Probiotic Fermented Dairy Products and their Effect on Metabolic Syndrome

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Probiotics are Everywhere

- Probiotics are frequently advertised
- Many Sources:
  - Capsules
  - Fortified Yogurts
  - Kombucha
  - Kimchi
  - Kefir
Probiotics

Live and non-pathogenic microorganisms that have beneficial effects on the hosts when consumed on appropriate doses

Many Claims

- Reduce serum cholesterol
- Immune health
- Anticarcinogenic properties
- Improvement of normal microflora
- Alleviation of intestinal bowel disease systems
- Production of folate to help with homocysteine metabolism
- Improve glucose sensitivity
- Reduce inflammation

(N. Alihosseini et al., 2017)
Metabolic syndrome

- A combination of metabolic risk factors that increase the risk of cardiovascular disease (CVD) and type II diabetes

- Risk Factors:
  - Dyslipidemia
  - Elevated blood pressure
  - Elevated plasma glucose
  - Prothrombotic state
  - Proinflammatory state
  - Elevated homocysteine levels

(Nutrition Care Manual, 2020)
What Causes Metabolic Syndrome?

- A single cause is unclear
- Possible Causes:
  - Abdominal Obesity
  - Insulin Resistance
  - Physical Inactivity
  - Aging
  - Hormonal Imbalance
  - Genetic or ethnic predisposition

(Nutrition Care Manual, 2020)
Diagnosis

- Need to meet at least three of the five following criteria for a clinical diagnosis of metabolic syndrome:
  - Elevated waist circumference
  - Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator)
  - Reduced high-density lipoprotein (HDL) cholesterol (drug treatment for reduced HDL cholesterol is an alternate indicator)
  - Elevated blood pressure (drug treatment for hypertension is an alternate indicator)
  - Elevated fasting glucose (drug treatment of elevated glucose is an alternate indicator)

Nutrition Care Manual, 2020
MNT for Metabolic Syndrome

- Suggest food choices to promote a reduced energy intake
  - Goal: Reduce body weight by 7%-10% within the first year
- Encourage a cardioprotective diet
  - Increase whole grains and fiber
  - Decrease saturated fats, trans fats, and added sugars
- Promote physical activity
  - Goal: At least 30 minutes of activity 5 days per week
- Counseling Support

(Nutrition Care Manual, 2020)
Why probiotics and metabolic syndrome?

- Cardiovascular disease and Type 2 Diabetes are increasing in prevalence
  - Predicted 366 million patients with diabetes by 2030
  - Important healthcare and socioeconomic issue

- *Lactobacillus* and *Bifidobacterium*
  - Anti-inflammatory

(Alihosseini, N. et al., 2017), (Bellikci-Koyu E., 2019)
Lab Value Terms

- **HOMA-IR (Homeostatic Model Assessment of Insulin Resistance)**
  - Optimal Range: 0.5-1.4
  - Serum Insulin x Blood Glucose = HOMA-IR
  - High = insulin resistance

- **QUICKI (Quantitative Insulin Sensitivity Check Index)**
  - Optimal Range: above 0.339
  - $1/[\log(\text{fasting glucose}) + \log(\text{fasting insulin})]$
  - Low = insulin resistance

- **Homocysteine**
  - Protein synthesis
  - Broken down by Vitamin B12, B6 and folic acid
  - High = Greater risk for heart disease, inadequate vitamin B12, B6 or folic acid

Effects of Regular Kefir Consumption on Gut Microbiota in Patients with Metabolic Syndrome: A Parallel-Group, Randomized Controlled Study

Izmir, Turkey

Published in 2019

Study 1

**Purpose:** To investigate the effects of regular kefir consumption on gut microbiota composition and their relationship to the components of metabolic syndrome

**Study Type:** Randomized, Controlled Clinical Trial

**Intervention:**
- 22 participants were randomly allocated into two groups
  - Group 1: Consumed 180 mL/day of Kefir
  - Group 2: Consumed 180 mL/day of Unfermented Milk
Study 1:
Criteria

