

The Gut Microbiome and Multiple Sclerosis

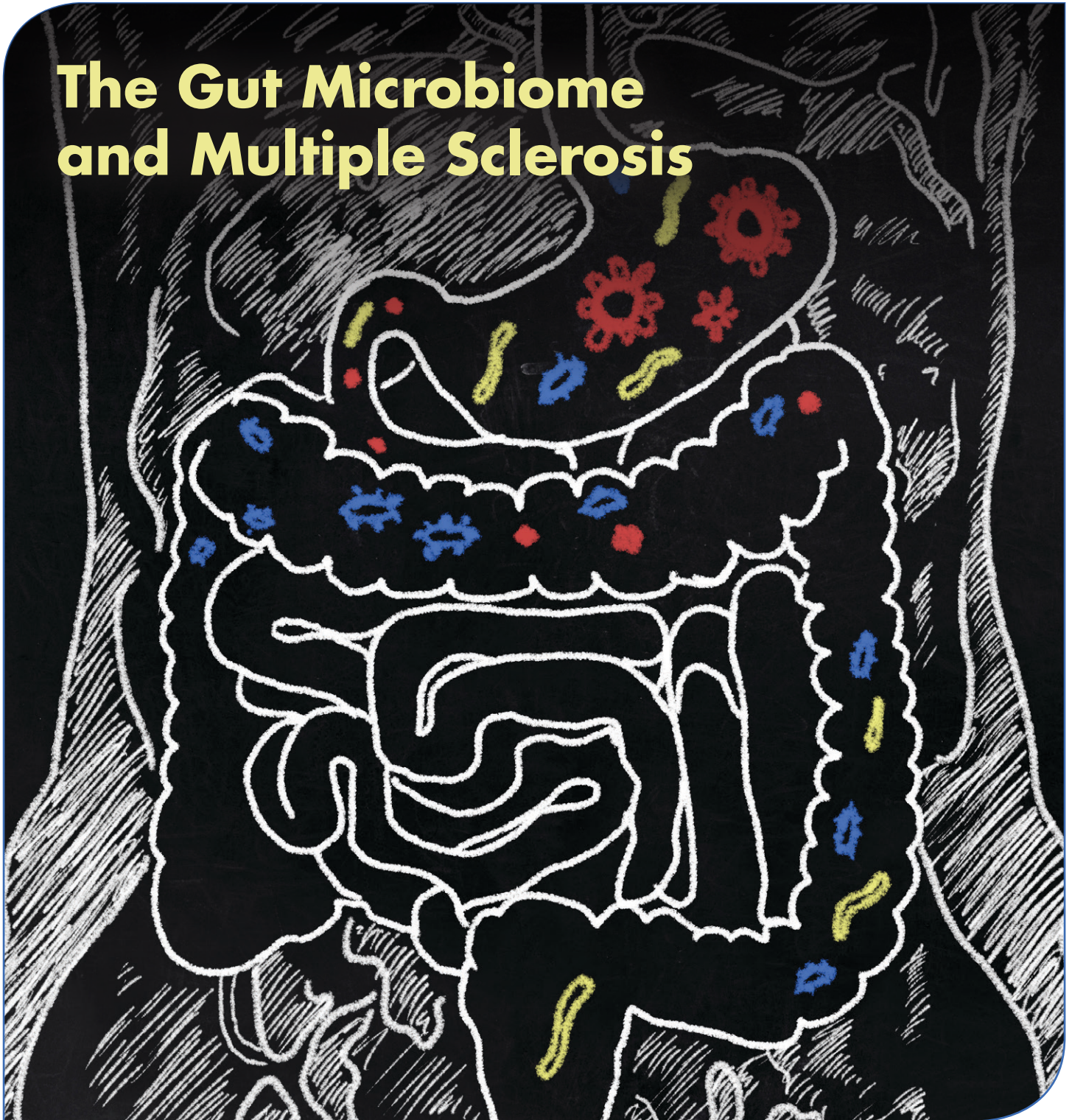


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INFOCORNER



What is NARCOMS?

NARCOMS is a registry for people who have multiple sclerosis (MS). Registry participants complete two surveys each year to provide information about themselves and their experience of having MS. Data from these surveys are used in research studies and to help further our understanding of MS. Participation in the registry is voluntary, and responders' identity and privacy are carefully secured.



What is the Goal of NARCOMS?

The NARCOMS Global MS Patient Registry helps to facilitate research about multiple sclerosis in North America and around the world. Collaboration between MS centers of excellence throughout the world helps to increase knowledge, improve clinical care, and enhance the quality of life for persons with MS.



How Private Is My Information?

We will keep the information that you provide us private and confidential by storing your data in a secure database. All information will be used for research purposes only. We do not share any personally identifying information with any person or research institution. We follow all Federal (HIPAA) laws regarding confidentiality.



Not Yet a NARCOMS Participant?

Please contact us at www.NARCOMS.org to enroll online, or call toll free at 1-800-253-7884.



Tell Us Your Thoughts!

Have an idea? We would love to hear from you!
Send us your questions, comments, and suggestions.

Call: 1-800-253-7884 (toll-free U.S.)

Email: MSRegistry@narcoms.org

Online: www.narcoms.org/contact-us

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DIRECTOR'S LETTER

Dear *NARCOMS Now* Readers:

The gut microbiome is the theme for this issue of *NARCOMS Now*. Many microbes, including bacteria, fungi, and viruses, live on and inside the human body, including the gut. The “microbiome” refers to the collection of these organisms. This is a topic of interest to many. Medical researchers continue to look closely at how the bacteria and other organisms living in our intestinal tract may affect our health. We know that the lining of the intestines is rich with immune cells. Some populations with a different composition of intestinal “bugs” tend to have lower rates of many diseases like multiple sclerosis (MS). These findings have led to a surge of studies on the gut microbiome and how changing it might affect diseases like MS.



