KEM.

Kompetenz
Exzellenz
Menschlichkeit

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Microbiome: the role in breast cancer therapy

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Conflicts of interest

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Research support:

- 02/2018 to 04/2021 Alois Schnaubelt habilitation program of the Karl and Veronica Carstens Foundation
- 03/2019 to 02/2020 Josepha and Charlotte von Siebold habilitation support program

Lecturing activity: Novartis, Pfizer, Roche, Seagen, Lilly, Gilead

Consultant activity: WALA, Novartis

Definitions

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Microbiota: all microorganisms in a habitat

(ca. 1.000.000.000.000.000.000)

Microbiome: all microorganisms and their genome

Symbiosis: Physiological balance of a reciprocal relationship between two organisms of different species

Dysbiosis: Imbalance in the structural or functional composition of the microbiota

Der Internist 5 · 2017

Intestinal bacteria perform a variety of functions:

- Prevent the colonization of foreign (pathogenic) microorganisms as resident flora (high microbial diversity offers special protection against disturbances in microbiota homeostasis)
- Are metabolically highly active and produce short-chain fatty acids (SCFA)

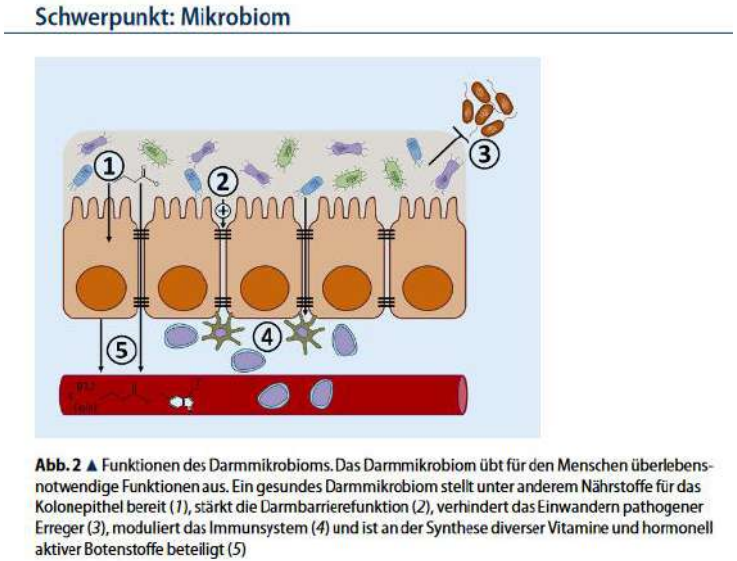


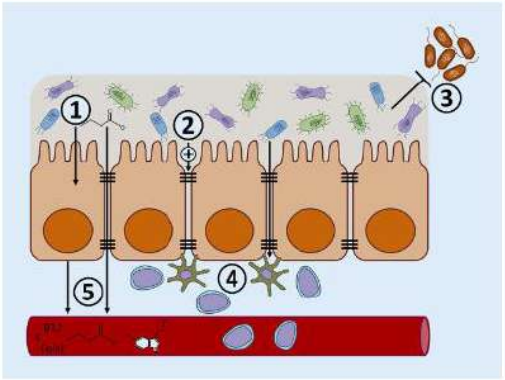
Abb. 2 ▲ Funktionen des Darmmikrobioms. Das Darmmikrobiom übt für den Menschen überlebensnotwendige Funktionen aus. Ein gesundes Darmmikrobiom stellt unter anderem Nährstoffe für das Kolonepithel bereit (*1*), stärkt die Darmbarrierefunktion (*2*), verhindert das Einwandern pathogener Erreger (*3*), moduliert das Immunsystem (*4*) und ist an der Synthese diverser Vitamine und hormonell aktiver Botenstoffe beteiligt (*5*)

Die Innere Medizin 10 · 2022

Intestinal bacteria perform a variety of functions:

- Lactic acid synthesizing bacteria (e.g. Bifidobacterium) inhibit the TNF-α secretion induced by lipopolysaccharides (LPS) and thus have an anti-inflammatory effect and stabilize the intestinal barrier
- Intestinal microorganisms provide metabolic pathways for the biosynthesis of vitamin K and various B vitamins

Schwerpunkt: Mikrobiom



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Strains in healthy individuals

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- Firmicutes
- Bacteroidetes

→ > 80 % of the gastrointestinal microbiome

- Verrucomicrobia
- Actinobacteria
- Proteobacteria
- Tenericutes
- Cyanobacteria

Factors influencing the human microbiome

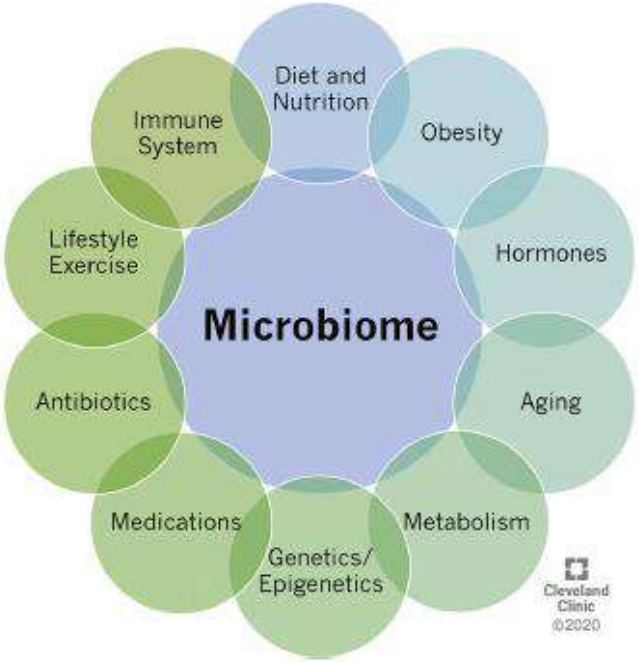

Fig. 1. Factors that influence the human microbiome.

