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Physical Activity and Women's Health

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Director, NIH Office of Research on Women's Health
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Exercising regularly is one of the most important things you can do to improve your health. Regular exercise confers a wide range of health benefits, including reduced anxiety, improved well-being, and a lower risk of cardiovascular disease, obesity, osteoporosis, and certain cancers.

Although the benefits of exercise are evident in both men and women, most exercise science research has been conducted on men—resulting in an incomplete and potentially biased picture of how exercise affects women's health.

In 2016, the National Institutes of Health (NIH) launched the Molecular Transducers of Physical Activity Consortium to understand the molecular mechanisms that lead to exercise's many health benefits. The Consortium recently published preclinical data showing that sex differences in the molecular-level responses to exercise are more widespread than previously thought. In this issue, we describe these preclinical data as well as several recent human studies that find numerous sex differences in exercise-driven molecular changes. Collectively, these studies suggest that although men and women may obtain similar health benefits from exercise, the molecular mechanisms involved may differ by sex—underscoring the importance of studying sex as a biological variable.

This issue also describes recent research on the biological mechanisms involved in ovarian aging and sex differences in health outcomes after experiencing childhood trauma. Several recent and upcoming NIH events relevant to women's health are also highlighted.

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Janine Austin Clayton, M.D., FARVO
Director, NIH Office of Research on Women's Health
NIH Associate Director for Research on Women's Health

Physical Activity and Women's Health

Euan A. Ashley, M.D., Ph.D., Stanford University

From heart health to increased strength, from stronger bones to a slower rate of muscle loss and cognitive decline with age—exercise confers a strikingly wide array of health benefits.

No known drug benefits multiple systems throughout the body or helps prevent and treat numerous diseases as well as exercise, and without significant downsides—assuming one avoids overtraining, says Euan A. Ashley, M.D., Ph.D., the Arthur L. Bloomfield Professor of Medicine and Professor of Genetics, of Biomedical Data Science and, by courtesy, of Pathology at Stanford University and cardiologist at Stanford Medicine.

Dr. Ashley serves as the Principal Investigator (PI) for the Bioinformatics Center for Molecular Transducers of Physical Activity Consortium (MoTrPAC), a program launched by NIH in 2016 to examine how endurance and resistance (strength) exercise—both acutely and over time—affects the body's cells and tissues.

MoTrPAC aims to understand the molecular mechanisms by which exercise causes health benefits. How does regularly hopping on a bike or going for a run translate into a lower risk for heart disease or cognitive decline? What changes occur within cells and tissues to cause these benefits?

To this end, MoTrPAC has funded several preclinical (rodent) and clinical (human) studies that assess exercise-induced changes in gene expression, protein abundances, immune cells, fats, gene regulation within different tissues, and other molecular changes. The preclinical studies were critical, because they enabled analysis of a much wider range of tissues (19 tissues) than could be studied in humans (three tissues).

To date, MoTrPAC has only released the preclinical data on endurance exercise training—but the findings are already transforming the field of exercise science.

In rodents, endurance exercise training, lasting from one to eight weeks, induced molecular-level changes in all 19 of the tissues studied. Changes were seen in the immune system, in mitochondria (the organelles that generate energy within cells), and in cellular heat-shock responses (which help protect cells from damage related to cellular stress).[1] Some of the molecular changes further suggest that exercise may protect against non-alcoholic fatty liver disease and inflammatory bowel disease, two conditions that severely limit quality of life in humans.

Sue Bodine, Ph.D., Oklahoma Medical Research Foundation

In several tissues, the observed changes were more widespread than anticipated.[2] For example, exercise extensively altered gene expression in the adrenal glands, says Sue Bodine, Ph.D., Professor in the Aging & Metabolism Program at the Oklahoma Medical Research Foundation and a PI and a member of MoTrPAC Executive Steering Committee. The adrenal glands are found above the kidneys and help orchestrate the body's stress responses by secreting cortisol, adrenaline, and noradrenaline, and help regulate mineral and fluid volume homeostasis.

