissue accumulation [27].

**In vitro models**

**Trans FA** The study by Flores-Sierra et al. evaluated the effect of TFA elaidic acid (EA; tC18:1) on global DNA methylation and gene transcription in cultured human THP-1 monocytes. They found a biphasic dose-dependent response and global hypermethylation was described in the 1–50 μM concentration range, whereas global hypomethylation was observed in concentrations up to 200 μM. The main results showed that EA affected the expression of genes related to pro-inflammatory and adipogenic profiles, but it also affected DNA methylation, suggesting that EA can target gene-body or intergenic regulatory elements [27].

**Saturated FA** Investigations carried out by Kumar and et al. studied models of IR in human-urine derived podocyte-like epithelial cells (HUPECs) and in male Sprague-Dawley rats, which were fed a high-fat diet. HUPECs were stimulated with 750 μM palmitate, a concentration that is two to three times higher than the palmitate level in normal non-esterified fatty acids (NEFA) [29]. The results showed that an excess of circulating palmitate generated a FA–induced metabolic memory possibly by altering the levels of H3K36me2 and H3K27me3 on the FOXO1 promoter region, increasing its activity. In conclusion, palmitate favored IR-induced gluconeogenesis and hyperglycemia, and this effect persisted even after normalization of lipid levels both in vitro and in vivo, representing cellular metabolic memory [29].

In this context, other researchers have analyzed the effect of palmitate on genome-wide mRNA expression and DNA methylation, in human pancreatic islets in vitro [30]. They reported an increase in the average global DNA methylation in different gene regions including TSS1500, 5’UTR, gene body, 3’UTR and intergenic regions, and a small decrease in global methylation in TSS200 and the 1st exon. Palmitate altered DNA
methylation levels in 290 genes, 73 of which were related
to BMI. The expression of 1860 genes were also affected
by palmitate, including genes involved in T2D (TCF7L2,
GLIS3, HNF1B, and SLC30A8), and genes associated
with glycolysis and gluconeogenesis, FA metabolism dys-
regulation, and one carbon pool by folate [30].

On the other hand, Ishikawa et al. differed from the
other reports, finding that palmitate did not affect DNA
methylation levels of the Ins1 gene promoter in normal
or high glucose conditions, which could be due to differ-
ences in the doses and genes considered in both studies
[31].

Furthermore, Maples et al. found that oleate-palmitate
(250 μM oleate-palmitate 1:1 ratio) favored DNA methyla-
tion in relation to PPAR δ expression in human skel-
etal muscle cells (HSKMC) from lean and severely obese
women. However, this increase in DNA methylation was
lower in HSKMC from obese women, suggesting that
obesity can activate transcriptional regulators of FA oxi-
dation in response to FA exposure. In conclusion, the
occurrence of different epigenetic alterations in HSKMC
after lipid stimulation suggests that a specific epigenetic
programming may occur in obese subjects as a response
to their own environmental conditions [32].

The effects of stearate and palmitate on the methyla-
tion of Pparg promoter were investigated in Raw264.7
murine macrophages. The incubation with these SFA in-
creased IL-4 levels and the methylation of Pparg, sug-

ggesting that Pparg hypermethylation could mediate the
proinflammatory effects of these SFA and contribute to
IR in obesity [33].

The harmful effects of some SFA are well known. For
example, palmitic and stearic FA have been involved in
pro-inflammatory and metabolic alterations. Different
investigations have demonstrated their contribution to
the modulation of DNA methylation and histone acetyl-
ation in relation to their effects on IR, obesity, hypergly-
cemia, T2D, lipotoxicity, dysregulation of lipid
metabolism, and abnormal lipid accumulation [29–33].

In the last years, the increased consumption of process-
ed and industrialized food, with higher amounts of SFA and
TFA, has been associated with inflammation, adipogene-
sis, abnormal accumulation of adipose tissue, alterations
in lipid metabolism, and carcinogenesis processes, which
could be mediated by changes in DNA methylation, co-
valent histone modifications, and some miRNAs.

**Short-chain fatty acids** Short-chain fatty acids (SCFA)
are products of microbial fermentation that can be
absorbed in the large intestine [56]. These SCFA can
modify epigenetic landmarks (i.e., histone acetylation)
and modulate the expression of genes related to path-
ways associated with cancer, lipid metabolism, glucose
homeostasis, and insulin sensitivity, among others. For
example, sodium butyrate (NaB) has been demonstrated
to inhibit HDAC activity [57–59].

**Animal models**

**Sodium butyrate (NaB)** Research by Khan et al. studied
the effect of NaB supplementation in juvenile diabetic
rats, demonstrating a role for NaB as an HDAC inhibitor
associated with a decrease in glucose and Hba1c, favor-
ing insulin sensitivity and reducing the risk of develop-
ing diabetes [34].