Ruth Ann Marrie, MD, PhD

For this issue, *NARCOMS Now* interviewed Lloyd Kasper, MD, a professor at Dartmouth University and a pioneer in gut microbiome research in MS. Dr. Kasper explains the latest research findings. We hope you will find this topic of interest. It was among the topics suggested by *NARCOMS Now* readers, and we enjoy listening to your feedback and ideas. Some of the MS News items reflect recent clinical studies related to MS, and provide updates on other NARCOMS research. As always, thank you for taking the time to complete the NARCOMS surveys and for your ongoing participation in the registry. We value your contributions highly and we are always open to hearing from you.

Sincerely,

Ruth Ann Marrie, MD, PhD
Scientific Director, NARCOMS



The Gut Microbiome— Is It Hiding Secrets About MS?

About 80% of the immune system resides in the gastrointestinal (GI) tract, or the “gut.” Just a few years ago, this concept might have seemed far-fetched. However, research by Lloyd Kasper, MD, of Dartmouth University and many others suggests that the gut may be a good place to focus for answers about the cause of multiple sclerosis (MS) and possibly even new treatments.

The significance of the gut as a sensory organ—and even the main headquarters of the immune system—has taken a while to catch

on. For people with MS, changes in the brain and spinal cord may seem far removed from the GI tract. However, scientists are beginning to gain more understanding about the interactions among the microbes of the body, the foods and nutrients we consume, and the behavior of the immune system as it affects conditions such as MS.

“The lining of the intestinal tract contains the largest mass of lymphoid tissue in the body,” explained Dr. Kasper, Professor of Microbiology and Immunology at Dartmouth. Lymphoid tissue refers to organs or tissue (such as lymph nodes) where immune cells are generated. The gut is also the largest body surface that is exposed regularly to the external environment.

Do Gut Bacteria Affect the Risk for Autoimmune Diseases?

Neurons and immune cells are present in the gut, but they are not the most plentiful living cells there. Also residing in our GI tracts are over 100 trillion separate microorganisms. These include an estimated 10,000 species of bacteria. These organisms, collectively known as the microbiome, have evolved over time while cohabitating with the human body. They can be either beneficial, just neutral



(“commensal”), or pathologic (capable of producing illness).

Not all human populations have the same makeup of bacteria in the gut, Dr. Kasper explained. People in the Western world tend to have a different gut bacterial profile than do those living in parts of Africa, where MS is virtually unknown. The difference in MS risk is believed to be due to a combination of many factors. Genetic factors are believed to play a role, as well as vitamin D from sun exposure. The gut bacteria, influenced by local diets and practices, might also be protective of the immune system in some populations.

Italian researchers have compared gut bacteria types from children living in different parts

of the globe. Children in Europe have a traditional Western diet—low in fiber and high in animal protein, sugar, and calories. However, children from a rural village in Burkina Faso, Africa, consume mostly high-fiber grains and legumes—a diet largely unchanged over centuries. With scarce water for cleaning dishes or bathing, the children have close contact with bacteria residing in the dirt.

These investigators found substantial differences in the bacterial profiles among these populations. African children’s guts were mostly colonized by bacteria known as *Bacteroidetes* while the children consuming a Western diet had mostly *Firmicutes* type bacteria (See Figure). This research did not