**Inclusion**
- 18-65 years old
- Diagnosed with metabolic syndrome

**Exclusion**
- Use of antibiotics in the past month or during the intervention period
- Use of probiotic, prebiotic or symbiotic supplements during the past three months or during the intervention
- Pregnant or lactating
- Severe liver, kidney, heart or immune deficiency
- Chronic gastrointestinal system diseases, type 1 diabetes or cancer
- Dairy allergy or lactose intolerance
- Currently taking prescribed drugs that modify lipid profile or glycemic control
- Non-compliance with the consumption of test drinks
**Timeframe**

- **Screening Period**
  - Screening for inclusion and exclusion criteria
  - Assessing dietary intake
  - Anthropometric measurements
  - Baseline blood and fecal samples
  - Information about consumption and storage of test drinks for participants

- **Week 0**
  - Participants begin consuming test drinks

- **Week 1**
  - Assessment of compliance

- **Week 4 & Week 8**
  - Assessment of dietary intake
  - Anthropometric measures
  - Final blood and fecal samples

- **Week 12**

- **End of Study**
Table 2. Dietary intake, anthropometrical measurements, biochemical parameters, and blood pressure in kefir and unfermented milk groups.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Kefir Group</th>
<th>Unfermented Milk Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Week 12</td>
</tr>
<tr>
<td><strong>Dietary intake</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Energy (kcal/day)</td>
<td>1694.16</td>
<td>1995.73</td>
</tr>
<tr>
<td>(1590.92−1936.72)</td>
<td>(1567.23−2351.80)</td>
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<tr>
<td>Carbohydrate (%)</td>
<td>44.00</td>
<td>42.50</td>
</tr>
<tr>
<td>(38.00−45.75)</td>
<td>(37.55−48.75)</td>
<td></td>
</tr>
<tr>
<td>Protein (%)</td>
<td>16.50</td>
<td>13.50</td>
</tr>
<tr>
<td>(15.25−19.00)</td>
<td>(12.00−18.50)</td>
<td></td>
</tr>
<tr>
<td>Fat (%)</td>
<td>39.50</td>
<td>41.00</td>
</tr>
<tr>
<td>(37.00−44.75)</td>
<td>(38.00−46.00)</td>
<td></td>
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<tr>
<td>Fibre (g)</td>
<td>26.11</td>
<td>26.81</td>
</tr>
<tr>
<td>(18.42−36.90)</td>
<td>(21.58−32.65)</td>
<td></td>
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<tr>
<td><strong>Anthropometrical measurements</strong></td>
<td></td>
<td></td>
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<tr>
<td>Weight (kg)</td>
<td>84.05</td>
<td>83.50</td>
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<tr>
<td>(69.23−88.78)</td>
<td>(66.90−88.75)</td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>30.67</td>
<td>30.58</td>
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<tr>
<td>(26.94−34.66)</td>
<td>(26.24−34.31)</td>
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<tr>
<td>Body fat mass (%)</td>
<td>37.05</td>
<td>35.85</td>
</tr>
<tr>
<td>(31.32−44.05)</td>
<td>(30.58−44.23)</td>
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<tr>
<td>Waist circumference (cm)</td>
<td>100.50</td>
<td>102.25</td>
</tr>
<tr>
<td>(90.75−110.00)</td>
<td>(102.25−119.00)</td>
<td></td>
</tr>
<tr>
<td>Hip circumference (cm)</td>
<td>111.50</td>
<td>110.00</td>
