Probiotic B420 and Body Weight Regulation

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Outline

- The clinical issue—obesity
- Microbiome and body weight regulation
- Development pathway of probiotic strain B420
- B420 mechanisms of action
- Clinical data with B420

The clinical issue—obesity

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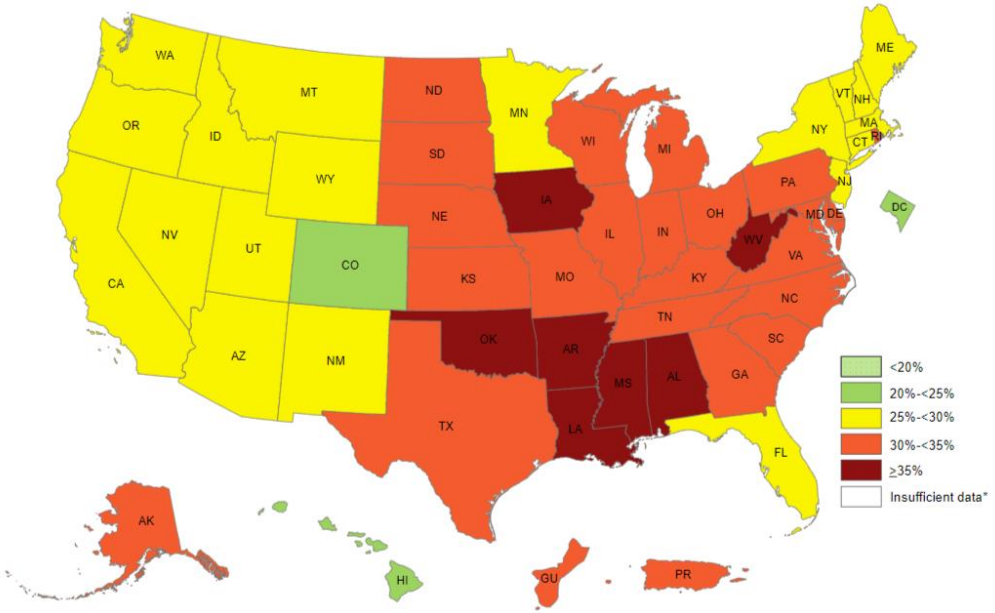
The clinical issue

The prevalence of obesity (BMI >30kg/m^2) is ~40% in US adults

- Non-Hispanic blacks (46.8%)
- Hispanics (40%)
- Non-Hispanic whites (37.9%)
- Non-Hispanic Asians (12.7%)



US Adult Obesity Rate, 2017

CDC. https://www.cdc.gov/obesity/data/adult.html. Accessed July 22, 2019.

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Obesity and the practitioner

Survey* reveals that more than 50% of their patient population suffers from obesity

What percent of your patient population has a BMI > 30?	What percent of your patient population suffers from chronic conditions due to obesity?	How many of your patients have you assisted in losing between 10-20 lbs?	How many of your patients have you assisted in losing between 25-30 lbs?	How many of your patients have you assisted in losing between 25-30 lbs?	How many patients have you treated this year, in part or full, with a medically supervised weight loss program?	How many of your weight loss patients have you achieved success with?	Of the patients in question #7, how long did they maintain their weight loss goals?	Did you utilize Healthy Transformation for any of your weight loss patients?
6 stated 50% or more Of patients have BMI > 30	4 stated 50% or more	6 stated 50% or more	4 stated 50% or more	4 stated 50% or more	All CC members have treated range 50- 250 patients	100% achieved success	8 stated that success lasted 1 year or more	7 stated they do not use HT
4 stated 20%	6 stated 20%	4 stated 20% between 20%-40%	6 stated 20% between 15%-40%	6 stated 20% between 10%-40%			2 stated weight loss lasted between 1-3 months	3 stated they use HT

*From a small internal survey of 10 practitioners

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Obesity is a driver of chronic disease—Benefits of modest weight loss

Obesity complication	Weight loss required for therapeutic benefit (%)	Notes
Diabetes (prevention)	3-10	Maximum benefit at 10%
Hypertension	5 to >15	Blood pressure still decreasing at >15%
Dyslipidemia	3 to >15	Triglycerides still decreasing at >15%
Hyperglycemia (elevated HbA1c)	3 to >15	HbA1c still decreasing at >15%
NAFLD	10	Improves steatosis, inflammation and mild fibrosis
Sleep apnea	10	Little benefit at 5%
Osteoarthritis	5-10	Improves symptoms and joint stress mechanics
Stress incontinence	5-10	
Gastroesophageal reflex disease	5-10 in women; 10 in men	
Polycystic ovary syndrome	5-15 (>10 optimal)	Lowers androgens, improves ovulation, increases insulin sensitivity

Cefalu WT et al. *Diab Care.* 2015;38(8):1567-1582.

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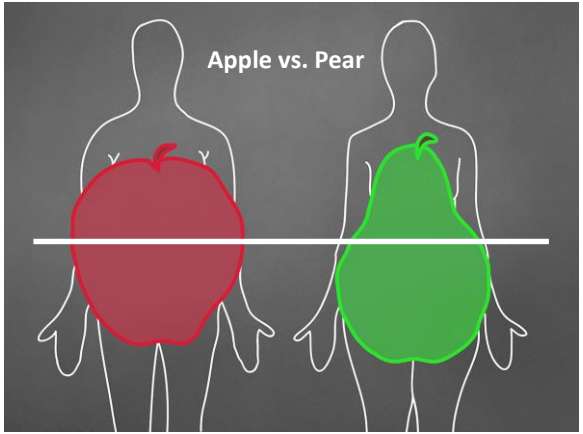
Clinically, waist circumference is a surrogate for disease risk



- Adipose tissue is an endocrine organ. Different depots have different metabolic activity

Visceral and subcutaneous abdominal adipose tissue

↑ Inflammatory cytokines
↓ Adiponectin

Associated with insulin resistance and atherogenic dyslipidemia.