M.M. AlHilli and V. Bae-Jump, Diet and gut microbiome interactions in gynecologic cancer, Gynecologic Oncology, https://doi.org/10.1016/j.ygyno.2020.08.027

Microbiome and immune system

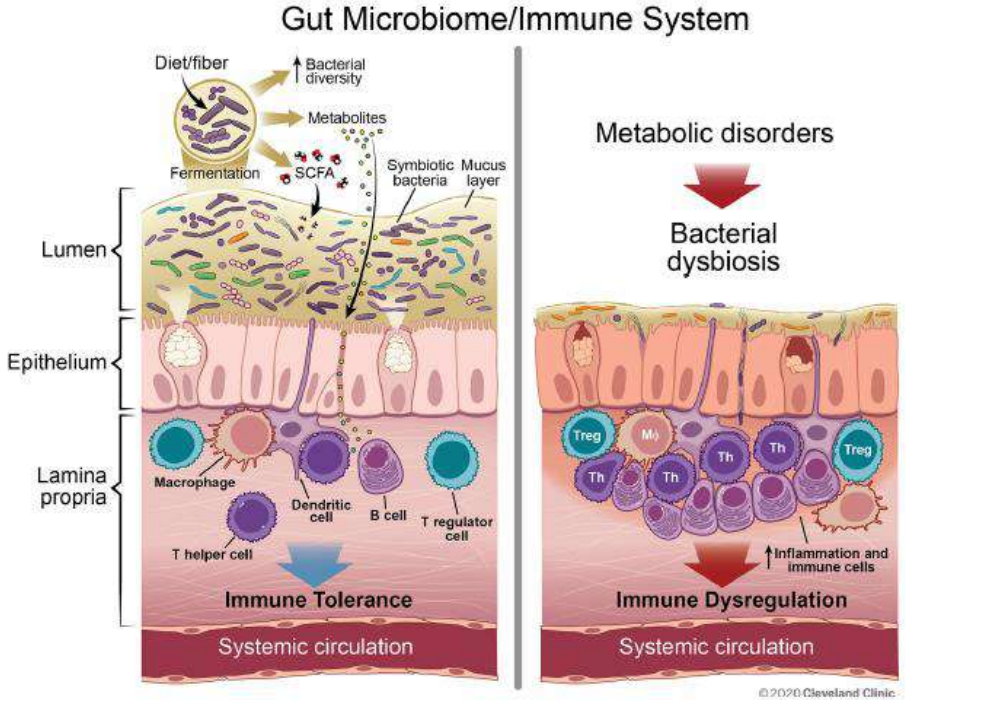

Fig. 3. The gut microbiome and immune system regulation: Increased gut microbial diversity (left) maintains gastrointestinal barrier function and produces short chain fatty acids (SCFA) and anti-inflammatory metabolites that promote immune tolerance. Bacterial dysbiosis and reduced bacterial diversity (right) attenuate the gut mucosal barrier and promote inflammatory cytokine release and systemic inflammation.

AlHilli MM, Bae-Jump V.. Gynecol Oncol. 2020 Nov;159(2):299-308.

Short-chain fatty acids (SCFA)

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- Acetic, propionic or butyric acid (Acetat, Propionat, Butyrat)
- End products of bacterial metabolism in the colon
- Starch (which is not absorbed in the small intestine) and indigestible oligosaccharides from dietary fiber are the main substrates of anaerobic microorganisms (Faecalibacterium, Ruminococcus, Roseburia or Eubacterium) in the colon
- Almost complete resorption of SCFA by the colonocytes (oxidation → ATP production!)

AlHilli MM, Bae-Jump V.. Gynecol Oncol. 2020 Nov;159(2):299-308.
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Short-chain fatty acids (SCFA)

- Contribute to improving the barrier function of the intestine by, among other things, stimulating the expression of proteins involved in the tight junctions
- SCFA also lower the pH in the colon and thus inhibit the growth of facultative pathogens such as Escherichia coli

AlHilli MM, Bae-Jump V.. Gynecol Oncol. 2020 Nov;159(2):299-308.
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Short-chain fatty acids (SCFA)

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- SCFA have an anti-inflammatory effect:
  - they influence the pool of regulatory T cells in the colon
  - they inhibit the secretion of pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α or interleukin-6
  - they promote the biosynthesis of intestinal antimicrobial peptides

AlHilli MM, Bae-Jump V.. Gynecol Oncol. 2020 Nov;159(2):299-308.
Die Innere Medizin 10 · 2022

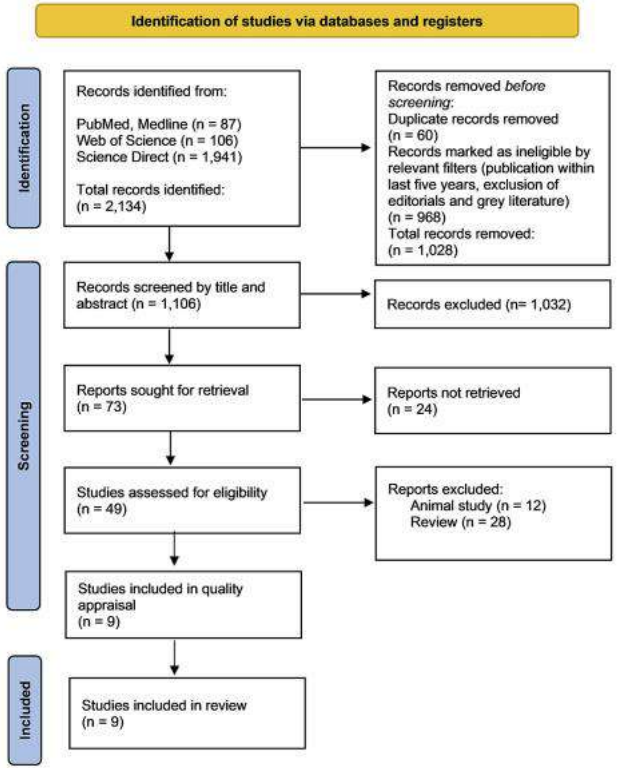

FIGURE 1: Preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2020 flow diagram

Study Characteristics

The nine included studies were comprised of three randomized controlled trials and six observational studies. Quality assessments of randomized controlled trials and observational studies are depicted in Tables 2, 3, respectively.