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<tr>
<td>(106.00−116.50)</td>
<td>(106.25−118.63)</td>
<td></td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.92 (0.86−0.99)</td>
<td>0.92 (0.86−0.95)</td>
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<tr>
<td><strong>Lipid profile</strong></td>
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<td></td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>243.50</td>
<td>222.00</td>
</tr>
<tr>
<td>(217.25−265.25)</td>
<td>(201.25−275.00)</td>
<td></td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>45.00</td>
<td>46.00</td>
</tr>
<tr>
<td>(39.00−55.75)</td>
<td>(41.00−63.00)</td>
<td></td>
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<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>154.50</td>
<td>144.00</td>
</tr>
<tr>
<td>(135.75−177.00)</td>
<td>(116.50−188.75)</td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>185.00</td>
<td>152.50</td>
</tr>
<tr>
<td>(114.50−216.75)</td>
<td>(116.50−191.25)</td>
<td></td>
</tr>
<tr>
<td>Homocysteine (µmol/L)</td>
<td>10.01</td>
<td>9.31</td>
</tr>
<tr>
<td>(8.64−12.40)</td>
<td>(7.45−12.70)</td>
<td></td>
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<tr>
<td><strong>Glycaemic status</strong></td>
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<td></td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>105.00</td>
<td>100.50</td>
</tr>
<tr>
<td>(93.75−109.75)</td>
<td>(96.50−103.00)</td>
<td></td>
</tr>
<tr>
<td>Insulin (mU/L)</td>
<td>15.94</td>
<td>13.64</td>
</tr>
<tr>
<td>(11.75−17.64)</td>
<td>(7.33−16.36)</td>
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</tr>
<tr>
<td>HbA1C (%)</td>
<td>5.60</td>
<td>5.65</td>
</tr>
<tr>
<td>(5.25−5.88)</td>
<td>(5.50−5.98)</td>
<td></td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>4.18</td>
<td>3.42</td>
</tr>
<tr>
<td>(2.86−4.59)</td>
<td>(1.93−4.22)</td>
<td></td>
</tr>
<tr>
<td>Characteristics</td>
<td>Kefir Group</td>
<td>Unfermented Milk Group</td>
</tr>
<tr>
<td>-----------------</td>
<td>------------</td>
<td>------------------------</td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>Week 12</td>
</tr>
<tr>
<td>Inflammation-related indicators</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hs-CRP (mg/dL)</td>
<td>0.22 (0.69–0.80)</td>
<td>0.16 (0.10–0.46)</td>
</tr>
<tr>
<td>TNF-α (pg/mL)</td>
<td>12.01 (0.76–43.05)</td>
<td>1.13 (0.49–8.33)</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td>15.82 (11.52–29.75)</td>
<td>13.47 (5.65–21.39)</td>
</tr>
<tr>
<td>IL-10 (pg/mL)</td>
<td>4.38 (1.13–32.90)</td>
<td>1.91 (1.13–14.77)</td>
</tr>
<tr>
<td>IFN-γ (IU/mL)</td>
<td>1.23 (0.12–2.19)</td>
<td>0.38 (0.04–0.85)</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>18.50 (16.50–24.00)</td>
<td>22.00 (19.50–24.00)</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>19.00 (18.00–20.00)</td>
<td>19.00 (17.00–22.50)</td>
</tr>
<tr>
<td>GGT (U/L)</td>
<td>15.00 (10.75–23.00)</td>
<td>14.50 (12.00–23.75)</td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>134.50 (115.25–140.50)</td>
<td>118.00 (103.25–137.75)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>85.00 (77.50–92.00)</td>
<td>78.50 (69.00–80.00)</td>
</tr>
</tbody>
</table>