Clinical measure
Waist circumference

Disease Risk

Type 2 diabetes
Heart disease
Hypertension

Bays H. *Curr Opin Endocrinol Diabetes Obes.* 2014;21(5):345–351

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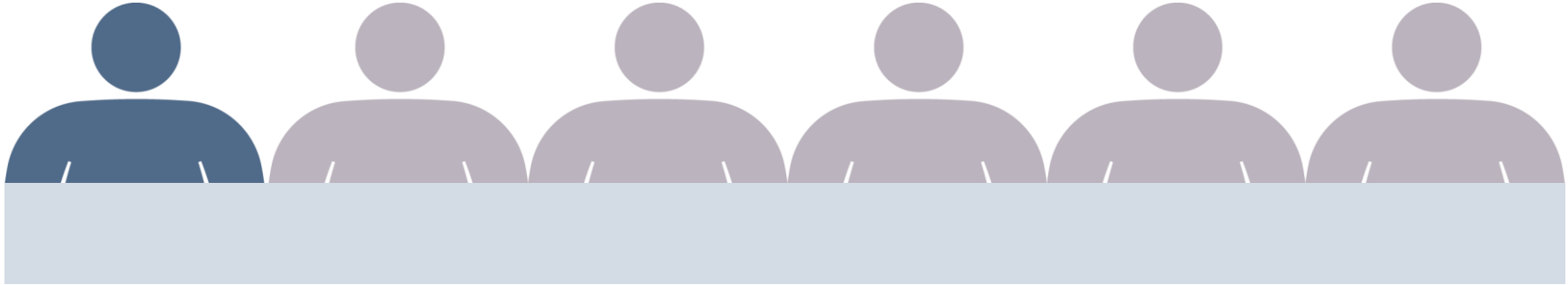
Weight loss maintenance is difficult

Only 1 in 6 overweight or obese US adults report ever having maintained weight loss of at least 10% for 1 year



Kraschnewski JL et al. *Int J Obes (Lond).* 2010;34(11):1644-1654.

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Helsinki Health Study—Slow weight gain over time

30% of the normal middle-aged population gained at least 11 lbs (~5 kg) over the 5-7 year study period

	Women		Men	
		Weight gain ≥11lbs		Weight gain ≥11lbs
Age	*n*	*% [95% CI]*	*n*	*% [95% CI]*
40	1075	34 [31.7-36.9]	208	32 [26.1-37.4]
45	1150	34 [31.0-36.1]	226	33 [27.3-38.2]
50	1198	26 [23.3-28.3]	252	28 [23.0-33.3]
55	1330	21 [18.1-22.8]	361	18 [13.7-22.3]
60	617	34 [10.5-17.4]	205	10 [4.0-15.5]

Loman T et al. *BMC Public Health.* 2013;13:259.

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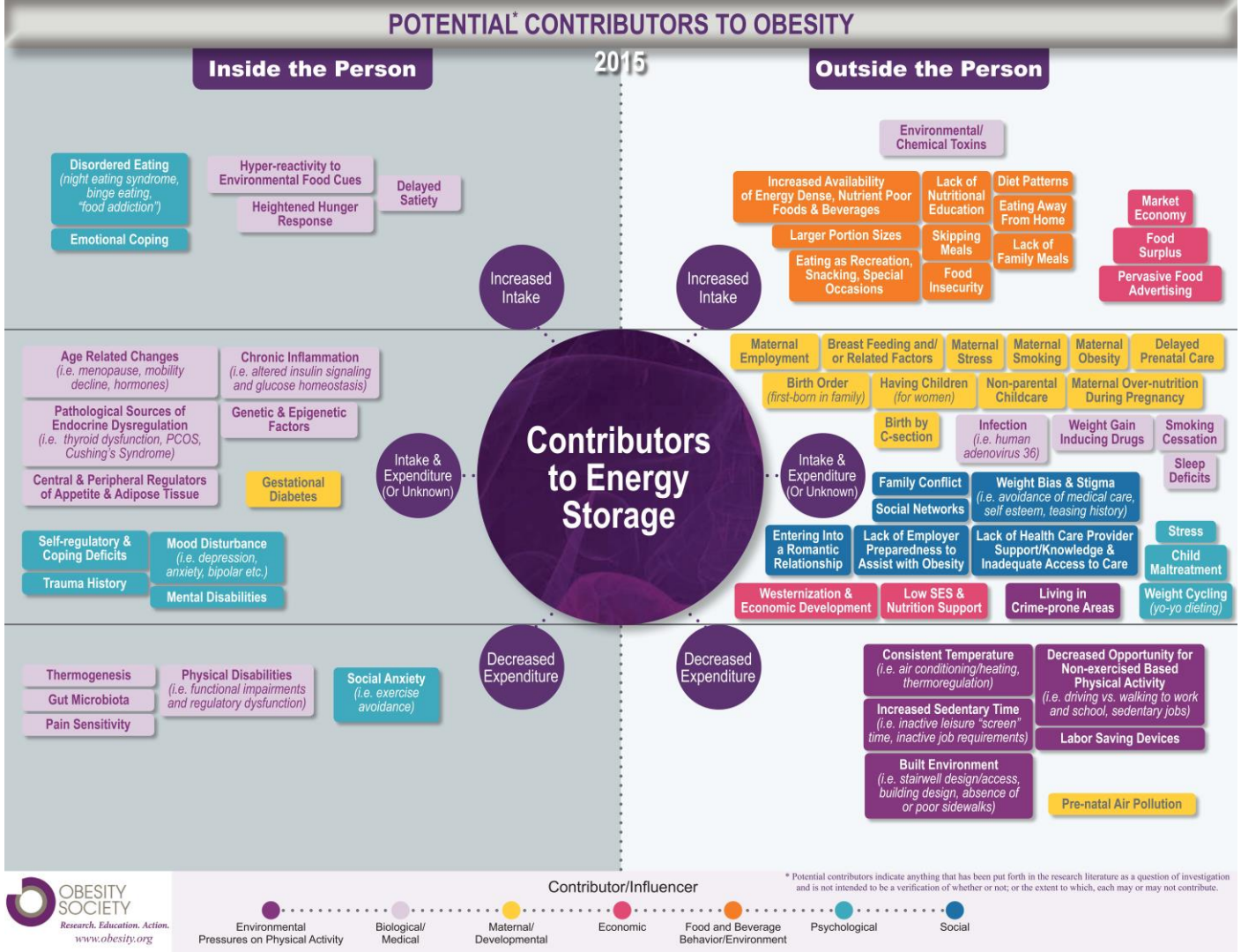