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Gastrointestinal Microbiota and Breast Cancer Chemotherapy Interactions: A Systematic Review

Csendes et al. (November 18, 2022). Cureus 14(11): e31648.

Gastrointestinal Microbiota and Breast Cancer Chemotherapy Interactions: A Systematic Review

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- Studies concerning chemotherapy and the gastrointestinal microbiota demonstrated complex interconnections!
- microbiota diversity and specific combinations of bacteria may be used to predict which patients are likely to have good prognoses and responses to chemotherapy!
- Microbiota diversity could also be used to predict the likelihood of developing chemotherapy side effects!

Csendes et al. (November 18, 2022). Cureus 14(11): e31648.

Gastrointestinal Microbiota and Breast Cancer Chemotherapy Interactions: A Systematic Review

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- In high-risk patients, the addition of a probiotic supplement may help mitigate anticipated side effects.
- The gut microbiome is rich with untapped potential for advancing personalized medicine.

Csendes et al. (November 18, 2022). Cureus 14(11): e31648.

IS THE MICROBIOME OR NUTRITION MORE IMPORTANT FOR RESPONSE TO IMMUNOTHERAPY?

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- Several clinical studies have now suggested a role of gut microbiota composition in response to treatment, including anti-PD-1 therapy.
- Various approaches to render the microbiome more responsive to therapy have been suggested, including the use of antibiotics, probiotics, prebiotics, diet and (fecal microbial transplant FMT).
- Future goals include the discovery of reliable microbiome-related biomarkers for prediction of response and stratification of patients and the identification of favorable microbiomes

Ascierto PA, et al. J Immunother Cancer 2020

IS THE MICROBIOME OR NUTRITION MORE IMPORTANT FOR RESPONSE TO IMMUNOTHERAPY?

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- Although the microbiome appears to influence response to immunotherapy, the factors that determine the microbiome and how patients can achieve a proresponse microbiome are less well known.
- There appears to be very limited overlap in terms of proresponse bacterial species across different cohorts, which could in part be attributed to differences in environmental influences and in particular diet. It may be that the real importance is not the particular bacterial species that are present, but rather their function.

Ascierto PA, et al. J Immunother Cancer 2020

IS THE MICROBIOME OR NUTRITION MORE IMPORTANT FOR RESPONSE TO IMMUNOTHERAPY?

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- Habitual diet is a key determinant of the gut microbiota, and gut microbiome composition can be rapidly changed by altering diet.
- The microbiota is a key mediator of the effects of diet on health, but is not the only one. For instance, the diet may exert a direct positive effect on the immune system, for example, antineoplastic effects exerted by polyphenols.

Ascierto PA, et al. J Immunother Cancer 2020

Dietary fiber and probiotics influence the gut microbiome and melanoma immunotherapy response

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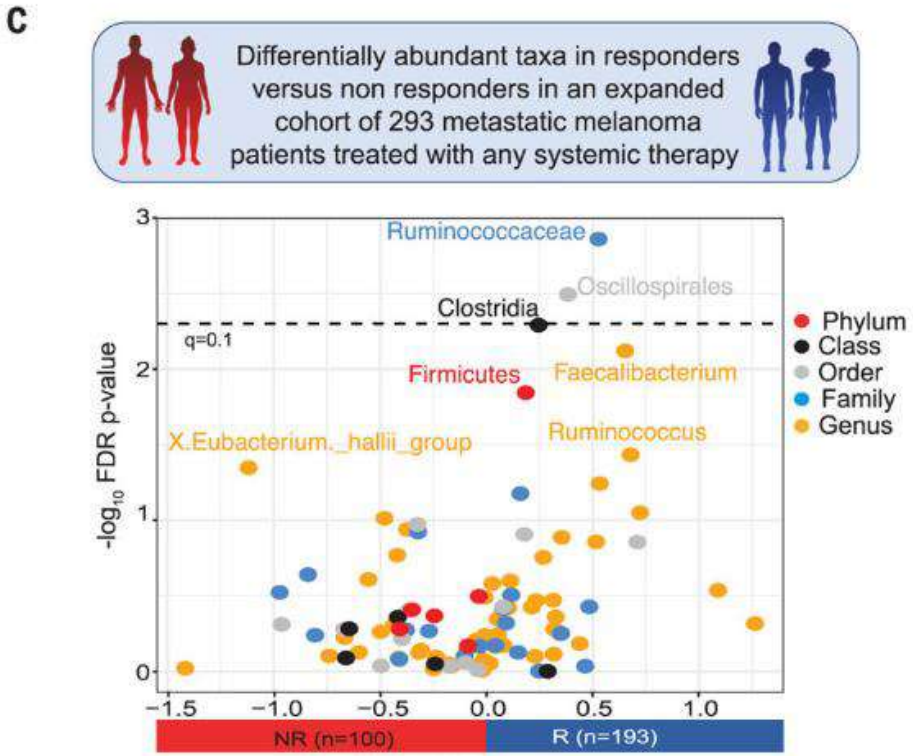

Spencer et al. Science. 2021 December 24; 374(6575): 1632–1640.