Protective anti-obesity and anti-diabetic effects of NaB
have been also reported in a model of C57BL/6 J mice
exposed to a high-fat diet [35]. NaB prevented the in-
crease of body weight and adiposity and improved insu-
lin sensitivity, increasing the percentage of type-1 fibers
and improving acylcarnitine profiles in muscle [35]. In
this context, Mátics et al. also found in chickens that NaB
improved body weight and favored cell function regu-
lation, which was mediated by epigenetic changes, such
as histone hyperacetylation [36].

**Transgenerational** In a transgenerational study, Huang
et al. demonstrated that an unbalanced maternal diet
was determinant in the development of IR and obesity in
the offspring. Moreover, they analyzed the effect of ma-
ternal butyrate supplementation on insulin sensitivity
and lipid metabolism in the skeletal muscle of the off-
spring. The rats received butyrate diet (1% NaB) during
gestation and lactation for 60 days. The offspring of
dams that were supplemented with NaB had impaired
glucose tolerance and a higher HOMA index (insulin re-
sistance), which was associated with an overexpression
of lipogenic genes. This was accompanied by an increase
in histone H3 (Lys9) and H3 (Lys27) acetylation in rela-
tion to lipogenic genes in the skeletal muscle of the off-
spring. The authors concluded that, in this model, buty-
rate impaired lipid metabolism and insulin sensitivity
in the offspring [37]. This negative effect of butyrate
was inconsistent with other investigations, suggesting that
dose and duration might be important, and indicating
that more studies are necessary to elucidate the role of
NaB and other SCFA in the prevention or treatment of
chronic diseases.

**In vitro models**

Chinese hamster ovary (CHO) cells were used to analyze
the effect of NaB on the transcriptome and epigenome.
In this study, NaB induced hypomethylation in genes be-
longing to pathways associated with the cell cycle, sig-
aling and apoptosis, whereas hypermethylation was
observed in genes implicated in protein transport and
RNA processing. On the other hand, genes related to
protein biosynthesis, the differentiation process and
RNA metabolism, were both hyper and hypomethylated. Besides, authors hypothesized that the affected gene regions presented regulatory regions closely linked with the cellular response to butyrate stimulation [38].

Another study performed in bovine cells analyzed the effect of NaB supplementation on histone modifications. The main findings of the investigation were that the inhibition of HDAC caused by NaB promoted hyperacetylation of histones and modified the expression of genes associated with cell growth, proliferation, energy metabolism, cell cycle, apoptosis, and differentiation [39].

Likewise, another study found that both, butyrate and propionate were able to increase histone acetylation in HELA and HEK293 epithelial cells, and enhance NF-κB activation (in response to TNF-α) by means of the induction of toll-like receptors (TLRs) These SCFA had an effect on the proinflammatory response, cell proliferation and differentiation, redirection of innate immune response, and cytokine/chemokine expression [40].

Paskova et al. demonstrated that NaB was able to modify the expression of androgen receptors in prostate cancer cells through an increase of H4 (Lys8) and H4 (Lys12) acetylation, favoring the suppression of tumor growth. However, this effect was minimal in normal cells, suggesting a protective role of NaB in the development of prostate cancer mediated by epigenetic modifications [41].

Consistent with this finding, other authors have reported protective effects of NaB in human gastric cancer cells, inducing demethylation and histone modifications at the promoter region of SFRP1/2, and restoring SFRP (Secreted Frizzled-Related Protein) expression in human gastric cancer cells. The authors proposed that NaB induced apoptosis, favored complex formation, promoted caspase activation, and blocked the potential of cancer cells [42].

Finally, an in vitro study combining 5 mM NaB plus 50 μM DHA, evaluated histone modification and DNA methylation in genes involved in apoptosis. It was demonstrated that this combination had a hypomethylation effect on proapoptotic genes (Bcl2l11, Cideb, Dapk1, Ltbr, and Tnfrsf25) and an increase in global H4 histone acetylation in cells treated with NaB combined with DHA; this induction of apoptosis had an anticancer effect [44].

Other authors studied the effects of NaB on histone modifications and its consequence on G1-specific cell cycle regulators in vascular smooth muscle cells (VSMC), trying to explain the interaction between chromatin remodeling and the antiproliferative action of butyrate. In this model, NaB acted as an HDAC inhibitor and caused a reorganization of chromatin, affecting the expression of negative and positive cell cycle regulators and arresting VSMC proliferation. Hence, NaB was considered a possible therapeutic agent against atherosclerosis [43].

The metabolic effects of butyrate are controversial because some studies have reported positive outcomes, such as a reduction in plasma glucose levels and HBA1c, and an improvement in insulin sensitivity and glucose homeostasis, preventing the increase of body weight and adiposity and inducing proapoptotic genes related to cancer. On the other hand, other studies have described negative effects of butyric acid, including IR, increased risk of T2D, lipid accumulation and a pro-inflammatory profile. Hence, more studies are needed to elucidate the metabolic effects of SCFA and the underlying epigenetic mechanisms, such as HDAC inhibition, in order to clarify their role as therapeutic tools against metabolic alterations and chronic diseases.