They also synthesize several steroid hormones. Endurance exercise induced changes in the regulation of approximately half of all mitochondria-associated genes in the adrenal glands.[2] Few researchers expected such a widespread response, as little prior research had examined how exercise affects the adrenal glands.

Perhaps the most surprising finding was that although cardiorespiratory fitness improved in both the male and female rats, many exercise-driven molecular changes varied by sex.[2]

When the MoTrPAC team used "unsupervised," or hypothesis-agnostic, approaches to analyzing the molecular changes, sex differences repeatedly emerged as a primary signal, says Dr. Ashley. The widespread nature of these differences took the field by surprise, because most previous studies have focused on one sex or the other to constrain research costs, he explains.

Sex differences were especially pronounced in subcutaneous white adipose tissue, a type of body fat.[3] The female rats displayed changes in -omic signatures (e.g., changes in gene expression, protein and lipid abundances) linked to insulin signaling and the creation of fat cells, whereas the male rats displayed -omic signatures related to aerobic metabolism. These changes could have contributed to another notable sex difference: male rats lost weight over the course of eight weeks of endurance training, whereas female rats maintained their baseline weight.

"In the adrenal gland, many of the exercise-induced changes in mitochondria went in opposite directions in the male and female rats, and we are not sure why," says Dr. Bodine. Sex differences were also observed in exercise-induced molecular changes in the lungs and the brain.

These findings underscore the critical importance of studying sex as a biological variable when examining the health impacts of exercise.

Longer term, understanding exercise-induced molecular changes could help inform personalized exercise recommendations based on individual characteristics, such as age, sex, and fitness level. It could also help researchers develop new drugs, or repurpose existing drugs, that target the molecular pathways affected by exercise.

Finding such drugs or other adjuvants could be valuable because, while everyone reaps health benefits from exercise, not everyone benefits to the same degree, says Marcas Bamman, Ph.D., Senior Research Scientist and Director of Healthspan, Resilience, and Performance Research at the Florida Institute for Human & Machine Cognition. Drugs or other adjuvants could potentially augment some of exercise's beneficial effects for suboptimal responders.

Marcas Bamman, Ph.D., Florida Institute for Human & Machine Cognition

Human Sex Differences in Training

The MoTrPAC preclinical findings indicate important, widespread sex differences in the molecular responses to exercise—at least in rodents. However, rodents generally exhibit larger male-female differences than humans, so examining molecular adaptations to exercise in humans is essential for understanding the import of the preclinical findings. Several recent studies have found sex-specific molecular impacts similar to those found in MoTrPAC's preclinical studies—suggesting that important sex differences occur in humans as well.

For example, a recent study by Dr. Bamman and his colleagues revealed overlapping but also divergent sex-specific molecular responses to a single bout of combined resistance (strength) and endurance exercise.[4] He became interested in the effects of combined training, because the latest Health and Human Services Guidelines recommend that adults get at least 150 minutes of moderate *or* 75 minutes of vigorous (endurance) physical activity every week *and* engage in some form of resistance training at least twice per week,[5] but little research has examined the molecular effects and systemic health benefits of combined resistance and endurance training.

Dr. Bamman and his colleagues randomly assigned exercise-naïve young men and women to one of two groups: a high (HITT)- or moderate (TRAD)-intensity, 12-week, combined endurance and resistance training program. The TRAD program included supervised, progressive endurance and resistance training sessions three times per week. The HITT program included supervised, progressive high-intensity tactical training—a mix of explosive whole body interval training and high-intensity resistance training, also performed three times per week. Notably, the HITT sessions were about half the duration of the TRAD sessions.