TNF-α = Tumor Necrosis Factor alpha
IFN-γ = Interferon gamma
Strengths and Limitations

**Strengths:**
- 12 Week study
- Objective measurement of data

**Limitations:**
- Small number of participants
- Attrition Rate: 55%
Conclusions

- Kefir could provide some improvements
  - Glycemic status
  - Inflammation-related indicators
  - Blood pressure
- None of the improvements are significant when compared to unfermented milk consumption
- Actinobacteria increased in the Kefir group compared to baseline, but unfermented milk produced a similar change
- **Overall:** Kefir may help improve parameters of metabolic syndrome, but unfermented milk produced a similar result.
- **Neutral Rating**
The effect of daily fortified yogurt consumption on weight loss in adults with metabolic syndrome: A 10-week randomized controlled trial

Shiraz, Iran

2018

Study 2

**Purpose:** To determine the effects of daily consumption of a probiotic fortified yogurt on weight loss in overweight and obese patients with metabolic syndrome on a calorie restricted diet

**Study Type:** Randomized, Controlled Clinical Trial

**Intervention:**
- 87 participants were randomly allocated into two groups
  - Group 1: Consumed 500 g/day fortified yogurt
  - Group 2: Consumed 500 g/day low-fat plain yogurt
**Criteria**

**Inclusion**
- Have metabolic syndrome
- 20-65 years old
- BMI 25-34.9 kg/m^2

**Exclusion**
- Pregnant or breastfeeding
- Antibiotic use
- Cigarette smoking and regular alcohol consumption
- Vitamin, mineral or Omega-3 supplementation
- Regular consumers of yogurt and probiotic products
- Weight loss greater than 10% of body weight within 6 months before the study
- Recent change in physical activity level
Design

- Participants instructed to consume 500 calories less than their calculated energy needs
- Participants consumed fortified or plain yogurt twice daily
  - Fortified Yogurt:
    - Whey protein, calcium, vitamin D, prebiotic fiber and probiotic cultures
  - Yogurts were isocaloric
  - A daily reminder was sent to consume the yogurt
  - Participants had to return the empty yogurt containers
- Anthropometric and Biochemical data was taken three times
  - Baseline, week 5 and week 10
Results

Table 4: Body Composition and metabolic measures at baseline and 10 weeks in overweight adults with metabolic syndrome

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P-value&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mass (kg)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body fat percent (%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fat free mass</td>
<td>0.077</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>0.034</td>
</tr>
<tr>
<td>FBS (mg/dl)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Insulin (mU/l)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>QUICKI</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dL)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>25(OH)D (nmol/l)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

P-value<sup>a</sup> = Difference from baseline for the fortified yogurt group
P-value<sup>b</sup> = Different between groups
Strengths and Limitations

**Strengths**
- High adherence to consuming the yogurt in both groups
  - Attrition Rate: 96.7%
- Very specific composition of the fortified yogurt

**Limitations**
- Short duration of the study
- Did not look at differences between males and females in the study
- Calorie-restricted conditions
  - Unknown fortified yogurt would help under normal circumstances
Conclusions

- Consumption of fortified yogurt may:
  - Reduce fat mass
  - Preserve lean body mass
  - Improve insulin sensitivity
  - Improve triglyceride and HDL-C levels

- Only studied in overweight and obese individuals on a calorie restricted diet

- Diet and exercise are still important

- Positive Rating
Study 3

Effect of probiotic fermented milk (Kefir) on serum level of insulin and homocysteine in type 2 diabetes patients

Tabriz, Iran
2017

**Purpose:** To investigate the effect of probiotic fermented milk on serum level of insulin and homocysteine in type 2 diabetes patients

**Study Type:** Randomized, Double-blind, Placebo-Controlled Clinical Trial

**Intervention:**
- 60 participants were randomly allocated into two groups
  - Group 1: Consumed 600 mL/day probiotic fermented milk
  - Group 2: Consumed 600 mL/day conventional fermented milk (sourdough)
Criteria

**Inclusion**
- Diagnosed with type 2 diabetes
  - Fasting blood glucose $\geq 125$ mg/dL
- Age 35-65 years old
- No insulin therapy
- Illness duration less than 20 years

**Exclusion**
- Pregnancy or breastfeeding
- Conventional medical disorders
  - Thyroid, gastrointestinal, cardiovascular, kidney, autoimmune systems diseases
- Cigarette smoking
- Use of steroidal anti-inflammatory drugs
- Vitamin and mineral use
- Hormone replacement therapy
Design

- Products were consumed twice daily for 8 weeks
  - Supply received weekly
  - Probiotic fermented milk (kefir)
    - *Streptococcus thermophiles, Lactobacillus casei, Lactobacillus acidophilus* and *Bifidobacterium lactis*
  - Conventional fermented milk (dough)
    - *Streptococcus thermophiles* and *Lactobacillus bulgaricus*

- Participants were instructed to:
  - Maintain usual dietary intake
  - Lifestyle
  - Non-probiotic containing vitamin and mineral supplements
  - Medications