http://www.obesity.org/obesity/resources/facts-about-obesity/infographics/potential-contributors-to-obesity
Accessed February 8, 2017.
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Microbiome and body weight regulation

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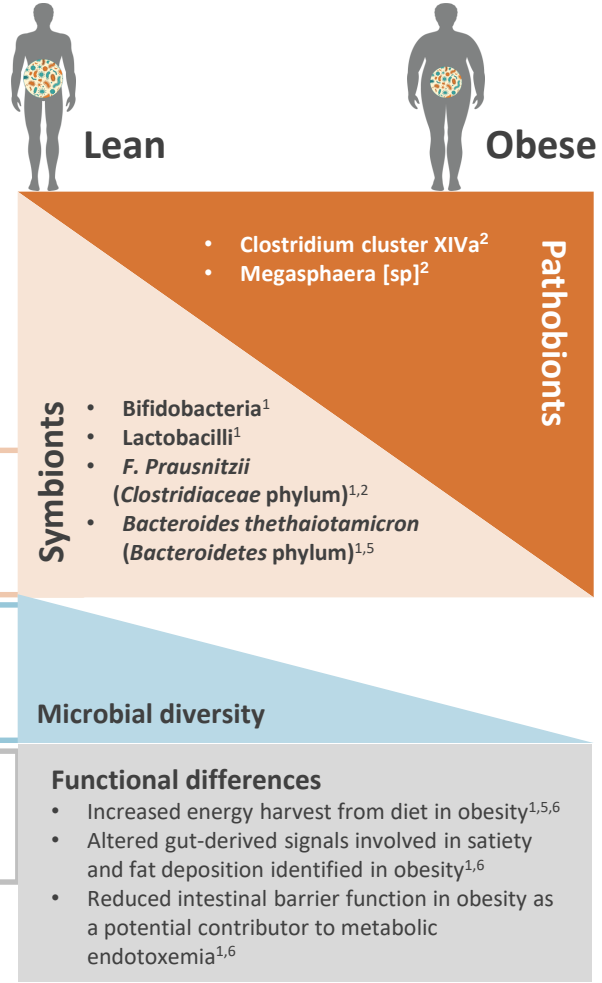
Microbiome and body mass regulation— Differences between lean vs. obese



Microbiota commonly identified in samples from lean and obese individuals differ[4]

A less diverse microbial community has been identified in obesity[4]

Differences in microbial metabolism genes and microbial products affecting host metabolism have been shown in some studies to differ between lean and obese microbiome samples[3,5,6]

1. Boulangé CL et al. *Genome Med.* 2016;8:42.
2. Walters WA et al. *FEBS Lett*. 2014;588(22):4223–4233.
3. Ridaura VK et al. *Science*. 2013;341(6150):1241214.
4. Turnbaugh PJ et al. *Nature*. 2009;457(7228):480–484.
5. Turnbaugh PJ et al. *Nature.* 2006;444(7122):1027-1031.
6. Cox LM et al. *Cell Metab*. 2013;17(6):883-894.

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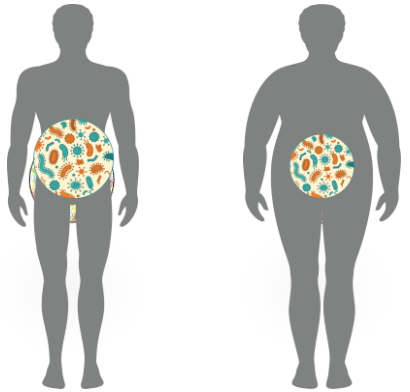
Microbiome and body mass regulation—What is the evidence?

Microbiome samples were taken from female twin pairs discordant for obesity (one lean, one with obesity)

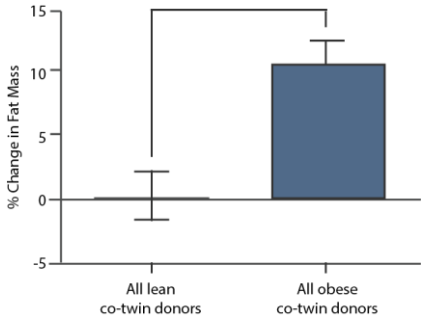


Lean twin

Obese twin

Microbiota transfer

When the human microbiome samples were transferred to mice, those receiving the obese microbiome sample gained significant body fat



Ridaura VK et al. *Science*. 2013;341(6150):1241214.