Comparison of different types of fatty acids

Human studies

In order to analyze the effects of excessive palmitic acid and n-6 PUFA intake, subjects were instructed to continue with their habitual diet just with the addition of an extra high calorie (750-kcal) muffin rich in either palmitic acid (n = 17) or n-6 PUFA-rich sunflower oil (n = 14). An adipose tissue biopsy was obtained before and after the intervention period (7 weeks). In particular, SFA overfeeding increased the mean methylation of 125 genes and PUFA overfeeding changed the mean methylation of 1797 genes, only 47 genes overlapped between the two diets, which ones were related to adipose tissue accumulation, obesity, FA uptake, transport, and lipid metabolism insulin resistance and inflammation pathways. These results suggest that DNA methylation may be involved in the individual response to FA overfeeding [45].

Voisini et al. studied the impact of different ratios of PUFA, MUFA and SFA in 91 Greek preadolescents (< 10 years). They analyzed the effects of low PUFA:SFA ratio, low MUFA:SFA and low MUFA+PUFA:SFA ratios on genome-wide DNA methylation. The genes altered in the lower PUFA:SFA ratio were associated with adipogenesis, gene regulation by PPARs, regulation of energy intake, the inflammatory process and obesity. The low MUFA+PUFA:SFA ratio was related to pathways linked to NF-κB (inflammation process). These results suggest that different types of FA have different effects on the epigenome, leading to different physiological responses [46].

On the other hand, Lind et al. designed a study encompassing 133 (9 month-old infants) that were supplemented with a teaspoon of fish oil (1.5 g/day n-3, 400 mg DHA and 1100 mg EPA) or sunflower oil (3.8 g/day) during a 9 month period. They analyzed global DNA methylation and did not find statistical differences between groups; however, they reported that 43 CpG had a 10% difference or more in the absolute methylation level
between groups, demonstrating differential effects of both FA. In the PUFA group, they found a higher amount of n-3, EPA and DHA, but lower levels of n-6 and AA in red blood cells (RBC), which was associated with an improvement of arterial pressure and a tendency of lower IL-6 levels [47].

Another study including two different human cohorts, lactating infants, and adult men, attempted to assess if there was an association between DNA methylation and different types of FA, in both fasting and the postprandial state. In the postprandial state, the participants received a representative meal of the western diet (hamburger, fries and coke) and blood was taken after the meal consumption and every 2 h until 6 pm. In the fasting day, volunteers were maintained in the fasted state from 10 am until 6 pm and blood was taken every 2 h. Furthermore, the subjects were separated according to BMI in normal-weight, overweight and obese. Results evidenced a different methylation pattern depending on the BMI and the fasting/postprandial state. The study found that DNA methylation and histone deacetylation mediated by PUFA were related to a cardioprotective and normal-weight status, in contrast to epigenetic landmarks modulated by MUFA (palmitoleic acid) and SFA (palmitic acid) that were associated with pathways implicated in obesity, dysregulation of lipid metabolism, and glucose misbalance [48].

Animal and in vitro models

A study in 34 rats and 3 T3-L1 cells compared the administration of different types of FA: sunflower oil rich in linoleic acid as PUFA, olive oil rich in oleic acid as MUFA, and coconut oil rich in palmitic acid as SFA. In rats, DNA methylation of the Tnf promoter was analyzed in the visceral adipose tissue. While both linoleic acid (PUFA) and oleic acid (MUFA) did not change Tnf methylation levels, palmitic acid increased Tnf methylation and was associated with inflammation, adiposity, and obesity. The study also concluded that FA may regulate adipocyte TNF-α levels through changes in the methylation levels of the Tnf promoter [49].

Moreover, Monastero et al. analyzed the dietary FA-mediated epigenetic regulation induced by the Vascular Endothelial Growth Factor B (VEGF-B) in adipose tissue of rats and in 3 T3-L1 cell lines [50]. Rats fed with coconut oil presented higher levels of VEGF-B expression and levels of protein, which was associated with the methylation levels of the promoter. Rats fed sunflower oil showed the lowest levels of VEGF-B while higher VEGF-B levels were associated with IR and T2D, as well as an impaired lipid metabolism [50].

Transgenerational A trasgenerational trial was designed by Hoilea et al. to determine the effect of maternal FA consumption on the PUFA status and the epigenetic regulation of fatty acid desaturase 2 (Fads2) involved in PUFA synthesis. The dams received two different FA-rich foods, butter (rich in SFA) or fish oil (rich in n-3 PUFA) and afterwards, the offspring were evaluated. They found a negative correlation between Fads2 expression and the promoter methylation levels. The methylation level of Fads2 was higher in the fish-oil group that in the butter group, which was related to a higher accumulation of fat in the liver and a dysregulation of the vascular tone in the butter group. In conclusion, the type of FA affected the regulation of the PUFA synthesis through epigenetic mechanisms [51].