Dietary fiber and probiotics influence the gut microbiome and melanoma immunotherapy response

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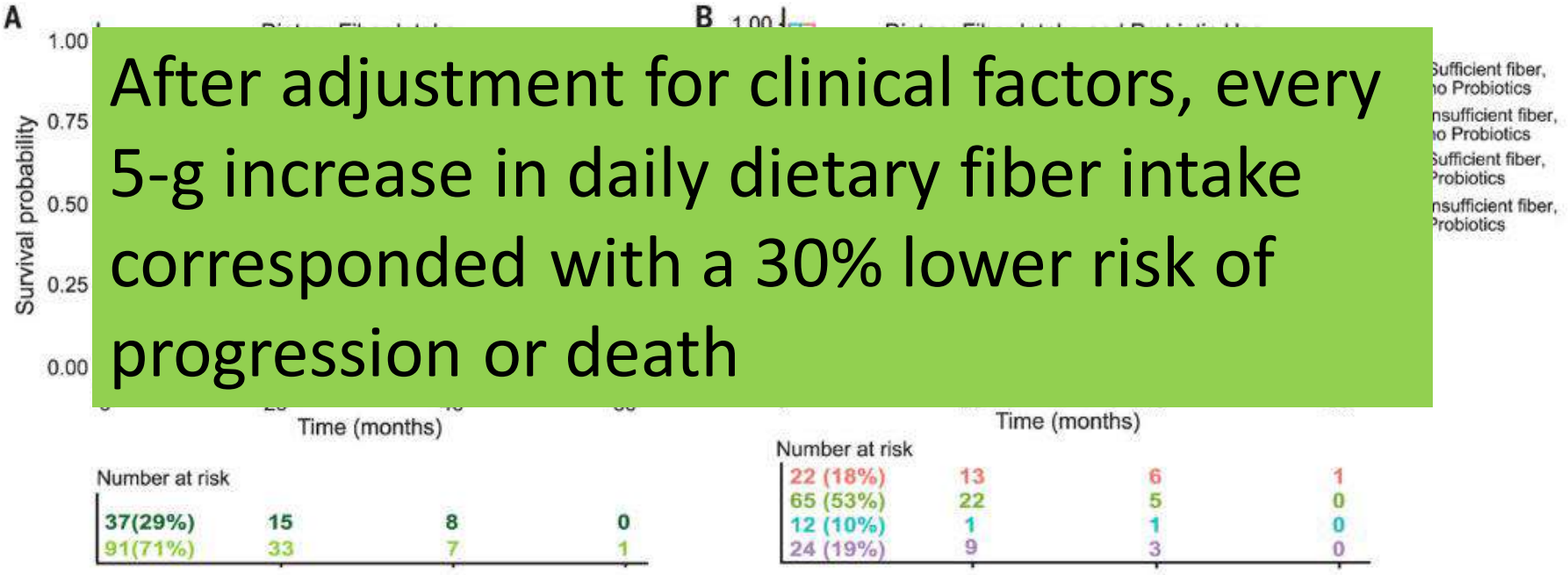
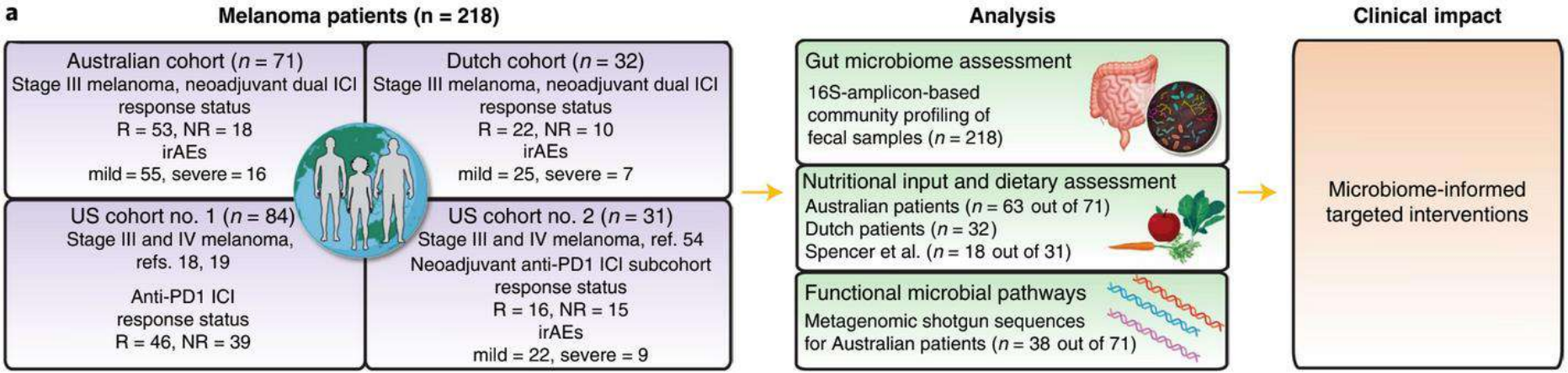


After adjustment for clinical factors, every 5-g increase in daily dietary fiber intake corresponded with a 30% lower risk of progression or death

Spencer et al. Science. 2021 December 24; 374(6575): 1632–1640.

Diet-driven microbial ecology underpins associations between cancer immunotherapy outcomes and the gut microbiome



All patients were treated with nivolumab (anti-PD-1) combined with ipilimumab (anti-CTLA-4)

Nature Medicine | VOL 28 | November 2022 | 2344–2352

Diet-driven microbial ecology underpins associations between cancer immunotherapy outcomes and the gut microbiome