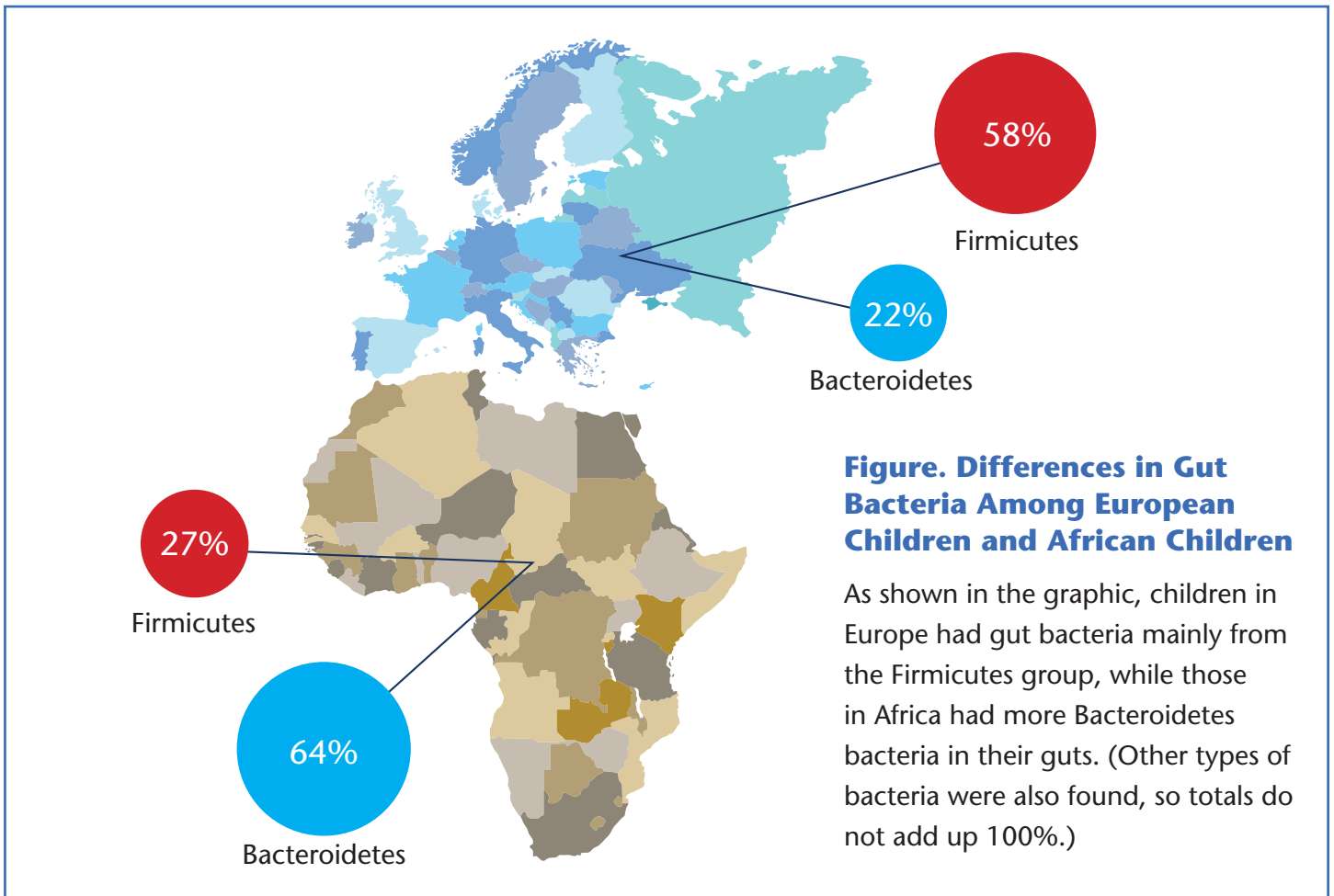



Figure. Differences in Gut Bacteria Among European Children and African Children

As shown in the graphic, children in Europe had gut bacteria mainly from the Firmicutes group, while those in Africa had more Bacteroidetes bacteria in their guts. (Other types of bacteria were also found, so totals do not add up 100%.)

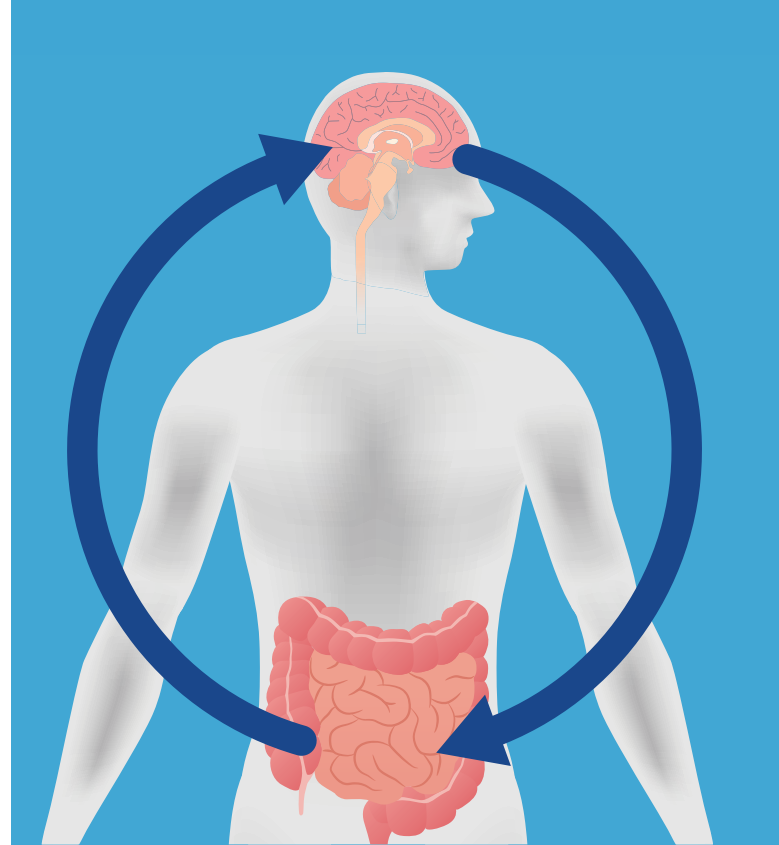
address MS specifically. But the authors suggested that recent improvements in hygiene in these African regions seem to be coupled with rising rates of allergic, autoimmune, and inflammatory disorders in these populations. In addition, lower levels of *Bacteroidetes* have a possible link to obesity.

Certain types of gut bacteria may be present in higher numbers in people with MS. This includes bacteria from the order “Clostridiales.” Clostridial organisms have received much attention in studies of demyelinating disorders. In particular, two bacteria types within the Clostridia group seem to be more plentiful in people with MS than in control participants without MS. (For more on this, see News article on page 11.)

 *“Residing in our GI tracts are over 100 trillion separate microorganisms, including an estimated 10,000 species of bacteria. These organisms, known as the microbiome, have evolved over time while coexisting with the human body.”*

The Hygiene Hypothesis in MS

In our zeal to eliminate infectious and parasitic diseases in modern society, have we thrown out too many “good bugs” with the bathwater? The “hygiene hypothesis” is based on the principle that many intestinal bacteria, fungi, and even parasites are not harmful contaminants of the gut, but necessary “friends.” The human immune



system has evolved in partnership with these friends. Although it is not proven, the hygiene hypothesis offers a possible explanation for the growing epidemic of allergic and autoimmune diseases in some parts of the world, and the lack of them in regions with poor sanitation.

For example, loss of certain parasitic worms from the human microbiome might be related to allergic and autoimmune diseases. Helminths—a group of parasitic worms including roundworms, whipworms, and pinworms—have coexisted with the human immune system over millions of years. They leave strong genetic signatures that affect immune response. Infestation with these worms is common in areas of poor sanitation but has been largely eliminated with modern sanitation. Having too many helminths can cause illness and malnutrition, but when they are kept in check these parasites are thought to regulate some immune functions (see Sidebar, “Pass the Helminths”).