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Akkermansia muciniphila, obesity, and metabolic disease—The evidence

- Human cohort studies report that abundance of this species is reduced in the microbiomes of individuals with obesity,[1,2] type 2 diabetes (T2D),[1,2] impaired glucose control,[3] and high blood pressure.[4]
- Greater abundance of *Akkermansia muciniphila* is linked with a leaner body weight and lower body fat mass,[5] and greater improvement in insulin sensitivity after caloric restriction.[1]
- Studies in genetic and diet-induced mouse models of obesity and diabetes also show that abundance is reduced.[6-8]
- Roux-en-Y gastric bypass (RYGB) surgery-induced weight loss was shown to increase the abundance of *Akkermansia muciniphila*.[9-11]
- In women following laparoscopic sleeve gastrectomy (LSG), increased *Akkermansia* abundance was associated with reduced hedonic eating, or the drive to eat for pleasure.[12]
- In T2D, treatment with metformin led to an increased abundance.[13-14]

1. Dao MC et al. *Gut.* 2016;65(3):426-436.
2. Yassour M et al. *Genome Med.* 2016;8(1):17.
3. Zhang X et al. *PLoS One.* 2013;8(8):e71108.
4. Li J et al. *Microbiome.* 2017;5(1):14.
5. Fruge AD et al. *J Acad Nutr Diet.* 2018.
6. Everard A et al. *Proc Natl Acad Sci U S A.* 2013;110(22):9066-9071.
7. Everard A et al. *Diabetes.* 2011;60(11):2775-2786.
8. Schneeberger M et al. *Sci Rep.* 2015;5:16643.
9. Yan M et al. *World J Gastrointest Surg.* 2016;8(4):301-307.
10. Liou AP et al. *Sci Transl Med.* 2013;5(178):178ra141.
11. Palleja A et al. *Genome Med.* 2016;8(1):67.
12. Sanmiguel CP et al. *Psychosom Med.* 2017;79(8):880-8870.
13. de la Cuesta-Zuluaga J et al. *Diab Care.* 2017;40(1):54-62.
14. Lee H et al. *Gut Microbes.* 2018;9(2):155-165.

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Summary of microbiome differences

There are three key differences between the microbiomes of lean and obese individuals:

1. **Composition**—Obese individuals tend to have more pathobionts (unwanted or potentially harmful bacteria)[1,2,4]
2. **Diversity**—Obese individuals tend to have a less diverse microbiome[3]
3. **Functionality**—Obese individuals tend to have altered gut-derived signals that impact satiety and fat deposition[1,5]

Akkermansia muciniphila has been identified as a potential therapeutic candidate.[6]

1. Boulangé CL et al. *Genome Med.* 2016;8:42.
2. Walters WA et al. *FEBS Lett*. 2014;588(22):4223–4233.
3. Turnbaugh PJ et al. *Nature*. 2009;457(7228):480–484.
4. Turnbaugh PJ et al. *Nature.* 2006;444(7122):1027-1031.
5. Cox LM et al. *Cell Metab*. 2013;17(6):883-894.
6. Cani PD et al. *Front Microbiol.* 2017;8:1765.

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Bifidobacterium animalis ssp *lactis* 420

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Bifidobacterium	*animalis*	*lactis*	420
Genus	**Species**	**Sub Species**	**Strain**

The complete genome of B420 has been characterized and was published in 2012[1]

Note: The scientific name is *Bifidobacterium animalis* ssp *lactis* 420, abbreviated form is B420

1. Stahl B et al. *J Bacteriol.* 2012;194(15):4131-4132.

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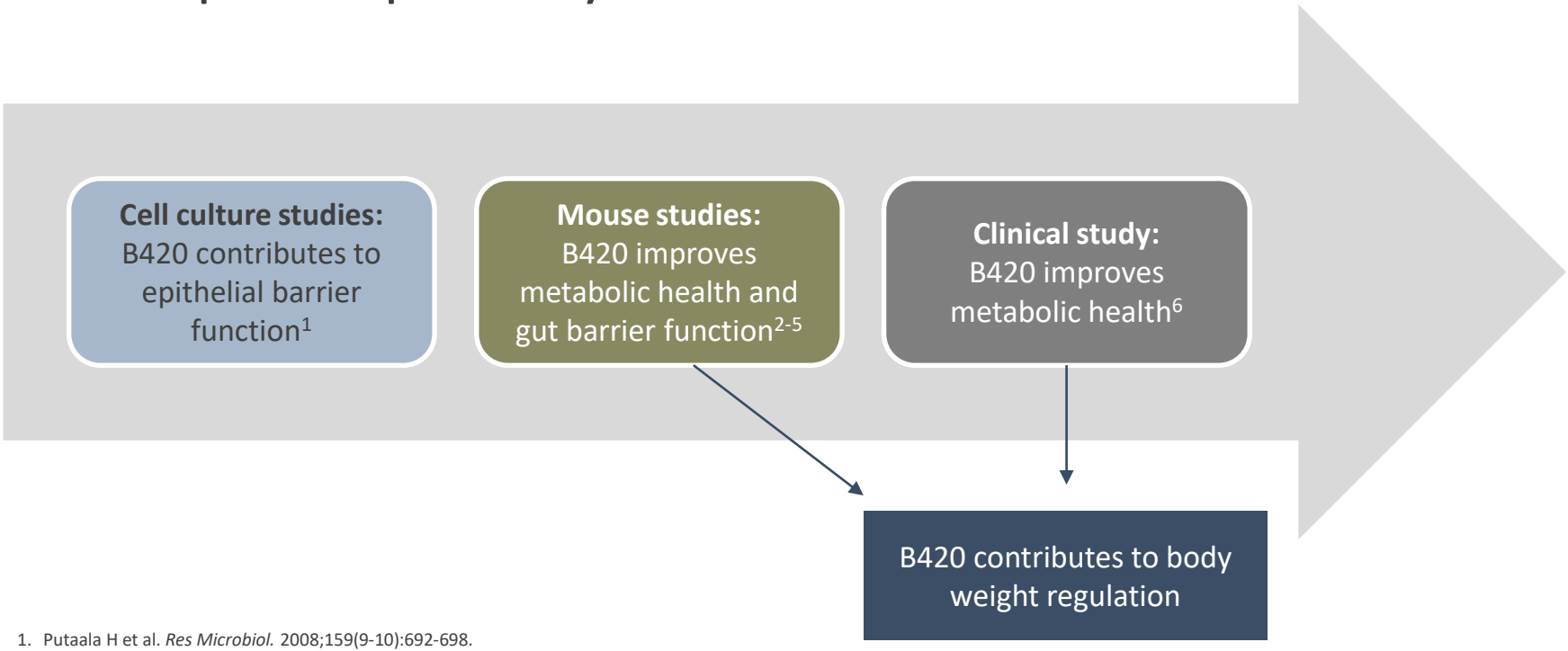
Development pathway of B420



1. Putaala H et al. *Res Microbiol.* 2008;159(9-10):692-698.
2. Amar J et al. *EMBO Mol Med.* 2011;3(9):559-572.
3. Lyra A et al. *Gastroenterol Res Pract*. 2012;615051.
4. Stenman LK et al. *Benef Microbes.* 2014;5(4):437-445.
5. Stenman LK et al. *Diabetol Metab Syndr.* 2015;12(7):75.
6. Stenman LK et al. *EBioMedicine*. 2016;13:190-200.