Faecalibacterium prausnitzii,

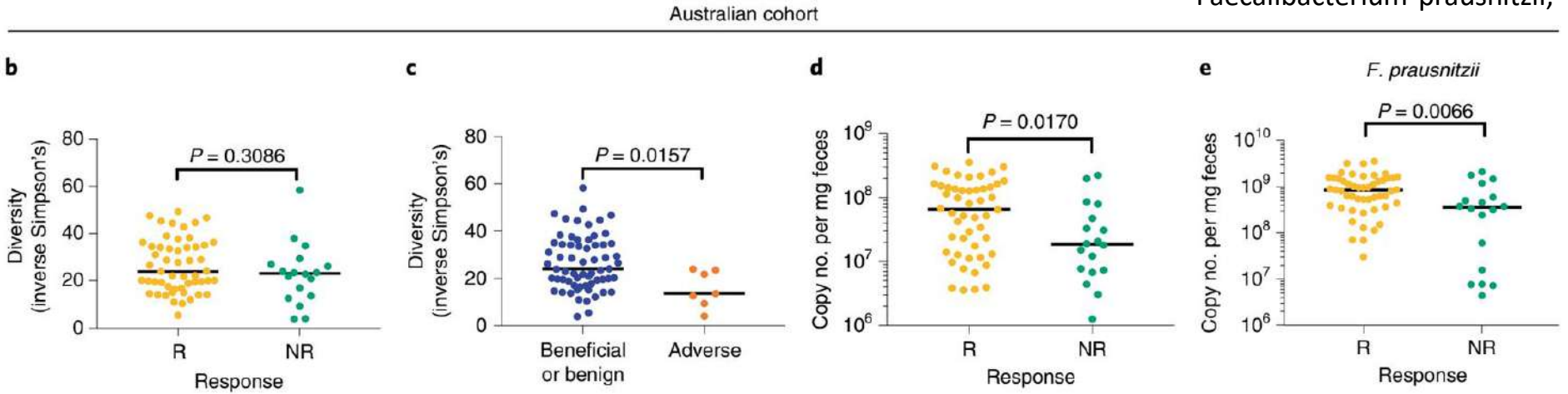


Fig. 1 | Associations between gut microbiota and treatment response and irAEs in Australian patients with melanoma. b,c, Bacterial community profiling of patient baseline fecal samples via 16S rRNA gene amplicon sequencing (AUS, n= 71). Inverse Simpson's index of alpha-diversity for individual patients grouped by R and NR (b) and beneficial or benign (all R or NR irAEs < G3) and adverse (NR, irAEs ≥ G3) outcomes (c). d, Absolute bacterial fecal loads assessed using qPCR were used to determine bacterial copy number per mg feces and were grouped according to response (n= 71).

Nature Medicine | VOL 28 | November 2022 | 2344–2352

Diet-driven microbial ecology underpins associations between cancer immunotherapy outcomes and the gut microbiome

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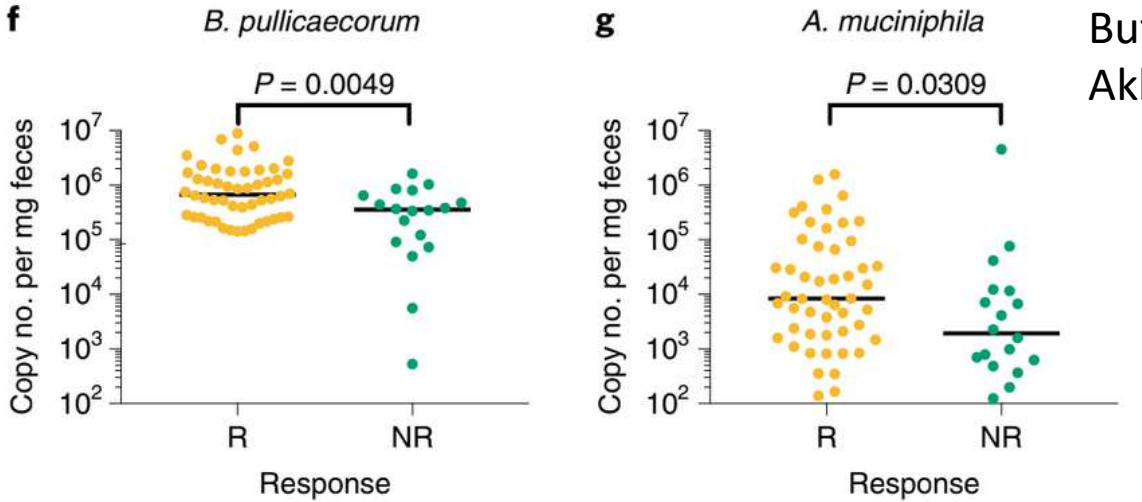

Butyricicoccus pullicaecorum
Akkermansia muciniphilia

Fig. 1 | Associations between gut microbiota and treatment response and irAEs in Australian patients with melanoma. e-g, qPCR using taxa-specific primers was used to determine bacterial copy number per mg feces of selected taxa identified using LEfSe analysis grouped according to response (n= 71). Each symbol represents data from an individual patient; bars indicate the median.

Nature Medicine | VOL 28 | November 2022 | 2344–2352

Diet-driven microbial ecology underpins associations between cancer immunotherapy outcomes and the gut microbiome

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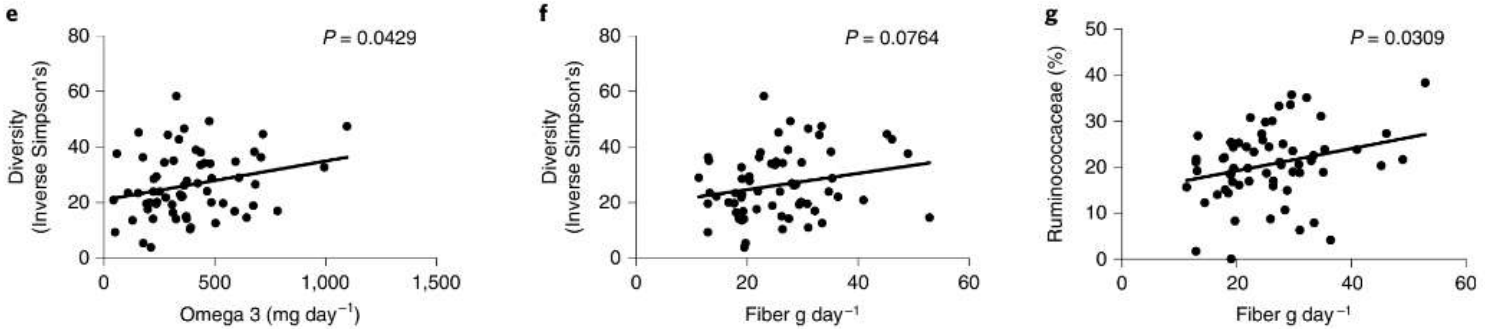

Fig. 2 | Microbial functions and dietary nutrient intake that promote gut integrity are associated with protection from irAEs and lack of response.
e,f, Correlations of omega 3 and fiber consumption and diversity.
g, Correlation of fiber consumption against the relative abundance of Ruminococcaceae.

