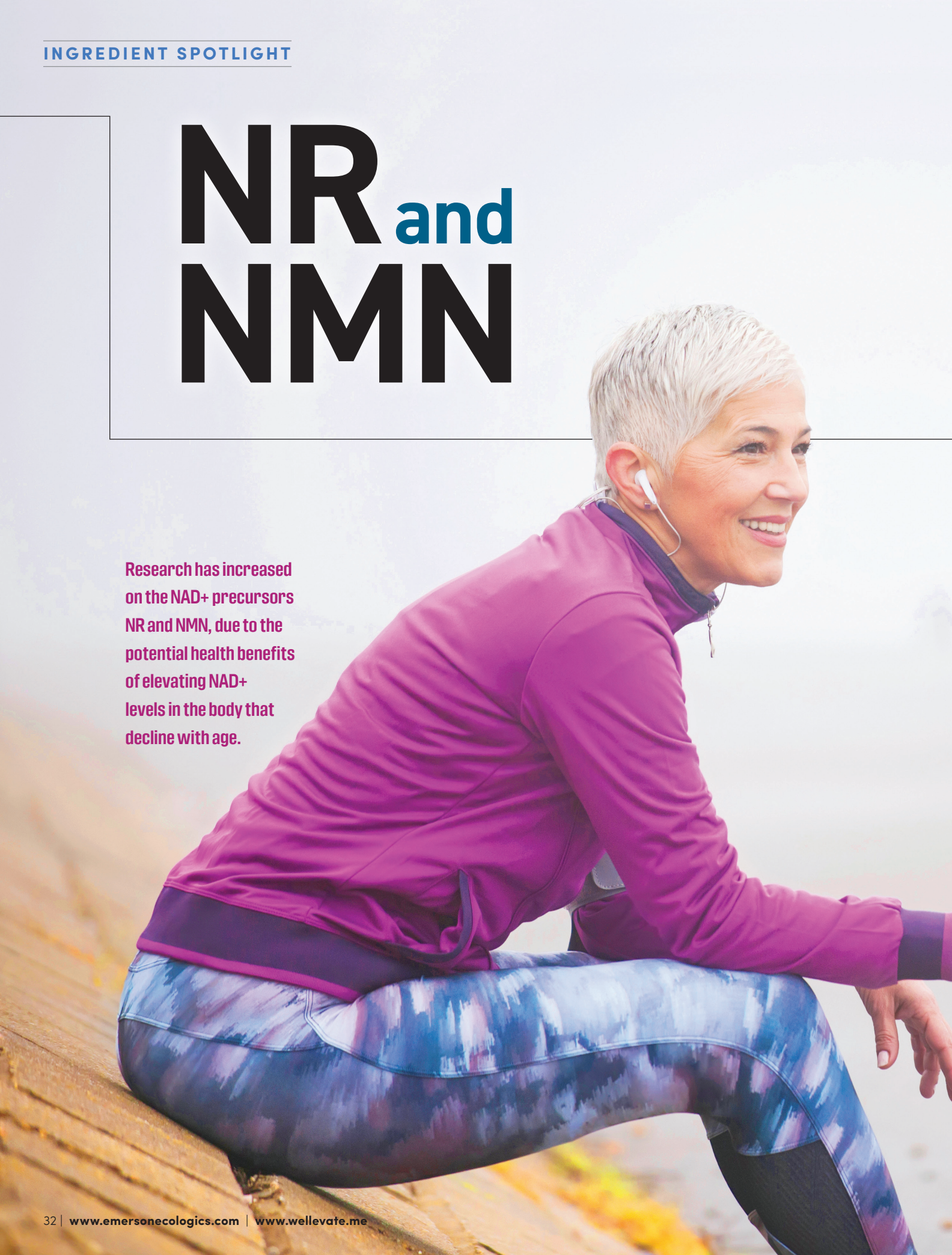
NR and NMN



Research has increased on the NAD+ precursors NR and NMN, due to the potential health benefits of elevating NAD+ levels in the body that decline with age.