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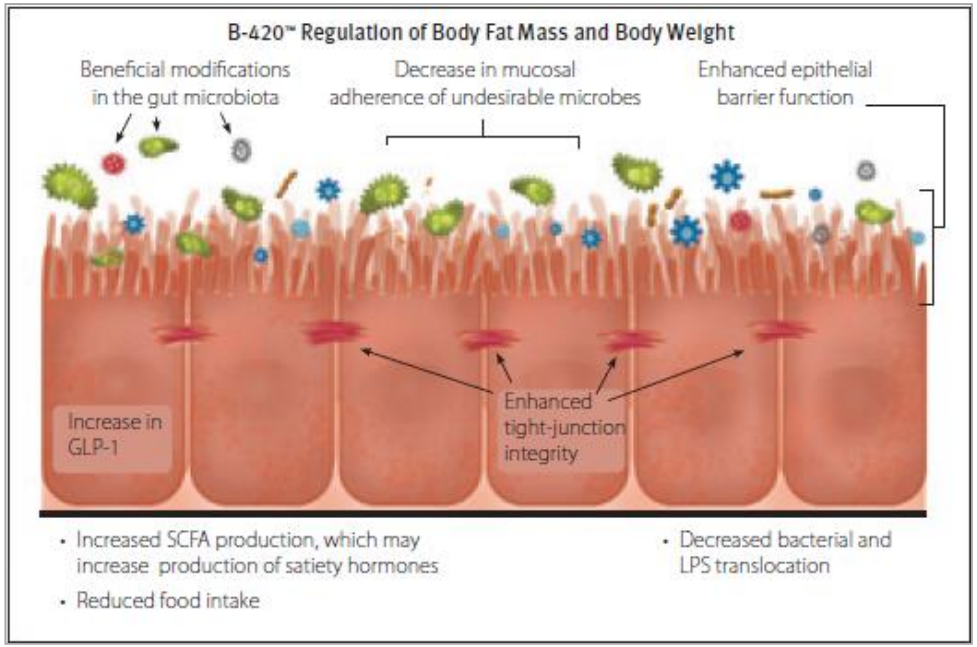
B420 probiotic strain—
Mechanisms of action

All of the actions below are supported by preclinical and/or clinical data with B420



Putaala H et al. *Res Microbiol.* 2008;159(9-10):692-698.
Amar J et al. *EMBO Mol Med.* 2011;3(9):559-572.
Lyra A et al. *Gastroenterol Res Pract*. 2012;615051.
Stenman LK et al. *Benef Microbes.* 2014;5(4):437-445.
Stenman LK et al. *Diabetol Metab Syndr.* 2015;12(7):75.
Stenman LK et al. *EBioMedicine*. 2016;13:190-200.

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Summary of mechanisms of action

Bifidobacterium animalis ssp *lactis* 420 has three key potential mechanisms of action that may explain its effects of reducing energy intake in the clinical study

1. Animal studies demonstrate that B420 may increase levels of the anorectic (appetite-reducing) gut peptide GLP-1[1]
2. The clinical study shows that B420 increases total intestinal short-chain fatty acid concentration,[2] which may promote the production of GLP-1.[3-5]
3. *In vitro* and animal studies demonstrate that B420 may improve gut barrier function,[6-9] which may reduce LPS and bacterial translocation from the gut, which may lower LPS signaling in adipose tissue, reducing the signals associated with weight gain.[10]

1. Stenman LK et al. *Diabetol Metab Syndr*. 2015;12(7):75.
2. Stenman LK et al. *EBioMedicine*. 2016;13:190-200.
3. Tolhurst G et al. *Diabetes*. 2012;61(2):364-371.
4. Psichas A et al. *Int J Obes (Lond).* 2015;39(3):424-429.
5. Lin HV et al. *PLoS One*. 2012;7(4):e35240.
6. Putaala H et al. *Res Microbiol.* 2008;159(9-10):692-698.
7. Lyra A et al. *Gastroenterol Res Pract*. 2012;615051.
8. Amar J et al. *EMBO Mol Med.* 2011;3(9):559-572.
9. Stenman LK et al. *Benef Microbes.* 2014;5(4):437-445.
10. Cox LM et al. *Cell Metabolism*. 2013;17(6):883-894.