Pass the Helminths: Parasite-Based Therapies for MS

What happens when researchers put some of the “old friends” back into the gut? Some people with MS have gamely volunteered to find out by ingesting live worms (helminths) in an effort to alter the microbiome and possibly influence the MS disease process.

In the HINT 1 study in 2011, researchers from the University of Wisconsin explored helminth-based therapy in 5 people newly diagnosed with MS who had never been on a DMT. The treatment, containing 2,500 microscopic live ova from a whipworm, was administered via a sports drink. The whipworms, which have no known disease-causing effects in humans, hatch in the intestine and die off within a few weeks. The intrepid subjects in this small study drank the worm concoction every 2 weeks for 3 months. New magnetic resonance imaging (MRI) lesions dropped significantly during treatment, but after helminth treatment was discontinued, some of the MRI signs of MS disease activity appeared to return.

HINT 2 in 2017 enrolled 16 people with early MS, treated for 10 months. This study showed modest improvement in MRI findings, but with much variation among individuals. Some participants in these and other worm studies developed GI



side effects (pain or diarrhea) that made it necessary to remove the worms.

In a larger study of 72 people with MS, WIRMS (Worms for Immune Regulation in Multiple Sclerosis), 36 people received the hookworm larvae and 36 received placebo. Instead of taking the worms regularly by mouth, the larvae were administered only once, by an injection under the skin. Results of WIRMS have not been published yet.

As Dr. Kasper pointed out, helminth trials have mixed results and some side effects. These trials do not necessarily match the effects of someone who is infected naturally with the parasites. Obviously, administering live worms is not an optimal way to treat humans. However, helminth studies may help researchers to identify the specific molecules produced by parasitic worms, which could then be developed into medications.

Can Probiotics Help to Reset the Immune System in the Gut?

If the gut microbiome is off balance, can taking a probiotic or prebiotic help to set it right? If so, might this strategy be used in people with MS to influence immune system behavior? Studies in MS are exploring this question

(see News article on page 9). In the future, specialized probiotics may be available to offer targeted therapy for diseases like MS.

Although we are not quite ready to prescribe either worms or probiotics to fight MS, these avenues of research may hold promise for the future.

RESOURCES

Information About Gut Microbiome and Health

International MS Microbiome Society

<http://imsms.org/home/>

American Gastroenterological Association

<https://www.gastro.org/>

(Select Gut Microbiome section)

Scientific Papers Mentioned in This Article

- Ochoa-Repáraz J, Kirby TO, Kasper LH. The gut microbiome and multiple sclerosis. *Cold Spring Harb Perspect Med*. 2018 Jun 1;8(6).

- Mielcarz DW, Kasper LH. The gut microbiome in multiple sclerosis. *Curr Treat Options Neurol*. 2015 Apr;17(4):344.
- Fleming J, Hernandez G, Hartman L, et al. Safety and efficacy of helminth treatment in relapsing-remitting multiple sclerosis: Results of the HINT 2 clinical trial. *Mult Scler*. Oct 1, 2017.
- Dixit A, Tanaka A, Greer JM, et al. Novel therapeutics for multiple sclerosis designed by parasitic worms. *Int J Mol Sci*. 2017 Oct 13;18(10).



MSMESSENGER

WHAT TO EXPECT ON THE NEXT NARCOMS SURVEY

Many thanks to all the participants who completed the fall update survey. Despite the busy holiday season, over 70% of the active registry participants found the time to respond. We are thrilled about the excellent response! We would also like to extend a special thank-you to the NARCOMS Ambassadors and other volunteers who provided feedback and comments on a new NARCOMS brochure and helped to improve the clarity of the survey questions on immunotherapies.

The spring 2019 update survey will be available by mid-April. If you do not receive your survey in the mail or do not receive an email with the survey link by the end of April, please contact us. As always, please let us know if you have any questions about the survey or would like assistance in completing it. Everyone's voice is important!

Thank you very much for all that you do to expedite MS research.

—The NARCOMS Team



Effect of Probiotic Use on the Gut Microbiome in People with MS

The gut microbiome has become a hot topic in medical research, including in multiple sclerosis (MS). The gut microbiome is the collection of all the living bacteria and human cells that reside in the human intestinal organs. Changes in the types of organisms present in the gut microbiome may be linked to autoimmune diseases such as rheumatoid arthritis and MS.

Researchers from Harvard Medical School studied the effects of taking a probiotic dietary supplement on the gut microbiome composition of people with MS. The study population included 22 people: 7 with MS who received treatment with glatiramer acetate, 2 with MS who were not on a disease-modifying treatment (DMT), and 13 people without MS.



“We need more information about the long-term effects of probiotic use and whether altering the gut microbiome is a lasting, or only temporary, effect.”

Study participants took a probiotic containing *Lactobacillus*, *Bifidobacterium*, and *Streptococcus* twice daily for 2 months. All of them followed the regimen at least 90% of the time. The probiotic supplement was safe and well tolerated. Although the study was small, the results suggested that a probiotic supplement may help reverse some abnormalities in the gut microbiome composition that are associated with MS. Using a probiotic in combination with a DMT may have an additive effect.

More studies are needed before regular probiotic use can be recommended for people with MS, the authors warned. In addition, we need more information about the long-term effects of probiotic use and whether altering the gut microbiome is a lasting, or only temporary, effect. Positive shifts in gut bacteria were not maintained after the people with MS stopped using the probiotic, which suggests that probiotic use would need to be continuous.

Reference: Tankou SK, Regev K, Healy BC, et al. A probiotic modulates the microbiome and immunity in multiple sclerosis. *Ann Neurol.* 2018;83(6):1147-1161.