Nature Medicine | VOL 28 | November 2022 | 2344–2352

Therapy

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- Prebiotics: “non-digestible food components that have a beneficial effect on their host by specifically stimulating the growth and/or activity of one or more bacterial species in the large intestine and thus improving the health of the host”. (Gibson und Roberfroid, 1995)

- Probiotika: Zubereitung, die lebensfähige Mikroorganismen enthält, Mutaflor® (E. Coli Stamm Nissle, 1917), Omniflora N® (Bifidobacterium Lyophilisat, Lactobacillus gasseri), VSL #3, OrthoDoc Flora
  - Bakterienlysat Colibiogen®, Synerga®, Prosymbioflor®

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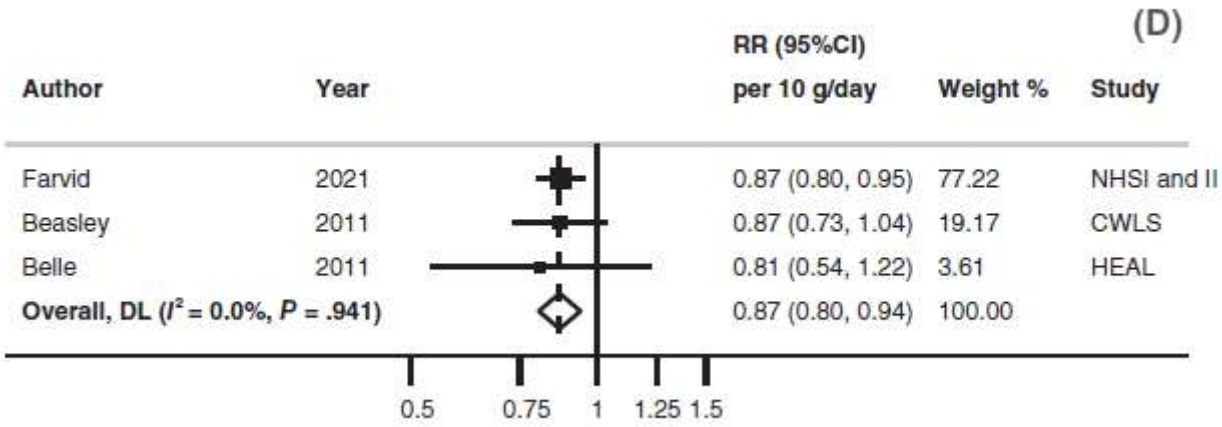

For every 10 g increase in fiber intake per day
a 13% lower risk of all-cause mortality

Becerra-Tomás et al., Int. J. Cancer. 2022;1–19.

Postdiagnosis body fatness, recreational physical activity, dietary factors and breast cancer prognosis: Global Cancer Update Programme (CUP Global) summary of evidence grading

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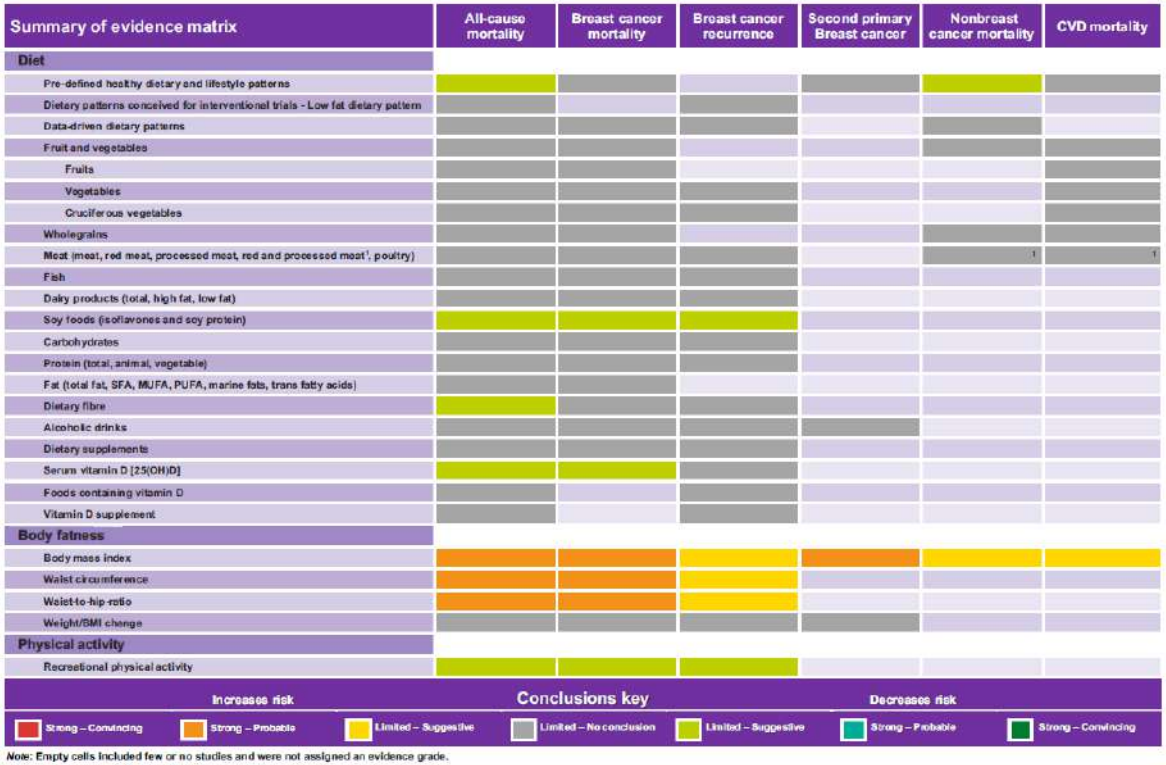