The type of FA can also affect other epigenetic mechanisms, such as the expression of miRNAs, which can modulate the expression of different genes [60]. A study in which pregnant rats were fed soybean oil, olive oil, fish oil, linseed oil, or palm oil diets from conception to day 12 of gestation, the aim was to analyze miRNA expression in adipose tissue and liver of dams and their offspring. The adipose tissue mass was lower in the fish oil and linseed oil groups compared with other groups. Some hepatic miRNAs, such as miR-192–5p, miR-10b-5p, miR-377–3p, miR-215, miR-21–5p and mir-26b-5p, were downregulated by fish oil compared with olive oil and palm oil diets. These miRNAs are involved in insulin homeostasis and glucose metabolism. This study concluded that the maternal intake of diverse types of FA during pregnancy can modulate miRNA expression in both maternal and offspring tissues, relating to epigenetic mechanisms and phenotypic outcomes in the adult offspring [52]. Other studies found that a high-fat diet in pregnancy and lactation modulated hepatic miRNAs in the offspring [61, 62]. Hence, it is necessary to design more studies to clarify the role of FA in the modulation of miRNA expression and its association with metabolic alterations.

Conclusions

Over the last years, a growing number of investigations have been focused on the protective/beneficial effects of different FA, including n-3 PUFA and SCFA, in NCCD. The most consistent literature shows that some of these effects could be mediated by epigenetic mechanisms which play a role in the regulation of gene expression. In addition to n-3 PUFA and SCFA, other FA types, such as n-6 PUFA, MUFA, SFA, and TFA may also alter epigenetic mechanisms, and their effects are still under research. The results show that different types of FA have a different effect on the epigenome, mainly on DNA methylation; however, it is necessary to perform more studies focused on other epigenetic mechanisms, such as histone modifications and miRNAs and their subsequent effects on the regulation of gene expression.
The existing results confirm that FA can influence DNA methylation (hyper or hypomethylation) as well as acetylation or deacetylation of histones, and miRNAs associated with the repression, or activation of genes. For example, n-3 PUFA (i.e., EPA-DHA), and MUFA (i.e., OA, palmitoleic) have been related to the prevention of metabolic alterations (lipid metabolism disturbances, inflammation, and IR) or chronic diseases (obesity, T2D, non-alcoholic fatty liver disease, cardiovascular risk and some types of cancer). On the other hand, n-6 PUFA, such as AA, SFA (stearic and palmitic), and TFA (elaidic acid), have been associated with the presence or development of obesity, T2D, inflammatory profile, atherosclerosis, hyperglycemia, IR, lipid alterations, lipotoxicity, dysregulation of lipid metabolism, and abnormal lipid accumulation (Fig. 2).

Concerning the effects of n-3 PUFA on the DNA methylation status, a possible mechanism that has been proposed is that n-3 PUFA can promote the conversion from C to 5mC conducted by DNA methyltransferases (DNMTs) by enhancing the expression of DNMTs and consequently influence DNA methylation [20]. Furthermore, a potential interaction between n-3 PUFA and MeCP2 (methyl CpG binding protein 2) has been proposed, mainly in promoter regions, and consequently could be associated with the regulation of gene expression [50]. Another possible mechanism by which n-3 PUFAs can affect methylation is that these FA are natural ligands of some transcriptional factors, such as PPARγ [51]. In this context, it has been reported that interactions between PPARγ and fatty acids result in a decrease in cytokine expression [52], and in murine models, Pparg expression is modulated by DNA methylation in its promoter region [61]. However, more studies are needed to elucidate the role of FA in the regulation of epigenetic mechanisms in the context of metabolic alterations and chronic diseases. Regarding the other types of FA, a specific mechanism in which they could alter epigenetic landmarks, has not been described.

The intake and supplementation of different types of FA has demonstrated to have an effect on transgenerational epigenetic mechanisms (being DNA methylation the most studied). These effects are implicated in the pathogenic or protective role of FA and can be modulated during pregnancy and lactation, suggesting that they could be interesting therapeutic targets.

---

**Fig. 2** Summary of the main metabolic effects of fatty acids that can be mediated by epigenetic mechanisms. PUFA: Polyunsaturated fatty acids, MUFA: Monounsaturated fatty acids, SFA: Saturated fatty acids, SCFA: Short chain fatty acids, EPA: Eicosapentanoic acid, DHA: Docosahexanoic acid, AA: Arachidonic acid, NCCD: Non-comunicable cronic disease, miRNAs: Non-coding microRNAs, IR: Insulin Resitance
In this term the role of nutraceuticals as a potent effect on lipids regulation should be considered, and more investigations are necessary to elucidate the role of nutraceuticals depending of the individual genetic variability [63], and their possible effect on epigenetic modifications for finally encourage the management of metabolic diseases as an integrative treatment. SCFA are especially interesting because they take part of a diet-microbiota-epigenetics axis. For example, butyrate is a potent non-competitive HDAC inhibitor that is implicated in the regulation of gene expression. However, more studies are necessary to understand the regulation of specific genes and consequently their metabolic effects, as well as to consider the integrative effect of other components like gut microbiota, because butyrate is mainly produced by gut microbes, so the interaction will be very important to understand the complete outcome [64].