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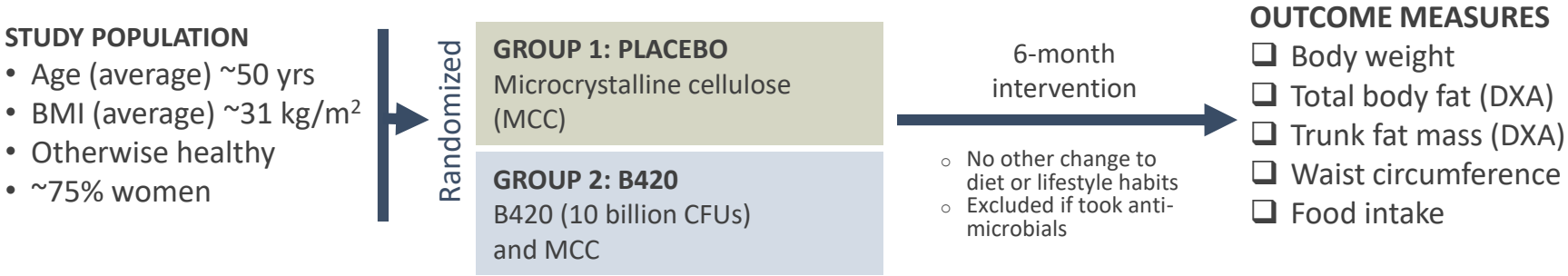
B420 clinical data[1] —
Study design and study population



1. Stenman LK et al. *EBioMedicine*. 2016;13:190-200.

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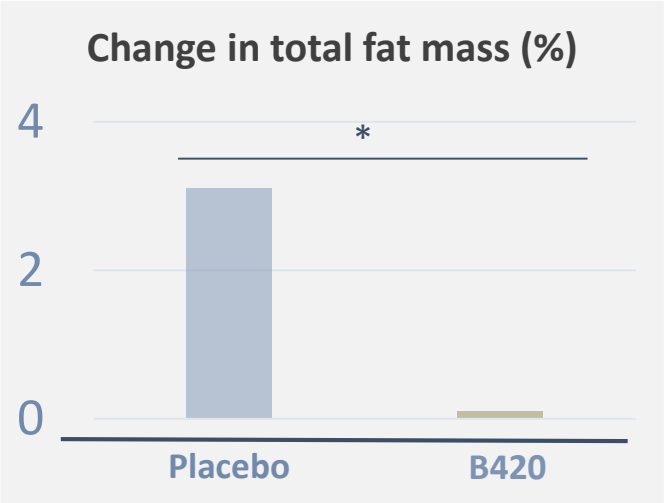
B420 clinical data[1] — Body fat

***Bifidobacterium animalis* ssp. *lactis* 420 helps control body fat**

In a 6-month clinical study of overweight individuals, those taking B420 showed reduced body fat mass compared to placebo group*



1. Stenman LK et al. *EBioMedicine*. 2016;13:190-200.

* Indicates placebo vs. B420 groups significantly different at 6 months ($p<0.05$; per protocol post-hoc analysis)

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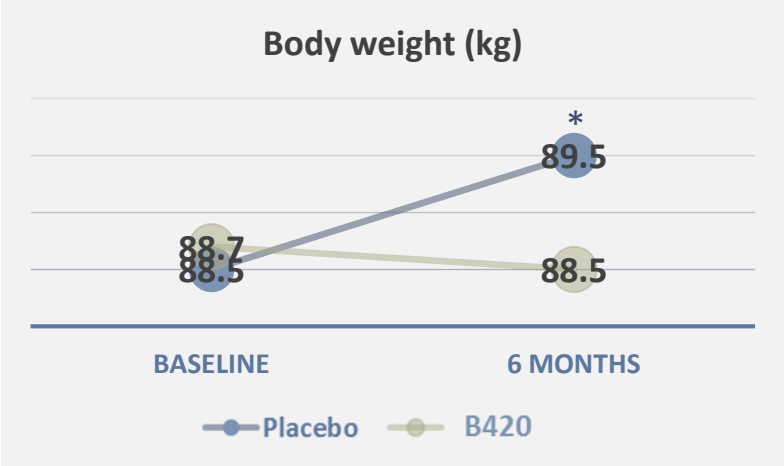
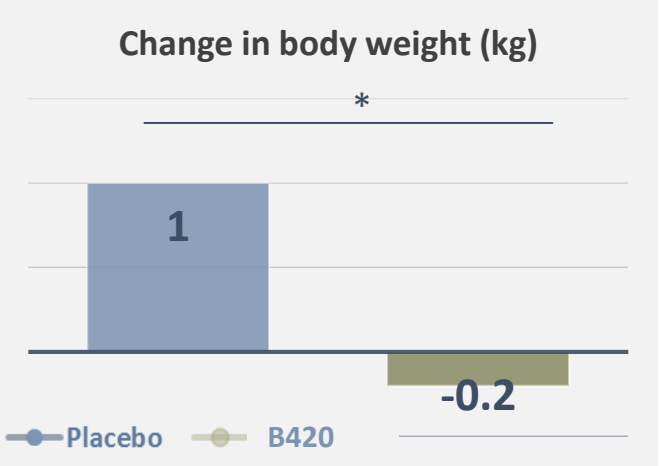
B420 clinical data[1] —
Body weight

- ***Bifidobacterium animalis* ssp. *lactis* 420 helps control body weight and body weight regulation**
- Preliminary evidence shows that B420 may **help contribute to long-term weight maintenance**





1. Stenman LK et al. *EBioMedicine*. 2016;13:190-200.

* Indicates placebo vs. B420 groups significantly different at 6 months ($p<0.05$; per protocol post-hoc analysis)

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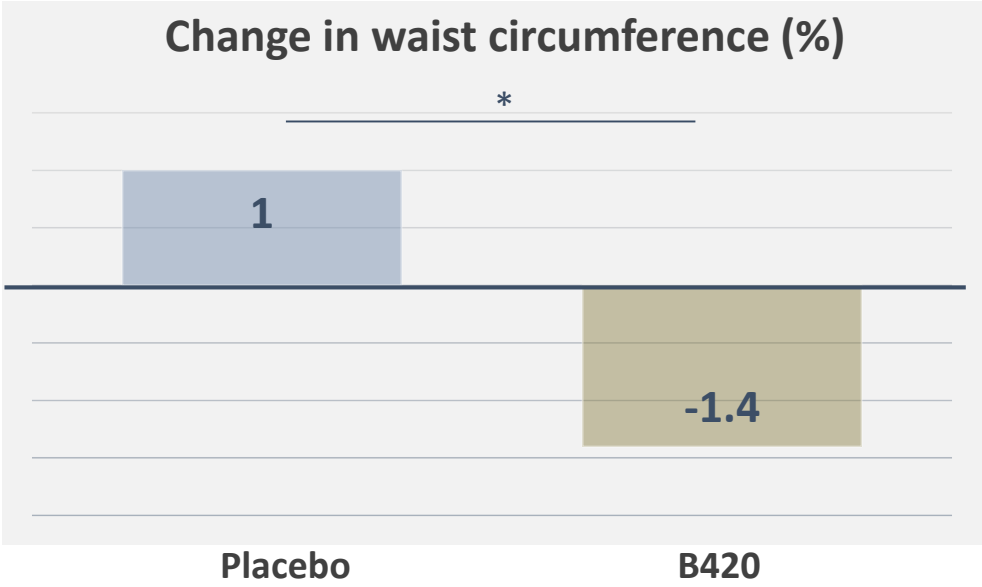
B420 clinical data[1] —
Waist circumference