Survey Shows High Use of eHealth Technology by NARCOMS Participants

Monica, a 36-year-old woman from New Hampshire, has recently had an MRI to monitor brain changes due to multiple sclerosis (MS). She lives a long distance from the MS clinic, so her neurologist arranges a video meeting using a special secure website. This is an example of how electronic health (eHealth) technology makes it easier for people to communicate with their doctors without meeting face to face. The popularity of mobile phones has led to new health-related applications (mHealth) as another way to facilitate these interactions. These “apps” may be helpful for people who have conditions that require them to stay in touch with health professionals.

How often do people with MS use eHealth or mHealth technologies, and how do they benefit from these tools? A research project led by NARCOMS Scientific Director Ruth Ann

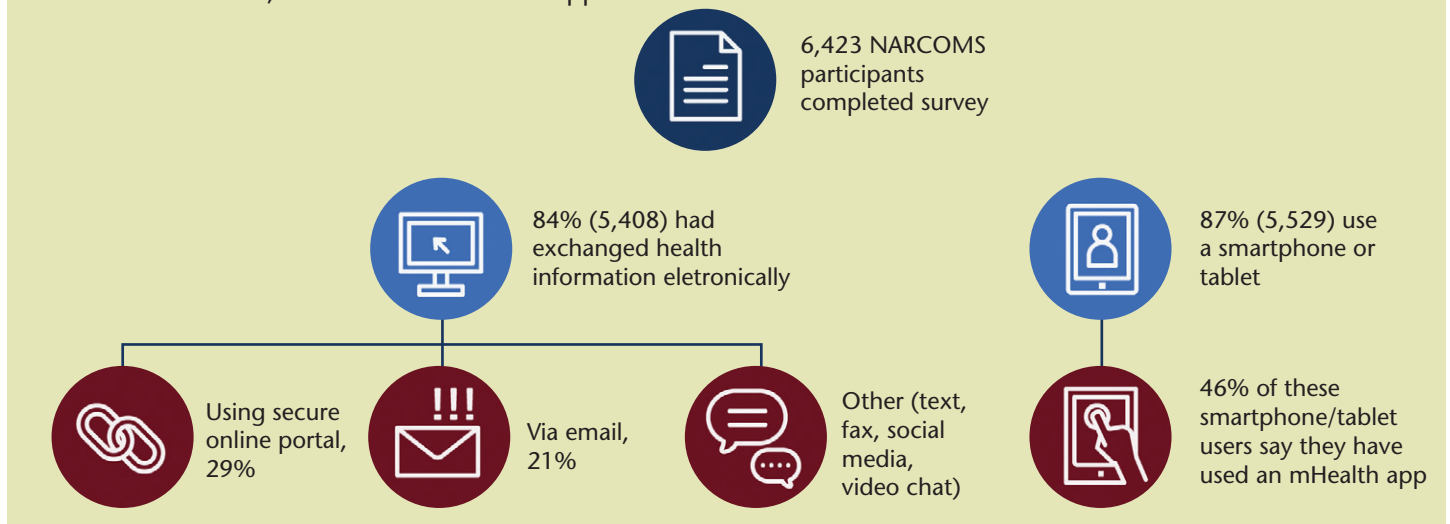
Marrie, MD, PhD, sought answers to these questions. In 2017, the NARCOMS update survey asked participants about their use of the internet, technology, eHealth or mHealth, the perceived benefits of the technology, and how they feel about exchanging health information in this way. More than 6,400 NARCOMS participants completed the survey, and more than 84% of them said they had sent medical information electronically (see chart, below).

The researchers concluded that use of eHealth technology is common among people with MS and facilitates the exchange of healthcare information with providers. Users of mHealth apps perceive this technology to have health benefits. The survey showed that NARCOMS participants who were younger, had higher income and/or education level, and had other medical conditions (comorbidities) were more likely to use mHealth apps and to regard them as beneficial.

Reference: Marrie RA, Leung S, Tyry T, et al. Use of eHealth and mHealth technology by persons with multiple sclerosis. *Mult Scler Relat Disord.* 2019 Jan;27:13-19.

How NARCOMS Participants Use Electronic Health Information

Survey results showing how often NARCOMS participants share medical information with healthcare providers using electronic methods, and use health-related apps.



How Do Disease-Modifying Treatments for MS Affect Organisms in the Gut?