Despite shorter training sessions, the HITT program led to improvements in indicators of health and physical fitness similar to those of the TRAD program, including comparable decreases in body fat mass and increases in muscle mass and cardiorespiratory fitness.[6] Intriguingly, however, the biological mechanisms involved in these improvements varied across the two programs. The

TRAD program caused greater increases in small blood vessel formation within muscle and greater activation of muscle stem cells, whereas the HITT program led to greater increases in intermyofibrillar mitochondria (a type of mitochondria found deep within muscle fibers).[6]

Echoing MoTrPAC's preclinical findings, men and women obtained comparable strength and fitness gains but exhibited several sex-specific changes in gene expression in both skeletal muscle and in the blood.[4] In future research, Dr. Bamman plans to examine the downstream consequences of these sex-specific molecular responses. He is also currently studying the effects of combined training in older individuals in a collaboration with Dr. Bodine and Dr. Benjamin Miller via the NIH-funded M^{3}AX Trial (R01AG089192, NCT06507189). In an earlier study on muscle aging, he had found that women experience more muscle fiber atrophy with age, whereas men appear to experience more muscle fiber loss,[7] suggesting that sex may also play an important role in how the body responds to exercise with age. Studying the molecular effects of exercise in older individuals is therefore critical for understanding how sex differences manifest.

The Menopause Transition, Exercise, and Metabolic Health

During and after menopause many women gain visceral fat—a type of fat found under the abdominal wall that accumulates around the internal organs.[8] Excessive visceral fat is linked with increases in insulin resistance and raises women's risk for heart disease, stroke, type 2 diabetes, and fatty liver disease.

"This weight gains happens even though women believe they have not changed how much they are eating or how much they are exercising—seemingly without their consent," notes Wendy Kohrt, Ph.D., Distinguished Professor of Medicine in the Division of Geriatric Medicine at the University of Colorado Anschutz Medical Campus and the Ludeman Center Nancy Anschutz Chair in Women's Health Research.

Wendy Kohrt, Ph.D., University of Colorado Anschutz Medical Campus

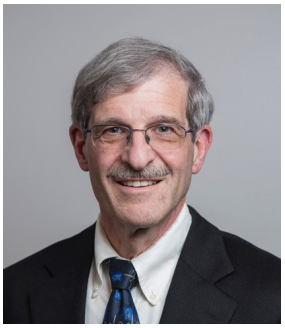
During the menopause transition, estrogen concentrations in the blood decline dramatically. Dr. Kohrt has conducted a series of studies to understand how this dramatic decline in estrogen affects women's metabolism and contributes to postmenopausal weight gain. To isolate the effects of the drop in estrogen from those of general aging, Dr. Kohrt studied these effects in premenopausal women.[8] She first lowered their estrogen levels to a postmenopausal state by giving them gonadotropin-releasing hormone analogues (GnRH-a), a medication sometimes used to treat uterine fibroids. She then randomly assigned them to estrogen replacement therapy (via estrogen patches) or to a placebo. Over the months that followed, women receiving the placebo tended to gain weight, particularly in the form of visceral fat, and to lose muscle mass and bone.[8–10] By contrast, women receiving replacement estrogen did not experience these changes.[8–10]

These studies found that the decline in estrogen affected body weight in a couple of ways, says Dr. Kohrt. First, the drop in estrogen lowered women's resting metabolic rate, or the amount of calories burned at rest. Women whose estrogen concentrations were suppressed without replacement burned approximately 50 fewer calories a day than they did prior to the suppression.[8,9] Fifty calories might seem like a small amount, like eating an extra half of a piece of bread a day, notes Dr. Kohrt, but it can add up quickly. If caloric intake and physical activity do not change, the drop in metabolic rate will result in women gaining about a pound of fat every two to three months. Second, sex hormones are potent regulators of spontaneous physical activity. This regulation is evident in both laboratory animals and humans.[10] For example, laboratory mice and rats with access to running wheels will run for several hours a day, says Dr. Kohrt. But, if you remove the females' ovaries, or the males' testes, their physical activity levels plummet, and not merely by 5–10%, but by 50–70%. If the animals receive replacement estrogen (for females) or replacement testosterone (for males), their activity levels return to normal.