The epigenetic and metabolic effects of the different types of FA depend on the dose and the model, but many examples demonstrate that they can modulate the epigenome. Nevertheless, more studies are necessary to clarify the specific genes and pathways that are affected by FA through epigenetic mechanisms and consider other nutritional components that have an effect on epigenetic landmarks, such as methyl donors (vitamin B12, folate, choline, betaine, methionine, serine, glycine, and histidine), vitamins (retinol, tocopherols, and ascorbate), and polyphenols (epigallocatechin 3-gallate, genistein, curcumin, resveratrol, and sulforaphane, among others).

Supplementary information
Supplementary information accompanies this paper at https://doi.org/10.1186/s12944-019-1120-6.

Additional file 1. Search strategy and data extraction.

Abbreviations
AA: Arachidonic acid; CVD: Cardiovascular Disease; DHA: Docosahexaenoic acid; DMRs: Differentially methylated regions; DNMTs: DNA methyltransferases; EA: Elaidic acid; EPA: Eicosapentaenoic acid; FA: Fatty acids; HDAC: Histone deacetylases; IR: Insulin Resistance; MBD2: Methyl-CpG-binding domain protein 2; MUFAs: Monounsaturated fatty acids; NAc: Sodium butyrate; NCED: Non-comunicable chronic disease; NEFA: Non-esterified fatty acids; OA: Oleic acid; PUFA: Polyunsaturated fatty acids; SCFA: Short chain fatty acids; SFA: Saturated fatty acids; T2D: Type 2 Diabetes; TFA: Trans fatty acids

Acknowledgements
Spanish Biomedical Research Centre in Physiopathology of Obesity and Nutrition (CIBERobn), Institute of Health Carlos III, Madrid, Spain and IdiSNA, University of Navarra, Pamplona, Spain. University of Guadalajara, Jalisco, Mexico and Autonomous University of Baja California, Mexico.

Authors’ contributions
KGB, EBC and ORL were substantially involved in the inclusion of the scientific contents and bibliographical search as well as in the careful reading and discussion of the final version. JAM, and EML contributed with funds, initial designed, as well as in the manuscript preparation and discussion. FIM and JIRB participated in data analysis and interpretation. All authors read and approved the final manuscript.

Funding
Not applicable.

Availability of data and materials
Not applicable.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
1Institute of Translational Nutrigenetics and Nutrigenomics, Health Sciences University Center, University of Guadalajara, Guadalajara, Jalisco, Mexico. 2Department of Nutrition, Food Science, Physiology and Toxicology, Centre for Nutrition Research, University of Navarra, Pamplona, Spain. 3Faculty of Medicine and Psychology, Autonomous University of Baja California, Tijuana, B.C., Mexico. 4Navarra Institute for Health Research (IdiSNA), Pamplona, Spain. 5Centro de Investigación Biomédica en Red Fisiopatología de la Obesidad y Nutrición (CIBERobn), Carlos III Health Institute, Madrid, Spain. 6Department of Molecular Biology in Medicine, Health Sciences University Center, University of Guadalajara, Sierra Mojada 950, 44340 Guadalajara, Jalisco, Mexico. 7Madrid Institute of Advanced Studies (IMDEA Food), Madrid, Spain.

Received: 1 April 2019 Accepted: 30 September 2019
Published online: 15 October 2019