AN EXPLORATION OF NAD+ PRECURSORS

BY LAURIE BUDGAR

In the first half of the 20th century, about 3 million people, mostly in the American South, mysteriously began developing dementia, diarrhea, and dark, scaly skin patches. About 100,000 people died before we learned they had a deficiency of vitamin B3, attributable to Southerners' inadequate corn-based diets.

Today, we rarely see this deficiency in developed countries because of our understanding of the link between nutrition and health. We now recognize that vitamin B3 has wide-ranging benefits and that it's prevalent in a variety of whole, natural foods. We've also learned that processing plant foods like grains can diminish their B content. As a result, flour, rice, and cereals have been fortified with vitamin B3 since the 1940s.

Other early research into B3 and other vitamins shows they often exist as "families" in our food supply. These families include multiple forms of the same vitamin—known as vitamers or derivatives—that have slightly different chemical structures and properties from one another. Some are more stable, some more active, and some require conversion to a different derivative before the body can use them.

The vitamin B3 family contains nicotinic acid (generically known as niacin) and its derivatives: niacinamide (also called nicotinamide), nicotinamide riboside (NR), and nicotinamide mononucleotide (NMN). Each of these derivatives is a precursor to NAD+ (nicotinamide adenine dinucleotide), a coenzyme that's necessary for cellular energy production.

Evidence indicates that NAD+ levels decline with age, which contributes to the development of age-associated health concerns. As a result, research on NAD+ precursors has increased due to the potential health benefits of elevating NAD+ levels in the body.

In addition to niacin and niacinamide, NR and NMN are now available in supplemental form. But NR and NMN differ in the manner and efficiency in which they produce NAD+, as well as in the specific effects they exert in the body. Understanding these distinctions can help you choose between these B3 precursors.

The B3-NAD+ connection

Not only is NAD+ omnipresent in the body, it's also multifunctional. Its chief purpose is to help mitochondria—the "powerhouses" of our cells—turn food and oxygen into ATP (adenosine triphosphate), and ultimately into energy for cells. NAD+ supports metabolism along with neuronal health, DNA repair, and even maintaining the body's circadian rhythm. It contributes to an overall feeling of energy and well-being. But because NAD+ has so many roles, its mechanism of action is poorly understood.

What's more, many of the body's ongoing biochemical reactions use NAD+, so it must be replenished four to 10 times each day. The body can recycle its existing stores of NAD+, but first it must produce sufficient amounts. Supplementing with one or more forms of vitamin B3 can help accomplish this.

The body can produce NAD+ in three ways. The first method converts dietary tryptophan (found in many proteins) in the eight-step *de novo* pathway. The Preiss-Handler pathway converts dietary niacin to NAD+ in three enzymatic steps, but consumes considerable energy when NAD+ reserves are low.