Dr. Kohrt also examined whether engaging in regular exercise would mitigate the gaining of visceral fat.[8] She again first gave women GnRH-a and randomized them to receiving either replacement estrogen or a placebo. Then, she randomly assigned the women to a strength training program. Contrary to expectations, however, strength training did not prevent women from gaining visceral fat. "If you had asked me beforehand, whether I thought the resistance exercise program would be effective at preventing visceral fat gain, my answer would have been an enthusiastic 'yes'," says Dr. Kohrt, "but it didn't." A second study by Dr. Kohrt and colleagues that investigated whether an endurance exercise program would mitigate visceral fat gain found that it reduced visceral fat gain by about 50%.[8] By contrast, the women receiving estrogen patches did not experience any visceral fat gain—underscoring the central role of estrogen in regulating fat deposition.

Estrogen May Modulate Exercise-Induced Increases in Insulin Sensitivity

Estrogen may not only affect fat deposition and spontaneous physical activity but also play a role in a key benefit of exercise: an increase in insulin sensitivity.



William E. Kraus, M.D., Duke University School of Medicine

One of the most important benefits of exercise is an increase in insulin sensitivity in skeletal muscle, says William E. Kraus, M.D., the Richard and Pat Johnson University Distinguished Professor, Professor of Medicine, and Professor in the School of Nursing at the Duke University School of Medicine.

Insulin levels are typically low during exercise, explains Dr. Kraus. During exercise, muscle first burns its glucose reserves for energy. As those reserves become depleted, muscle primarily relies on fats released from body fat stores for energy, taking up glucose from the periphery only relatively poorly. After eating, however, insulin promotes the absorption and storage of glucose by muscle in the form of glycogen and the storage of excess glucose as fat. Muscle should absorb about 80% of glucose after a meal, notes Dr. Kraus. In people with insulin resistance, this ability of muscle to absorb glucose after eating is impaired, leading to harmful post-meal elevations in circulating glucose and triglycerides.

In the 2000s, Dr. Kraus and his research team conducted a randomized controlled trial of the effects of endurance exercise training on insulin sensitivity in skeletal muscle. Many postmenopausal women in the study were receiving hormone replacement therapy (HRT), in the form of added estrogen and progesterone. Unexpectedly, these postmenopausal women experienced greater increases in insulin sensitivity following six months of aerobic exercise than did women who were not taking HRT.[11]

More recently, Dr. Kraus and his colleagues have identified changes in gene expression within skeletal muscle that may underlie exercise-driven increases in insulin sensitivity. They found evidence for two signaling pathways: a protein kinase C pathway, a known signaling pathway activated by muscle contractions, and an estrogen receptor signaling pathway.[12] These findings further point to the potentially important role of estrogen in exercise-driven increases in insulin sensitivity.

Sex Differences in Exercise

The widespread sex differences in molecular responses to exercise seen in rodents in MoTrPAC, as well as intriguing new data on molecular responses in humans, suggest that although regular exercise has many health benefits for both men and women, the mechanisms by which those benefits occur may vary by sex. There may be many paths up the mountain, and they may not arrive at the exact same place. What is clear, however, is that further careful study of the molecular effects of exercise in men and women will be essential for developing drugs that target these molecular pathways and for providing personalized exercise recommendations.

Probing the Mechanisms of Ovarian Aging

Yousin Suh, Ph.D., Columbia University

Biological aging occurs as organs and bodily systems undergo functional decline, increasing an individual's risk for mortality, says Yousin Suh, Ph.D., the Charles and Marie Robertson Professor of Reproductive Sciences in Obstetrics and Gynecology, Professor of Genetics and Development, and Director of Reproductive Aging at Columbia University. The ovaries are one of the first organs to undergo such a decline. People sometimes assume this decline happens at menopause, she says, but in fact, the ovaries begin to age 10–15 years before menopause, typically starting in the mid to late thirties.