References
1. Sharp GC, Relton CL. Epigenetics and noncommunicable diseases. Epigenomics. 2017;9:789–91.
2. García-Robles R, Ayala-Ramírez PA, Perdomo-Velázquez SA. Epigenética: definición, bases moleculares e implicaciones en la salud y en la evolución humana. Rev Ciencias Salud. 2012;10:59–71.
3. Corella D, Ordovas JM. Basic concepts in molecular biology related to epigenetics and epigenomics. Rev Esp Cardiol (Eng Ed). 2017;70:744–53.
4. Martínez JA, Milagro FL, Claycombe KJ, Schalinske KL. Epigenetics in adipose tissue, obesity, weight loss, and diabetes. Adv Nutr. 2014;5:71–81.
5. Handy DE, Castro R, Loscalzo J. Epigenetic modifications: basic mechanisms and role in cardiovascular disease. Circulation. 2011;123:2145–56.
6. Pollati V, Baccarelli A. Environmental Epigenetics. Heredity. 2010;105:105–12.
7. Milagro FL, Mansiego ML, De Miguel C, Martinez JA. Dietary factors, epigenetic modifications and obesity outcomes: progresses and perspectives. Mol Asp Med. 2013;34:782–812.
8. Kulkami A, Dangat K, Kale A, Sable P, Chavan-Gautam P, Joshi S. Effects of altered maternal folie acid, vitamin B12 and docosahexaenoic acid on placental global DNA methylation patterns in Wistar rats. PloS One. 2011;6: e17705.
9. Kiec-Wilk B, Sliwa A, Mikolajczyk M, Malecki MT, Mathers JC. The CpG island methylation regulated expression of endothelial proangiogenic genes in response to β-carotene and arachidonic acid. Nutr Cancer. 2011;63:1053–63.
10. Lee C, Kim BG, Kim JH, Chun J, JI JP, Kim JS. Sodium butyrate inhibits the NF-kappa B signaling pathway and histone deacetylation and attenuates β-carotene and arachidonic acid. Nutr Cancer. 2011;63:1053–63.
11. Cordain L, Eaton SB, Sebastian A, Mann N, Lindeberg S, Watkins BA. Origins and evolution of the Western diet: health implications for the 21st century. Am J Clin Nutr. 2005;81:341–54.
12. Morgan CS, Sørensen TA. Obesity: global trends in the prevalence of overweight and obesity. Nat Rev Endocrinol. 2014;10:513–4.
13. Dar A, Singer PA, Persad DL, Pramming SK, Matthews DR, Beagleshole R, Bernstein A, Borysiewicz LK. Grand challenges in chronic non-communicable diseases. Nature. 2007;450:494–6.
14. Ramos-Lopez O, Milagro FL, Alayyee H, Chmuryzinska A, Choi MS, Curi R, et al. Guide for experimental Nutrigenetic, Nutrigenomic, and Nutriepigenetic
approaches for precision nutrition involving the prevention and management of Chronic Diseases Associated with obesity. J Nutrigenet Nutrigenomics. 2017;10:43–62.

15. Umüta G, Borfili X. Déclaration PRSMA: une proposition pour majeur la publication de révisions systématiques et m-eraanalyses. Med Clin. 2010;135:507–11.

16. Tremblay BL, Guérin R, Rudkowski J, Lemieux S, Couture P, Voil ML. Epigenetic changes in blood leukocytes following an omega-3 fatty acid supplementation. Clin Epigenetics. 2017;9:43.

17. Aïsbilékyan S, Wiener HW, Havel PJ, Stanhope KL, O’Brien DM, Hopkins SE, et al. DNA methylation patterns are associated with n-3 fatty acid intake in Yup’ik people. J Nutr. 2014;144:425–30.

18. Arpón A, Milagro FI, Ruizquín C, Corrala D, Estruch R, Frisó M, Martí A, Martínez-González MA, Ros E, Salas-Salvado J, Rieu-Bou JI, Martínez JA. Impact of consuming extra-virgin olive oil or nuts within a Mediterranean diet on DNA methylation in peripheral white blood cells within the PREMID-Navarra randomized controlled trial a role for dietary lipids. Nutrients. 2018;10:1–15.

19. do Amaral CL, Milagro FI, Curi R, Martínez JA. DNA methylation pattern in overweight women under an energy-restricted diet supplemented with fish oil. BioMed Res Int. 2014;2014:1–10.

20. Hermsdorff HH, Manseau ML, Campion J, Milagro FI, Zulet MA, Martínez JA. TFN-α promoter methylation in peripheral white blood cells: relationship with circulating TNFα, trigonal fat and n-6 PUFA intake in young women. Cytobios. 2013;166:265–71.

21. Lee HS, Baraza-Villarel A, Bissey C, Duarte-Salles T, Sly PD, Ramakrishnan U, et al. Dietary supplementation with polysaturated fatty acid during pregnancy modulates DNA methylation at IGF2/H19 imprinted genes and growth of infants. Physiol Genomics. 2014;46:851–7.

22. van Dijk SJ, Zhou J, Peters TJ, Buckley M, Sutcliffe B, Oytam Y, et al. Effect of prenatal DHA supplementation on the infant genome: results from a randomized controlled trial. Clin Epigenetics. 2016;8:1–14.

23. Huang Q, Wen J, Chen G, Ge M, Gao Y, Ye X, et al. Omega-3 polyunsaturated fatty acids inhibited tumor growth via preventing the decrease of genomic DNA methylation in colorectal cancer rats. Nutr Cancer. 2016;68:113–9.

24. Shen W, Wang C, Xia L, Fan C, Dong H, Deckelbaum RJ, et al. Epigenetic modification of the leptin promoter in diet-induced obese mice and the effects of α-3 polyunsaturated fatty acids. Sci Rep. 2014;4:1–8.