THE SALVAGE PATHWAY

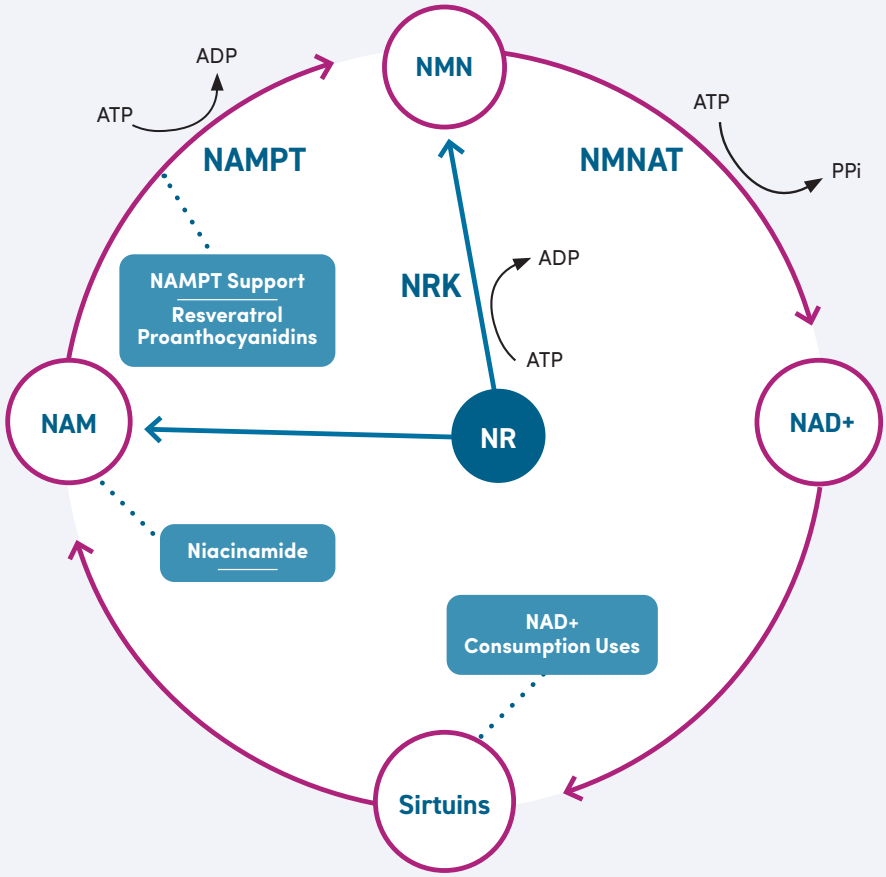
Synthesizing NAD+

NR (plus NRK enzymes) → **NMN**

NMN (plus enzyme NMNAT) → **NAD+**

NAD+ produced here is partially consumed by sirtuins → **NAM** produced as byproduct

NAM (plus enzyme NAMPT) → **NMN** → **NAD+**



The third and most efficient method, known as the salvage pathway, synthesizes NAD+ from either NR or NMN supplements and then recycles it, using the NAM it creates as a byproduct. Without this recycling pathway, no amount of dietary or supplementary B3 would produce enough NAD+ to keep cells and tissues in their optimal state.

The NR vs. NMN throwdown

NR appears to be more efficient than NMN in converting to NAD+. One reason is that NR can enter cells directly, while NMN, owing to its larger molecular size, must first convert to NR before entering the salvage pathway.

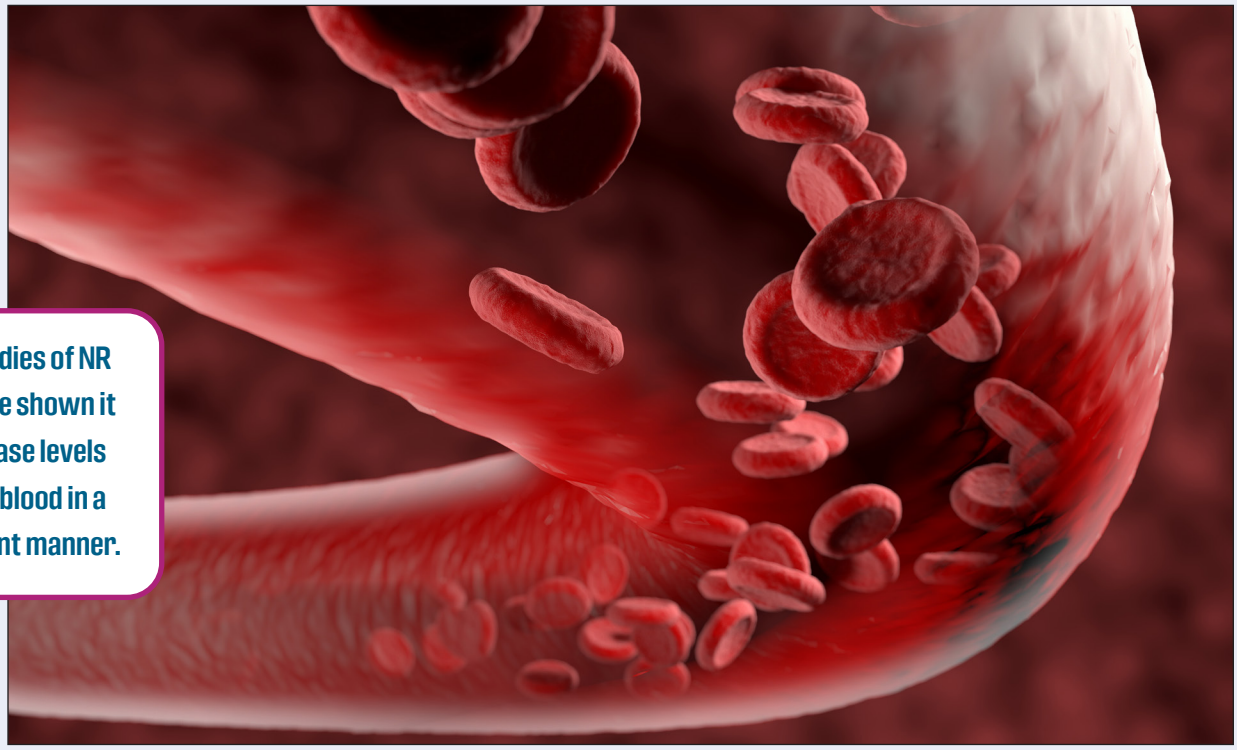
NR can also convert to NAD+ without relying, like NMN does, on the rate-limiting enzyme NAMPT (nicotinamide phosphoribosyltransferase). NAMPT expression has been found to decline with aging, and reduced expression of NAMPT is one of the major causes of NAD+ decline.