- Anthropometrics and fasting blood glucose
  - measured at baseline and end
### Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>Period of study</th>
<th>Probiotic group (Mean±SD) (n=30)</th>
<th>Conventional group (Mean±SD) (n=30)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin (micro IU/mL)</td>
<td>Baseline</td>
<td>16.80±9.58</td>
<td>13.74±5.69</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>After intervention</td>
<td>14.41±4.46</td>
<td>14.48±8.65</td>
<td>0.05</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>Baseline</td>
<td>7.05±4.83</td>
<td>6.30±3.03</td>
<td>0.17</td>
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<tr>
<td></td>
<td>After intervention</td>
<td>4.93±1.81</td>
<td>7.38±4.94</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Quicki</td>
<td>Baseline</td>
<td>0.29±0.22</td>
<td>0.29±0.18</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td>After intervention</td>
<td>0.30±0.15</td>
<td>0.29±0.24</td>
<td>0.07</td>
</tr>
</tbody>
</table>

*p paired t-test.  
Independent sample t-test.
### Results

Table 4. Effect of probiotic fermented milk (kefir) and conventional fermented milk on serum level of homocysteine

<table>
<thead>
<tr>
<th>Variable</th>
<th>Period of study</th>
<th>Probiotic group (Mean±SD) (n=30)</th>
<th>Conventional group (Mean±SD) (n=30)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homocysteine (µmol/L)</td>
<td>Baseline</td>
<td>8.91±2.42</td>
<td>8.53±3.27</td>
<td>0.23</td>
</tr>
<tr>
<td></td>
<td>After intervention</td>
<td>7.35±2.18</td>
<td>6.91±2.10</td>
<td>0.88</td>
</tr>
<tr>
<td>p</td>
<td></td>
<td>&lt;0.001</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Mean difference</td>
<td></td>
<td>1.55</td>
<td>1.61</td>
<td></td>
</tr>
</tbody>
</table>

A paired t-test. B independent sample t-test.

Table 5. Effect of probiotic fermented milk and conventional fermented milk on BMI index

<table>
<thead>
<tr>
<th>Variable</th>
<th>Period of study</th>
<th>Probiotic group (Mean±SD) (n=30)</th>
<th>Conventional group (Mean±SD) (n=30)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>Baseline</td>
<td>28.74±4.75</td>
<td>27.30±3.64</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>After intervention</td>
<td>28.18±4.77</td>
<td>27.47±3.55</td>
<td>0.25</td>
</tr>
<tr>
<td>p</td>
<td></td>
<td>0.29</td>
<td>0.97</td>
<td></td>
</tr>
</tbody>
</table>

A paired t-test. B independent sample t-test.
Strengths and Limitations

**Strengths**
- Participant adherence rate
  - Attrition Rate: 100%
- Clinical trial
- Controlled for BMI and Duration of type 2 diabetes

**Limitations**
- Short duration
- Did not track total energy intake
Fermented milk fortified with certain probiotics can:
- Decrease insulin serum level
- Decrease HOMA-IR
- Decrease serum level of homocysteine

Only the decrease in HOMA-IR and serum insulin level were significant between the two groups.

No affect on BMI

Positive Rating
<table>
<thead>
<tr>
<th>Study</th>
<th>Serum Insulin Reduction</th>
<th>HOMA-IR Reduction</th>
<th>Homocysteine Reduction</th>
<th>QUICKI Increase</th>
<th>BMI Reduction</th>
<th>Blood Pressure Reduction</th>
<th>Triglyceride Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>N/A</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>+*</td>
<td>+*</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+*</td>
</tr>
<tr>
<td>3</td>
<td>+*</td>
<td>+*</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**Key:**
* Effect of probiotic fortified item significantly reduced metabolic syndrome compared to conventional fermented item
+ Probiotic fortified item significantly reduced metabolic syndrome risk factor
- Probiotic fortified item did not significantly reduce metabolic syndrome risk factor
Implications for the Profession

- Probiotic fortified fermented products are beneficial for reducing the risk factors for metabolic syndrome.
- Non-probiotic fortified fermented products are also shown to reduce metabolic syndrome risk factors.
- Risk factors are interconnected and influenced by microbiome.
- Addition of probiotics to hospital menus and handouts.
Take Home Message

- More research needs to be done
- Keep up to date with evolving research
- Recommend probiotics and fermented foods
References

Questions?