25. Boddicker RL, Koltes JE, Fritz-Waters ER, Koesterke L, Weeks N, Yin T, et al. Epigenetic changes in blood leukocytes following an omega-3 fatty acid supplementation. J Lipid Res. 2017;58:1503–12.

26. Silva-Martínez GA, Rodríguez-Ríos D, Alvarado-Caudillo Y, Vaquero A, Esteller M, Aragón-Mejías C, et al. The trans fatty acid elaidate affects lipid exposure elicits differential responses in gene expression and DNA methylation in obesity. J Nutr Biochem. 2017;58:1–10.

27. Kumar S, Pamulapati H, Tikoo K. Fatty acid induced metabolic memory involves alterations in renal histone H3K36me2 and H3K27me3. Mol Cell Exp Biol Med. 2014;239:302–13.

28. Desgagné V, Guérin R, Guay SP, Corbin F, Couture P, Lamarche B, et al. Changes in high-density lipoprotein-carried miRNA contribution to the global DNA methylome. Epigenetics. 2016;11:321–32.

29. Perfilyev A, Dahlman I, Moschos G, Chrousos GP, Manios Y, Schöbit H. Dietary fat quality impacts genome-wide DNA methylation patterns in a cross-sectional study of Greek preadolescents. Eur J Hum Genet. 2015;23:654–62.

30. de la Rocha C, Pérez-Mojica JE, Zenteno-De León S, Cervantes-Paz B, Tristán-Molina M, Alvarado-Caudillo Y, et al. Epigenetic changes in blood leukocytes following an omega-3 fatty acid supplementation. J Lipid Res. 2017;58:1503–12.

31. Birkof H, Hoffrogge R, Noll T. Integrative analysis of DNA methylation and gene expression in butyrate-treated CHO cells. J. Biotechnol. 2017;257:150–61.

32. Shin JH, Xu L, Li RW, Gao Y, Birkof H, Liu GE, et al. A high-resolution whole-genome map of the distinctive epigenetic landscape induced by butyrate in bovine cells. Anim Genet. 2014;45:40–50.

33. Lin MY, de Zoete NR, van Putten JP, Snijbers K. Redirection of epithelial immune responses by short-chain fatty acids through inhibition of histone Deacetylases. Front Immunol. 2015;6:1–11.

34. Paskova L, Smersy-Trikova K, Falova B, Benedikova A, Langova K, Kolar Z. Different effect of sodium butyrate on cancer and normal prostate cells. Toxicol in Vitro. 2013;27:1489–95.

35. Shin H, Kim JH, Lee YS, Lee YC. Change in gene expression profiles of secreted frizzled-related proteins (SFRPs) by sodium butyrate in gastric cancers: induction of promoter demethylation and histone modification causing inhibition of Wnt signaling. Int J Oncol. 2012;40:1533–42.

36. Mathew OP, Ranganag K, Yatsu FM. Butyrate, an HDAC inhibitor, stimulates interplay between different posttranslational modifications of histone H3 and differently alters G1-specific cell cycle proteins in vascular smooth muscle cells. Biomol Pharmacother. 2016;74:333–40.

37. Cho Y, Turner ND, Davidson LA, Chapkin RS, Carroll RJ, Lupton JR, Colon cancer cell apoptosis is induced by combined exposure to the n-3 fatty acid docosahexaenoic acid and butyrate through promoter methylation. Exp Biol Med. 2014;239:302–10.

38. Paskova L, Smersy-Trikova K, Falova B, Benedikova A, Langova K, Kolar Z. Different effect of sodium butyrate on cancer and normal prostate cells. Toxicol in Vitro. 2013;27:1489–95.

39. Voisin S, Almén MS, Moschonis G, Chrousos GP, Manios Y, Schöbit H. Dietary fat quality impacts genome-wide DNA methylation patterns in humans. Sci Rep. 2016;6:33340.

40. Lind MW, Martino D, Harslid LB, Kyjovska ZO, Kristensen M, Lauritzen L. Epigenetic and differently alters G1-specific cell cycle proteins in vascular smooth muscle cells. Biomol Pharmacother. 2016;74:333–40.

41. Paskova L, Smersy-Trikova K, Falova B, Benedikova A, Langova K, Kolar Z. Different effect of sodium butyrate on cancer and normal prostate cells. Toxicol in Vitro. 2013;27:1489–95.

42. Mathew OP, Ranganag K, Yatsu FM. Butyrate, an HDAC inhibitor, stimulates interplay between different posttranslational modifications of histone H3 and differently alters G1-specific cell cycle proteins in vascular smooth muscle cells. Biomol Pharmacother. 2016;74:333–40.

43. Cho Y, Turner ND, Davidson LA, Chapkin RS, Carroll RJ, Lupton JR, Colon cancer cell apoptosis is induced by combined exposure to the n-3 fatty acid docosahexaenoic acid and butyrate through promoter methylation. Exp Biol Med. 2014;239:302–10.