***Bifidobacterium animalis* ssp. *lactis* 420 helps reduce waist circumference**

In a 6-month clinical study of overweight individuals, those taking B420 showed reduced waist circumference compared to placebo group*



1. Stenman LK et al. *EBioMedicine*. 2016;13:190-200.

* Indicates placebo vs. B420 groups significantly different at 6 months ($p<0.05$; per protocol post-hoc analysis)

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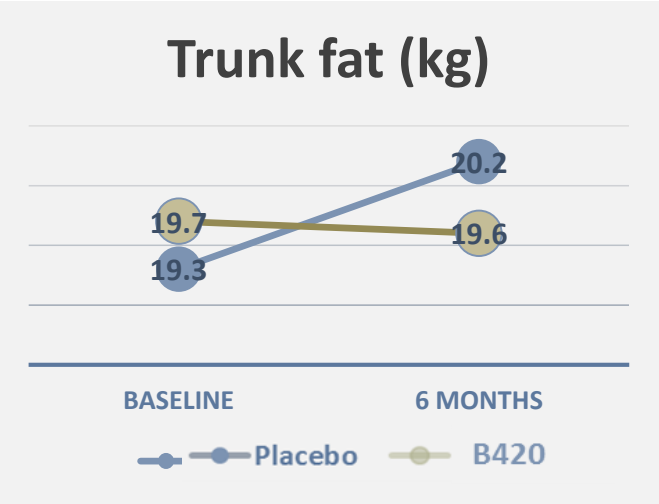
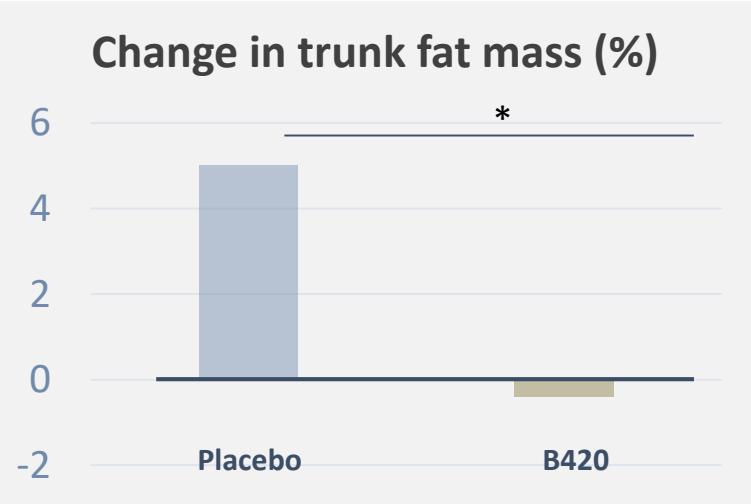
B420 clinical data[1] — Abdominal fat

***Bifidobacterium animalis* ssp. *lactis* 420 helps control abdominal fat**

In a 6-month clinical study of overweight individuals, those taking B420 showed reduced abdominal fat compared to placebo group*





1. Stenman LK et al. *EBioMedicine*. 2016;13:190-200.

* Indicates placebo vs. B420 groups significantly different at 6 months ($p<0.05$; per protocol post-hoc analysis)

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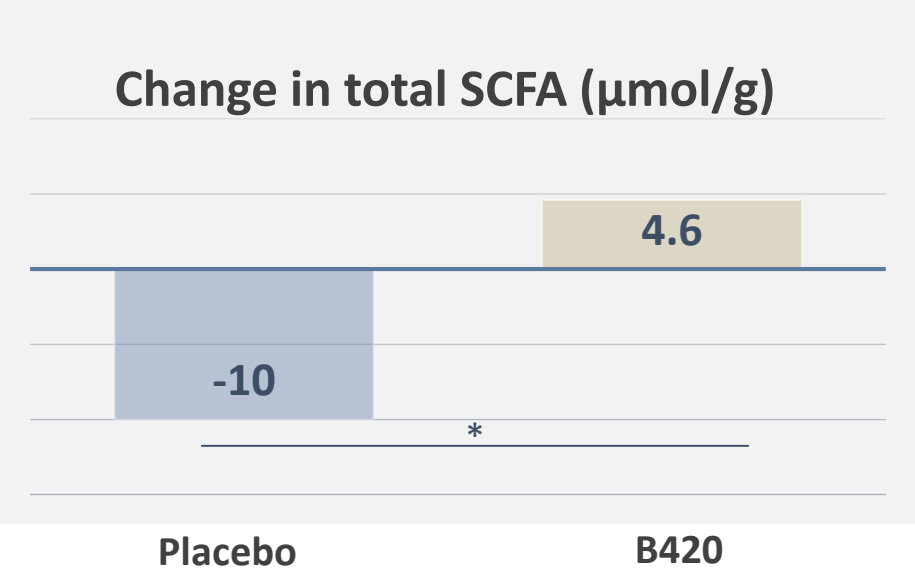
B420 clinical data[1]—
Short-chain fatty acids