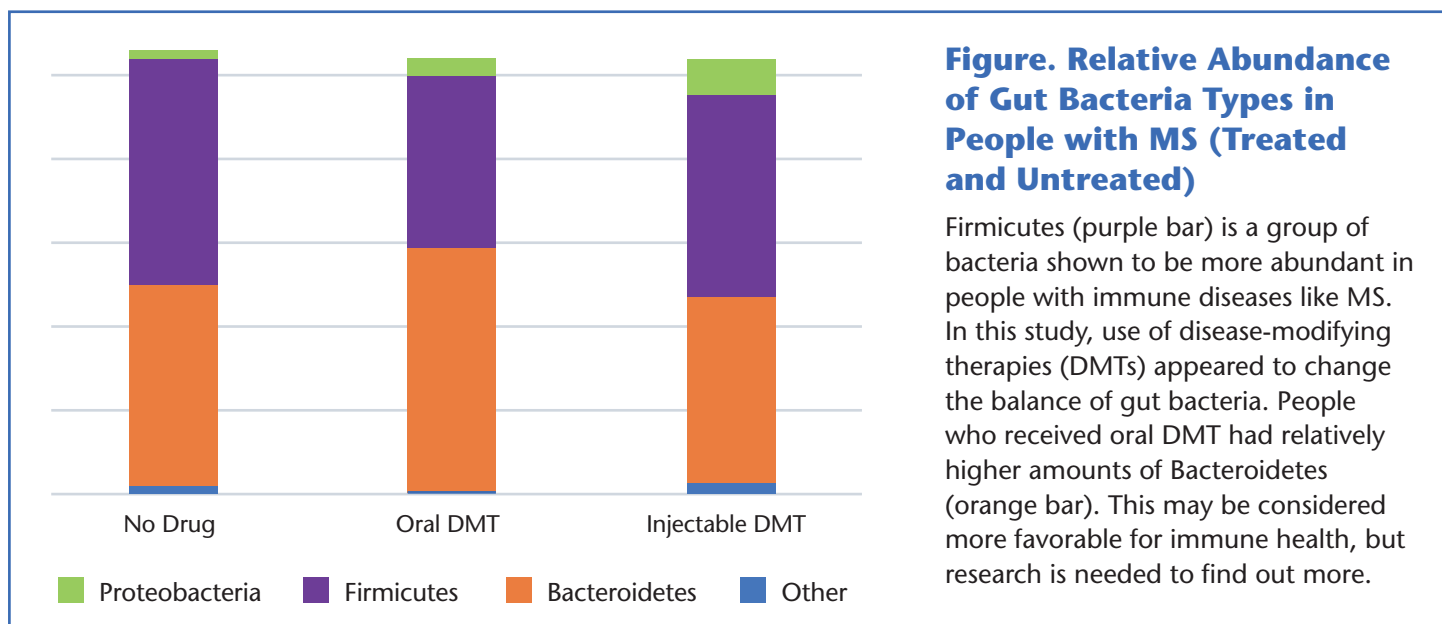
Many different types of bacteria live in the human intestinal tract, or “gut.” Most are either useful—by breaking down nutrients or fighting off disease—or just neutral (along for the ride). A change in the bacterial balance of the gut may affect a person’s overall health. Research has shown that the balance of these bacterial “families” may be different in people with diseases like multiple sclerosis (MS), compared with people who do not have MS.

One important question is, do disease-modifying therapies (DMTs) for MS affect the balance of these gut bacteria? To find out, researchers from Mount Sinai Medical Center in New York and the University of California San Francisco examined gut bacteria samples from people with MS. They extracted stool bacteria from 168 participants; 75 had never taken a DMT, 33 were taking an oral DMT, and 60 were taking an injectable DMT.

There were differences in the gut bacteria among the never-treated people with MS and those who were taking either of the DMTs. Bacteria from the Clostridia class is one group of particular interest. Two bacteria in that class (*Lachnospiraceae* and *Veillonellaceae*) tend to be increased in people with MS, compared to people without the disease. Taking an MS DMT reduced levels of Clostridia, the study found. The authors noted, “A decrease in the relative abundance of Clostridial members could be common to several MS DMTs.” People taking the oral drug appeared to have increased levels of another bacteria type, Bacteroidetes, which may be beneficial (see Figure).

Many MS therapies are anti-inflammatory, so this may explain part of their effect on the gut microbiome. This was a small study, and more research needs to be done to show how these changes might affect critical metabolic pathways that influence MS.

Reference: Katz Sand I, Zhu Y, Ntranos A, et al. Disease-modifying therapies alter gut microbial composition in MS. *Neurol Neuroimmunol Neuroinflamm.* 2019;6:e517.



NARCOMS Study Evaluates Rates of Uncontrollable Laughing or Crying in People With MS

Pseudobulbar affect (PBA) is a condition in which a person has uncontrollable outbursts of emotion such as laughing or crying. PBA can be embarrassing and socially debilitating for those affected. Family members or caregivers may be the first to notice symptoms, but many people do not report PBA to healthcare professionals.

Usually PBA occurs along with a neurologic condition, such as multiple sclerosis (MS) or Parkinson disease. Until recently, it was unclear how many people with MS are affected. For example, the National Multiple Sclerosis Society describes a range of anywhere from 7% to 95% of people affected by PBA.

A recent study among NARCOMS participants looked further into how often PBA occurs in people with MS. The participants were asked to complete a questionnaire that measures perceived frequency of PBA episodes. They also completed an assessment scale of MS disease status and indicated whether they had ever been diagnosed with depression. Of the 8,136 NARCOMS participants who responded, the scores suggested that 7% had experienced



PBA. Rates of PBA appeared to be much higher (22%) among those who also reported a diagnosis of depression. This suggests that depression and PBA may co-occur or overlap, and highlights the importance of assessing mood disorders among people who have symptoms that suggest PBA. NARCOMS participants who reported that they have trouble with memory or concentration were also more likely to have symptoms of PBA.

References: Fitzgerald KC, Salter A, Tyry T, et al. Pseudobulbar affect: Prevalence and association with symptoms in multiple sclerosis. *Neurol Clin Pract.* 2018 Dec;8(6):472-481.

National Multiple Sclerosis Society (NMSS). Pseudobulbar Affect (Uncontrollable Laughing and/or Crying). *Clinical Bulletin.* 2012. Available at: <https://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/Clinical-Bulletin-Pseudobulbar.pdf>

MORE RESOURCES ON PSEUDOBULBAR AFFECT (PBA)

National Multiple Sclerosis Society (NMSS)

<https://www.nationalmssociety.org/Symptoms-Diagnosis/MS-Symptoms/Emotional-Changes#section-8>

PBA Voices

Brain Injury Association of America: <https://pbavoices.org/resources/>



SNAPSHOT

WHAT WE CAN LEARN FROM NARCOMS SURVEYS

NARCOMS Surveys Show Change in Smoking Behavior Over the Years

Smoking is one of the lifestyle behaviors known to have a negative impact on health. It is also a risk factor for MS and can have a detrimental effect on symptoms and disease progression. NARCOMS has collected data on smoking behavior in select update surveys since 2004. Here's a brief summary of smoking trends among responders to fall surveys in 2004, 2010, 2014, and 2018. More than 7,000 registry participants completed each update survey. (This is a preliminary analysis, so the results have not

been adjusted for all the factors that may be associated with smoking behavior.)