44. Paskova L, Smersy-Trikova K, Falova B, Benedikova A, Langova K, Kolar Z. Different effect of sodium butyrate on cancer and normal prostate cells. Toxicol in Vitro. 2013;27:1489–95.

45. Mathew OP, Ranganag K, Yatsu FM. Butyrate, an HDAC inhibitor, stimulates interplay between different posttranslational modifications of histone H3 and differently alters G1-specific cell cycle proteins in vascular smooth muscle cells. Biomol Pharmacother. 2016;74:333–40.

46. Lind MW, Martino D, Harslid LB, Kyjovska ZO, Kristensen M, Lauritzen L. Epigenetic and differently alters G1-specific cell cycle proteins in vascular smooth muscle cells. Biomol Pharmacother. 2016;74:333–40.

47. Mathew OP, Ranganag K, Yatsu FM. Butyrate, an HDAC inhibitor, stimulates interplay between different posttranslational modifications of histone H3 and differently alters G1-specific cell cycle proteins in vascular smooth muscle cells. Biomol Pharmacother. 2016;74:333–40.

48. de la Rocha C, Pérez-Mojica JE, Zenteno-De León S, Cervantes-Paz B, Tristán-Molina M, Alvarado-Caudillo Y, et al. Epigenetic changes in blood leukocytes following an omega-3 fatty acid supplementation. J Lipid Res. 2017;58:1503–12.

49. Birkof H, Hoffrogge R, Noll T. Integrative analysis of DNA methylation and gene expression in butyrate-treated CHO cells. J. Biotechnol. 2017;257:150–61.

50. Shin JH, Xu L, Li RW, Gao Y, Birkof H, Liu GE, et al. A high-resolution whole-genome map of the distinctive epigenetic landscape induced by butyrate in bovine cells. Anim Genet. 2014;45:40–50.

51. Lin MY, de Zoete NR, van Putten JP, Snijbers K. Redirection of epithelial immune responses by short-chain fatty acids through inhibition of histone Deacetylases. Front Immunol. 2015;6:1–11.

52. Mathew OP, Ranganag K, Yatsu FM. Butyrate, an HDAC inhibitor, stimulates interplay between different posttranslational modifications of histone H3 and differently alters G1-specific cell cycle proteins in vascular smooth muscle cells. Biomol Pharmacother. 2016;74:333–40.
54. Orsavova J, Misurcova L, Ambrozova J, Vicha R, Mlcek J. Fatty acids composition of vegetable oils and its contribution to dietary energy intake and dependence of cardiovascular mortality on dietary intake of fatty acids. Int J Mol Sci. 2015;16:12871–90.
55. Frigolet ME, Gutierrez-Aguilar R. The role of the novel Lipokine palmitoleic acid in health and disease. Adv Nutr. 2017;8:173–81.
56. Bergman EN. Energy contributions of volatile fatty acids from the gastrointestinal tract in various species. Physiol Rev. 1990;70:567–90.
57. Arents G, Burlingame RW, Wang BC, Love WE, Moudrianakis EN. The nucleosomal core histone octamer at 3.1 a resolution: a tripartite protein assembly and a left-handed superhelix. Proc Natl Acad Sci. 1991;88:10148–52.
58. Goldberg AD, Allis CD, Bernstein E. Epigenetics: a landscape takes shape. Cell. 2007;128:635–8.
59. Li RW, Li C. Butyrate induces profound changes in gene expression related to multiple signal pathways in bovine kidney epithelial cells. BMC Genomics. 2006;7:1–14.
60. Lovis P, Roggli E, Laybutt DR, Gattesco S, Yang JY, Widman C, Abderrahmani A, Regazzi R. Alterations in MicroRNA expression contribute to fatty acid–induced pancreatic β-cell dysfunction. Diabetes. 2008;57:2728–36.
61. Benatti RO, Melo AM, Borges FO, Ignacio-Souza LM, Simon LA, Milanski M, et al. Maternal high-fat diet consumption modulates hepatic lipid metabolism and microRNA-122 (miR-122) and microRNA-370 (miR-370) expression in offspring. Br J Nutr. 2014;111:2112–22.
62. Zhang J, Zhang F, Dedolot X, Bruce KD, Cagampang FR, Watish M, et al. Maternal high fat diet during pregnancy and lactation alters hepatic expression of insulin like growth factor-2 and key microRNAs in the adult offspring. BMC Genomics. 2009;10:1–12.
63. Scicchitano P, Camelli M, Maiello M, et al. Nutraceuticals and dyslipidaemia: beyond the common therapeutics. J Functional Foods. 2014;6:11–32.
64. Kasubuchi M, Hasegawa S, Hiramatsu T, Ichimura A, Kimura I. Dietary gut microbial metabolites, short-chain fatty acids, and host metabolic regulation. Nutrients. 2015;7:2839–49.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.