Summary of evidence matrix	All-cause mortality	Breast cancer mortality	Breast cancer recurrence	Second primary Breast cancer	Nonbreast cancer mortality	CVD mortality
Diet						
Pre-defined healthy dietary and lifestyle patterns						
Dietary patterns conceived for interventional trials - Low fat dietary pattern						
Data-driven dietary patterns						
Fruit and vegetables						
Fruits						
Vegetables						
Cruciferous vegetables						
Wholegrains						
Meat (meat, red meat, processed meat, red and processed meat[1], poultry)					[1]	[1]
Fish						
Dairy products (total, high fat, low fat)						
Soy foods (isoflavones and soy protein)						
Carbohydrates						
Protein (total, animal, vegetable)						
Fat (total fat, SFA, MUFA, PUFA, marine fats, trans fatty acids)						
Dietary fibre						
Alcoholic drinks						
Dietary supplements						
Serum vitamin D [25(OH)D]						
Foods containing vitamin D						
Vitamin D supplement						
Body fatness						
Body mass index						
Waist circumference						
Waist-to-hip ratio						
Weight/BMI change						
Physical activity						
Recreational physical activity						

Note: Empty cells included few or no studies and were not assigned an evidence grade.

FIGURE 1 Summary quality of evidence matrix from the systematic literature reviews on postdiagnosis diet, nutrition, physical activity and survival in women with breast cancer

Tsilidis et al. Int. J. Cancer. 2022;1–10.

Exampel for fiber intake

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Food	Fiber
4 Slices of whole grain bread (250g)	16g
3 potatoes (200g)	3,5g
1 apple (150g), unpeeled, raw raspberries(50g)	3g, 2,5g
Boiled beans (150g),	3,5g
Mixed salad with corn (120g)	2,5g
Total amount	**31g**

Therapy

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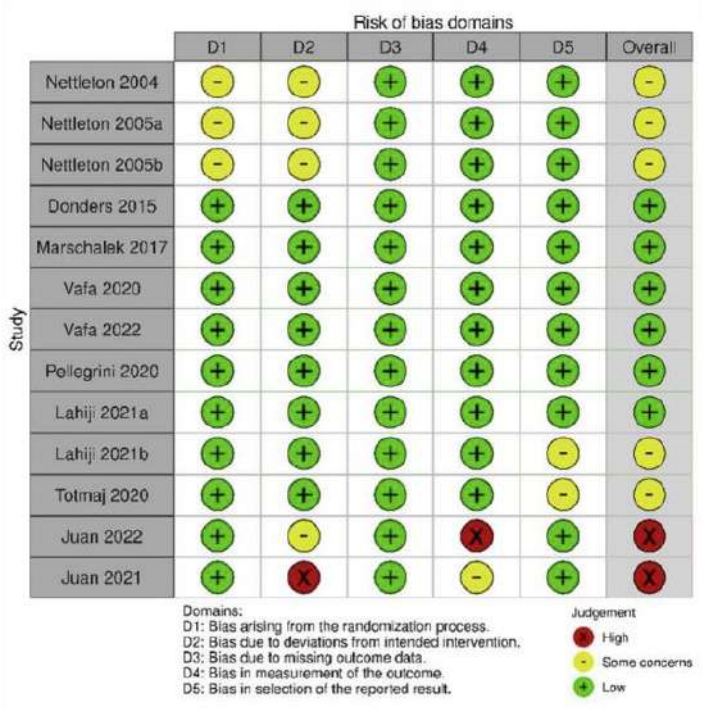
- Präbiotika: nicht verdaubare Lebensmittelbestandteile, die ihren Wirt günstig beeinflussen, indem sie das Wachstum und/oder die Aktivität einer oder mehrerer Bakterienarten im Dickdarm gezielt anregen und somit die Gesundheit des Wirts verbessern“ (Gibson und Roberfroid, 1995)

- Probiotics: Preparation containing viable microorganisms, Mutaflor® (E. Coli strain Nissle, 1917), Omniflora N® (Bifidobacterium Lyophilisat, Lactobacillus gasseri), VSL #3, OrthoDoc Flora
  - Bacterial lysate Colibiogen®, Synerga®, Prosymbioflor®

Effect of Probiotics in Breast Cancer: A Systematic Review and Meta-Analysis



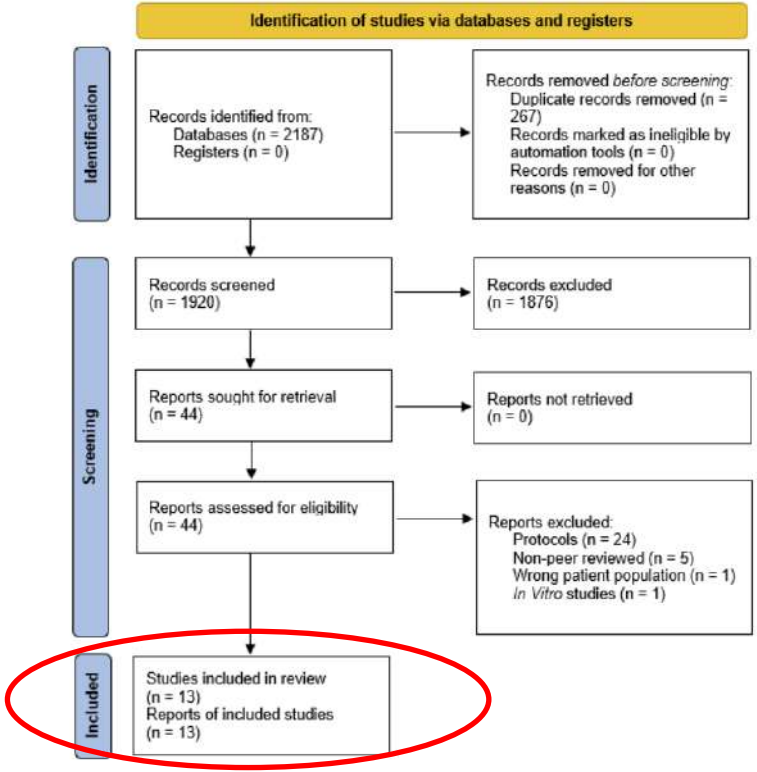


Figure 1. Flow diagram for identification of studies in the systematic review.