Overall, a relatively low percentage of registry participants reported smoking "every day" or "some days." Since 2004 the percentage of current smokers has steadily decreased from about 20% to about 7% among both genders (see Figure 1).

The change in smoking behavior is especially notable among participants under age 50 at the time of each survey. In this age group, the percentage of current smokers dropped from

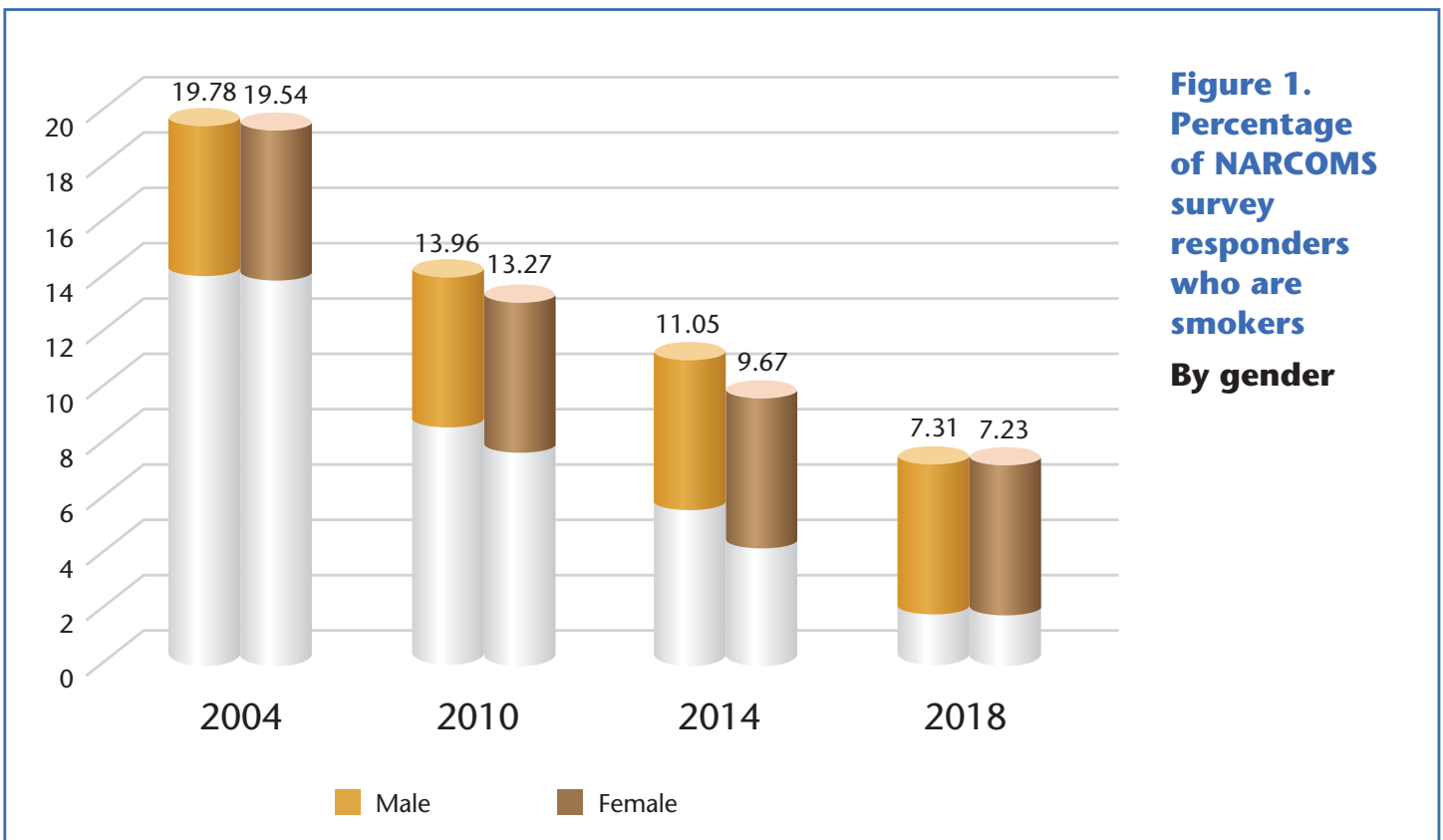
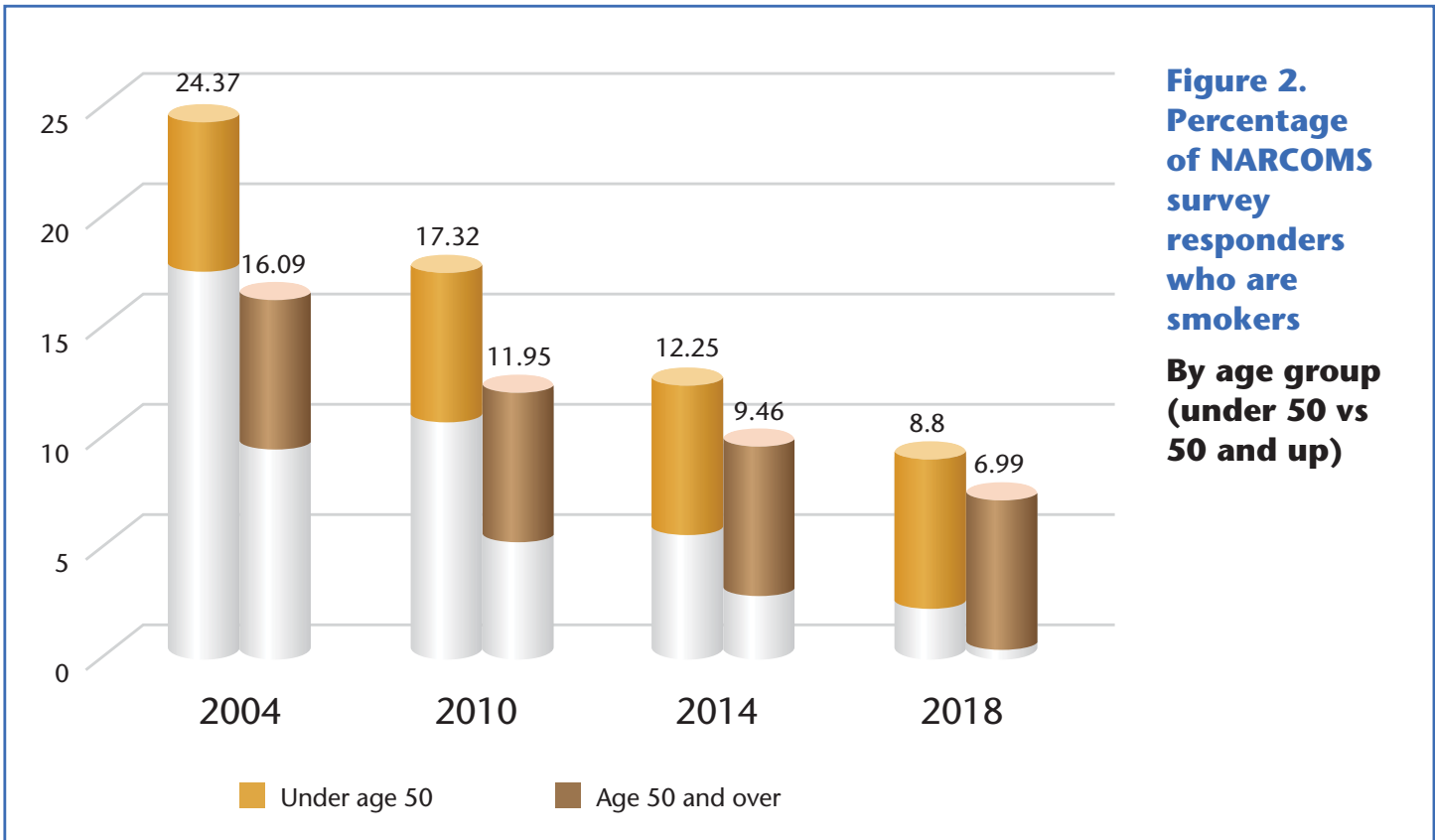