However, the requirement for NAMPT can be bypassed with the direct conversion of NR to NMN by two nicotinamide ribose kinases, NMRK1 and NMRK2 (also known as NRK1 and NRK2). This appears to make NR the choice for older patients.

So far, most of the NMN research has been done on rodents, with only three human trials to date, while NR has dozens of human studies. With that noted, here's how these two supplements stack up.

NMN. Research has shown that in rodents, NMN can support energy metabolism, insulin function, bone density, immune function, and lipid metabolism. It has also been shown in mice to support arterial function and mitochondrial function in skeletal muscle.

One small human study, published in 2020 in *Endocrine Journal*, showed that NMN was safe and well-tolerated in doses up to 500 mg. Another study, published in 2021 in *Science*, showed that NMN effectively raised NAD+ levels and supported glucose metabolism in muscles. And a third study, published in 2021 in the *Journal of the International Society of Sports Nutrition*, showed that NMN supported young and middle-aged runners' aerobic capacity during exercise.



Numerous studies of NR in humans have shown it can help increase levels of NAD+ in the blood in a dose-dependent manner.

NR. Numerous studies of NR in humans have shown it can help increase levels of NAD+ in the blood in a dose-dependent manner. In addition, studies have confirmed that NR is safe and well-tolerated in doses up to 2 grams daily, with minimal side effects. NR has had GRAS (generally recognized as safe) status since 2016.

Clinical studies have shown numerous health benefits resulting from NR supplementation.

- A 2018 study published in *Nature Communications* found that NR may support healthy blood pressure and aortic resiliency.
- A study published in 2020 in the *European Journal of Nutrition* showed that NR may help improve the fatigue index by 15 percent in the elderly.
- A research review published in 2020 in *Nutrients* demonstrated that NR may support a healthy immune system.

Practical considerations

NAD+ has a short half-life, so it's important to take a NAD+ precursor like NR or NMN daily—perhaps even twice daily. Most manufacturers recommend taking 250 to 500 mg a day. Because of the effects NAD+ has on energy production, people may prefer to supplement earlier in the day.

In addition to supporting NAD+ production with B3 vitamins, it's important to support the enzymes in the salvage pathway, especially NAMPT. Resveratrol has been shown to effectively help increase NAMPT.

Resveratrol also appears to help activate specific genes that up-regulate healthy-aging sirtuins, which in turn act as cellular switches that support mitochondrial function and increase the number of mitochondria in each cell. This extra mitochondria results in more efficient energy production, and possibly more efficient fat metabolism and increased longevity.

While there's more robust evidence in humans for using NR versus NMN to boost or replenish NAD+, some experts suggest using more than one NAD+ precursor at low doses to build in redundancy and synthesize NAD+ from multiple pathways. It's possible that we may eventually learn that each precursor provides different benefits in different types of tissues.

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