Thu et al.. Biology 2023, 12, 280.

Effect of Probiotics in Breast Cancer: A Systematic Review and Meta-Analysis

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Table 1. Baseline characteristics within the identified studies.

Study Number	First Author, Year (Reference)	Country	Study Type	Participant Numbers (*n*)	Age Range (Years)	Probiotic Regimen	Dose	Duration
1 2 3	Nettleton, 2004 [41] Nettleton, 2005a [42] Nettleton, 2005b [43]	USA	Randomized crossover trial	40	36–72	ProLB + FOS	3 capsules (10^9 CFU)/15–30 mg FOS before breakfast	6 weeks
4	Donders, 2015 [44]	Belgium/Germany	Randomized trial	16	52–63	Lacto + ultra-low dose 0.03 mg estriol (E3)	1 tablet (Gynoflor®) daily followed by maintenance therapy for 8 weeks	4 weeks
5	Marschalek, 2017 [45]	Austria	Randomized placebo-controlled trial	22	18–45 *	Lacto	1 capsule (2.5×10^9 CFU) daily, twice/day	2 weeks
6	Vafa, 2020 [46]	Iran	Parallel, randomized, placebo-controlled trial	135	50–57	ProLBS + FOS	1 capsule (10^9 CFU)/38.5 mg FOS daily	10 weeks
7 8	Vafa, 2022 [47] Totmaj, 2020 [48]	Iran	Randomized clinical trial	88	35–73	ProLBS + FOS	1 capsule (10^9 CFU)/38.5 mg FOS daily	10 weeks
9	Pellegrini, 2020 [49]	Iran	Randomized open-label trial	34	<70 *	ProLB	1 sachet (4×10^9 CFU) daily	2 months
10 11	Lahiji, 2021a [50] Lahiji, 2021b [51]	Iran	Randomized placebo-controlled	76	50–75	ProLBS + FOS	1 capsule (10^9 CFU)/38.5 mg FOS daily	8 weeks
12 13	Juan, 2022 [52] Juan, 2021 [53]	China	Randomized placebo-controlled trial	160 100	28–63	ProLBE	3 capsules (0.84 g) per time, twice/day	3 weeks

Abbreviations: Lacto, *Lactobacillus* spp. alone; ProLB, probiotics comprising *Lactobacillus* and *Bifidobacterium*; ProLBS, probiotics comprising *Lactobacillus*, *Bifidobacterium*, and *Streptococcus*; ProLBE, probiotics comprising *Lactobacillus*, *Bifidobacterium*, and *Enterococcus*; FOS, fructooligosaccharides. * inclusion criteria available only.

Thu et al.. Biology 2023, 12, 280.

Effect of Probiotics in Breast Cancer: A Systematic Review and Meta-Analysis

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3.11. Tumor Necrosis Factor-Alpha

The meta-analysis on tumor necrosis factor-alpha (TNF-α) revealed a significant improvement following intervention with ProLBS capsules plus FOS (MD = −15.06; 95% CI: −23.20 to −6.91; $p = 0.0003$); see Figure 7.

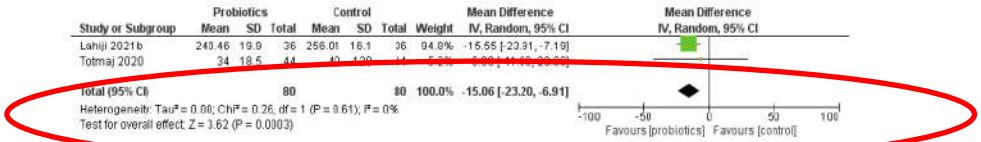

Figure 7. Meta-analysis for tumor necrosis factor-alpha (TNF-α).

3.12. High-Sensitivity C-Reactive Protein

Analysis of two studies including hs-CRP data in breast cancer survivors indicated that intervention with ProLBS plus FOS did not cause any overall alterations to hs-CRP levels detected (MD = 0.5; 95% CI: −0.97 to 1.96; $p = 0.51$). Furthermore, the between-study heterogeneity was significantly high ($I^2 = 82\%$, $p = 0.02$); see Figure 8.

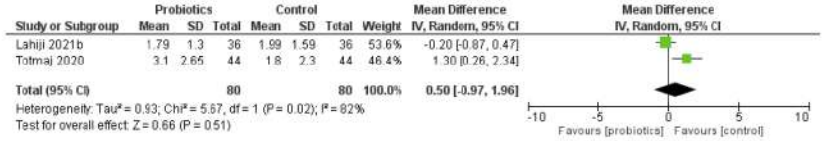

Figure 8. Meta-analysis for high-sensitivity C-reactive protein (hs-CRP).

Thu et al.. Biology 2023, 12, 280.

- The intake of Lactobacillus, Bifidobacterium, and Enterococcus (3 capsules (0.84 g) 2 x daily for 3 weeks) led to a significant reduction in body fat and body weight (Juan 2021)
- High risk of bias!

Conclusion

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- Diversity appears to be important for the tolerability/effectiveness of chemotherapy/immunotherapy!
- A well-tolerated, high-fiber (at least 25 to 30 g/day), plant-based, low-fat diet is recommended!
- The use of probiotics is controversial!
- Many questions are still unanswered!

Thank you for your attention

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