Figure 1.
Percentage of NARCOMS survey responders who are smokers
By gender



about 24% in 2004 to less than 9% in 2018 (see Figure 2).

Over the years, the proportion of every-day smokers was quite similar for men and women. However, compared to women, a larger percentage of men said they smoke “some days.”

The update surveys also asked about the average number of cigarettes smoked per day. These numbers were similar for both men and women and did not fluctuate much over the study period. In the fall 2018 update survey, half of the smokers said they smoke fewer than 10 cigarettes on the days they smoked.

“Since 2002, more people in the U.S. have quit smoking than there are current smokers.”

— Source: www.cdc.gov

However, 1 out of 4 smoked more than 16 cigarettes on the days they smoked.

If you are a smoker and have considered quitting, it is important to discuss this with your healthcare providers. They can recommend resources that will best meet your needs. Resources for quitting can be found on the Centers for Disease Control and Prevention (CDC) website (see the box below).

CDC Smoking Cessation Resources

For free assistance with smoking cessation, you can call the CDC help line at 1-800-QUIT-NOW (1-800-784-8669). You can find resources for quitting on www.cdc.gov/tobacco/

Play **WORDSEARCH**

Find the following hidden words relating to the gut microbiome.

BACTERIA

EVOLVE

BRAIN

HEALTH

IMMUNITY

MICROBIOME

VITAMINS

LINING

HYGIENE

GUT

HELMINTH

INTESTINE

PROBIOTIC

WORMS

COMPOSITION

C	B	Q	B	B	G	L	K	G	V	U	O	W	E	H
W	I	R	S	B	D	O	N	C	F	D	B	I	E	T
O	M	T	A	Z	A	I	U	L	Q	C	T	M	E	L
R	U	C	O	I	N	C	Z	H	O	B	J	M	E	A
M	Q	S	W	I	N	Q	T	M	B	P	T	U	N	E
S	D	Z	L	G	B	N	P	E	Y	N	E	N	I	H
Y	K	U	P	Y	I	O	N	Q	R	M	S	I	T	P
B	M	J	S	M	S	I	R	L	J	I	V	T	S	I
A	P	M	L	I	C	Q	M	P	C	I	A	Y	E	F
M	C	E	T	E	M	M	E	V	O	L	V	E	T	D
H	H	I	E	M	O	I	B	O	R	C	I	M	N	T
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I	B	V	Y	A	R	I	V	J	T	B	B	W	A	W

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NARCOMS NOW

BE PART OF NARCOMS—HELP TO ADVANCE RESEARCH IN MS

Whether you were recently diagnosed with multiple sclerosis (MS) or have lived with it for years, your personal history with the disease helps contribute to improving the lives of others with MS.

Participation in the NARCOMS registry allows you to be part of the process. The data provided by participants gives researchers a clearer picture of how a condition like MS impacts the lives of those affected.

Participation in NARCOMS is confidential—your information is kept secure and completely private. If you have MS and are not yet participating in NARCOMS, or have been out of touch for a while, we would love to hear from you! Contact us at 1-800-253-7884 (toll-free U.S.) or via email at MSRegistry@narcoms.org.



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instagram: [@narcoms_now](https://www.instagram.com/narcoms_now)

For more information on the CMSC visit www.mscares.org
www.NARCOMS.org