***Bifidobacterium animalis* ssp. *lactis* 420 promotes short chain fatty acid (SCFA) production**

In a 6-month study of overweight individuals, those taking B420 showed increased concentrations of short-chain fatty acids (SCFA)*



- ✓ **SCFA are produced by the microbiota**
- ✓ **Change in SCFA concentration indicates altered metabolism and changes in the composition of the gut microbiota[1]**
- ✓ **SCFA have been shown to activate satiety signaling in the intestine**

1. Stenman LK et al. *EBioMedicine*. 2016;13:190-200.

* Indicates placebo vs. B420 groups significantly different at 6 months ($p<0.05$; per protocol post-hoc analysis)

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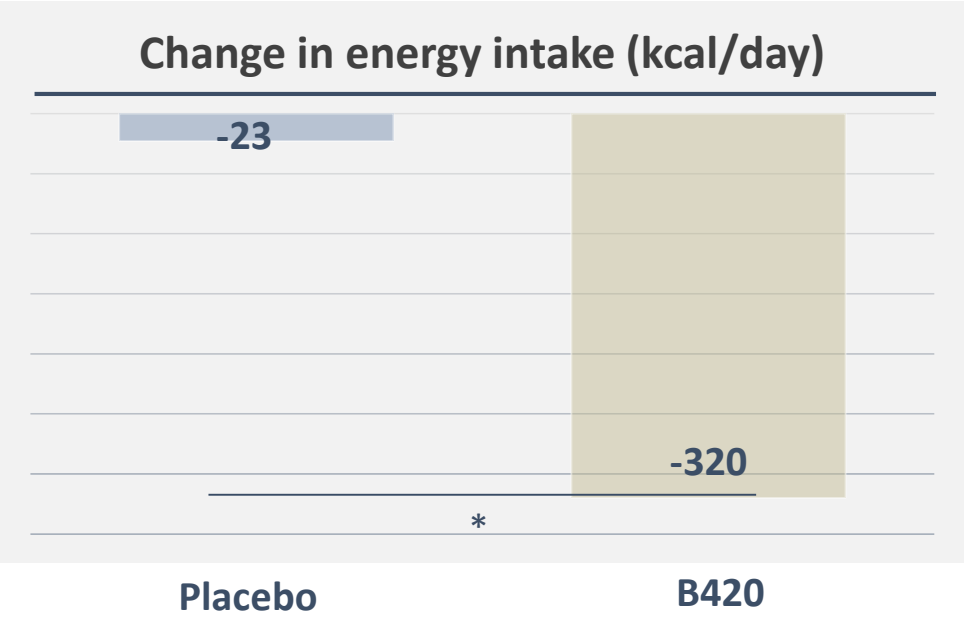
B420 clinical data[1]—

Energy intake

In a 6-month study of overweight individuals, those taking B420 showed reduced energy intake



1. Stenman LK et al. *EBioMedicine* 2016;13:190-200.

* Indicates placebo vs. B420 groups significantly different at 6 months ($p<0.05$; per protocol post-hoc analysis)

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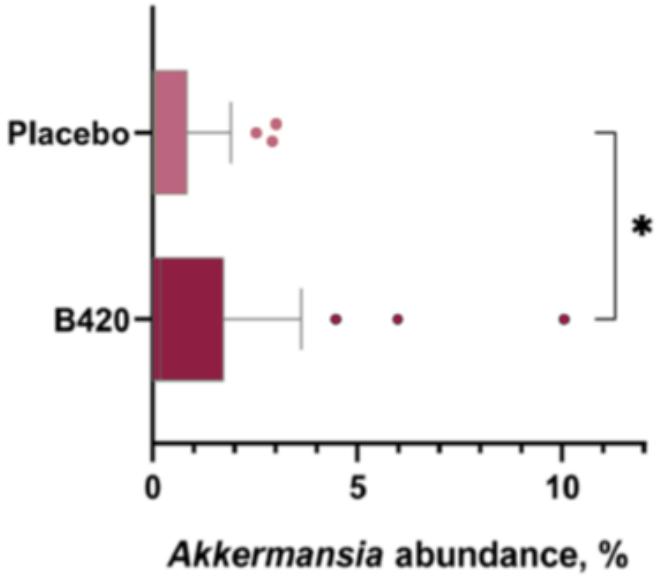
B420 clinical data[1] — Changes to *Akkermansia muciniphila*

- The abundance of *Akkermansia muciniphila* increased significantly in feces in the B420-supplemented group compared to placebo controls at the 6 month time point only (see Figure).[1]
- After 6-months of B420 supplementation, the relative mean *Akkermansia* abundance increased 73%. The relative mean abundance of *Akkermansia* abundance in the B420-supplemented group was 88% higher than that of the placebo group at the 6-month time point.[1]
- Since a recent review of the literature,[2] this current publication is the first human clinical study to demonstrate that a particular probiotic strain, specifically B420, increased *Akkermansia* in the human intestine.[1]



Adapted from: Hibberd AA et al. *Benef Microbes*. 2019;10(2):121-135.

1. Hibberd AA et al. *Benef Microbes*. 2019;10(2):121-135.
2. Zhou K. *J Funct Foods.* 2017;33:194-201.

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Key takeaways

- Obesity prevalence is of epidemic proportions, and healthcare practitioners need any and all tools to combat obesity.
- Over the past decade, increasing evidence has linked the intestinal microbiome with regulation of body weight and body fat mass
- Pre-clinical work with the probiotic strain *Bifidobacterium animalis* ssp. *lactis* 420 improved the following:
  1. Intestinal barrier function
  2. Satiety signaling
  3. Body weight and body fat regulation

- A 6-month clinical study showed that B420:
  - ✓ **Helps control abdominal fat and body weight**
  - ✓ **Helps reduce waist circumference**
  - ✓ **Promotes short chain fatty acid (SCFA) production**
  - ✓ **Reduces energy intake**
  - ✓ **Increases *Akkermansia muciniphila***

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