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LONG-TERM NMN TREATMENT INCREASES LIFESPAN AND HEALTHSPAN IN MICE IN A SEX DEPENDENT MANNER

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Levels of nicotinamide adenine dinucleotide (NAD⁺) decline by up to 50% in aging. NAD⁺ is an essential co-factor for many metabolic processes, including the deacetylase activity of sirtuins, and previous studies have demonstrated that supplementing NAD⁺ levels has a range of health benefits in both mice and humans. Here we investigate the effect of long-term (from 13 months of age) administration of the NAD⁺ precursor nicotinamide mononucleotide (NMN) on frailty and lifespan in male and female mice. NMN treatment delayed the onset of frailty in both sexes, improved metabolic health in male mice, and increased median lifespan by 8.5% in female mice. Exploration of the potential mechanisms of this protection showed that NMN treatment prevented age-related gene expression changes in skeletal muscle and led to a large increase in levels of *Anaerotruncus colihominis*, a microbe associated with reduced inflammation, in the gut. A thorough characterization of NMN metabolism across age, sex and tissues shows context-specific sex differences in metabolic pathways, including greater Preiss-Handler pathway metabolism in females than males, which may contribute to observed sex differences in health and lifespan. Overall, this data provides preclinical evidence that chronic NMN treatment increases lifespan and improves frailty and metabolic health in aging, and highlights the importance of using both sexes for interventional lifespan studies.