The aging of the ovaries affects the whole body, because the ovaries are an endocrine organ, Dr. Suh explains. They communicate with the brain, liver, pancreas, kidneys, skin and other organs throughout the body. In contrast to the gradual age-related decline in reproductive function seen in men, menopause acts as an aging inflection point for women. After menopause, women's risk for health conditions such as heart disease, immune system dysfunction, osteoporosis, and stroke rise dramatically,[13] suggesting that ovarian aging and the corresponding hormonal declines may precipitate dysfunction and aging in other organs. Consistent with this hypothesis, studies in mice have shown that replacing aged, post-reproductive ovaries in aged mice with ovaries from young mice reduces age-associated inflammation, improves heart health, and extends their lifespans.[14]

Aging in the ovaries reflects the same biological aging processes seen in other organs and tissues (e.g., declines in mitochondria, reduced DNA damage repair activity), Dr. Suh emphasizes, but for unknown reasons, these processes are accelerated in the ovaries. To understand the potential causes of this acceleration, she is studying genetic variants influencing the natural age at menopause.

Women vary in terms of the age at which they undergo menopause. While the average age of natural menopause in the United States is 52 years, some women undergo menopause in their thirties or early forties, whereas others do not experience menopause until their late fifties.[15]

Several large genome-wide association studies have identified several genetic variants that are linked with a

younger or older age at menopause. However, 94% of identified variants are found in noncoding regions of the genome (i.e., not within genes) and in stretches of the genome that are typically inherited as a block containing hundreds if not thousands of genetic variants. How, then, to identify which genetic variant within an identified stretch is causally linked with ovarian aging? The problem is akin to knowing a particular forest contains the oldest living tree, but not knowing which tree.

To tackle this problem, Dr. Suh performed single-nuclei RNA sequencing to determine which genes were actively expressed and their expression levels in ovarian tissue from young (23–29 years) and reproductively aged (49–54 years) donors.[16] By combining these data with data published by the NIH Common Fund, she could then determine which genetic variants in these noncoding regions were likely to have a causal impact.[16] She selected the most promising set of variants for further testing, based on whether they were (1) found in regulatory elements (parts of the genome that act as master switches to affect the transcription of other genes) that are active in ovarian cell types and (2) accessible to transcription factors and other macromolecules (i.e., not bound to chromatin, a protein that binds and regulates access to portions of the genome).[16]

This approach identified a variant, rs3741605, that was associated with a slower rate of ovarian aging in ovarian cells.[16] This variant reduces the expression of the *HELB* gene, which encodes DNA helicase B—a protein that suppresses homologous recombination (a form of DNA repair that uses information from undamaged DNA).

Dr. Suh is now working to study the effects of this variant in a mouse model, to confirm that the variant slows the rate of ovarian aging *in vivo* and to examine any impacts on the healthspan, or period of healthy life. This latter question, how slowing ovarian aging affects health over the life course, is a critical one. Although later menopause is associated with a slightly reduced risk of cardiovascular disease and a longer life, it is also associated with a slightly increased risk of breast and uterine cancers.[17]

Dr. Suh presented these and other findings related to ovarian aging at the NIH Director's Wednesday Afternoon Lecture Series on Wednesday, April 23, 2025. A video recording of her presentation is available online.

WOMEN IN SCIENCE

SCIENTIST SPOTLIGHT

Sue Bodine, Ph.D., Oklahoma Medical Research Foundation

Sue Bodine, Ph.D., FAPS, FIUPS, is a Professor of Aging & Metabolism at the Oklahoma Medical Research Foundation (OMRF). Prior to joining OMRF, she served as a Professor of Medicine at the University of Iowa Carver College of Medicine. Her research focuses on the neuromuscular system and its response and adaptations to positive and negative stimuli, such as exercise training, disuse, and aging.

Dr. Bodine received her Ph.D. from the University of California, Los Angeles, and throughout her career has worked in academic and industry settings. She is the President-elect of the American Physiological Society.

How would you describe your primary areas of research, and how did you become interested in those areas?
Broadly speaking, my research has focused on the neuromuscular system and the plasticity of skeletal muscle. Skeletal muscle is fascinating because it is such an adaptable tissue, one that is constantly responding to both positive and negative signals. So, over the years, my research has focused on understanding the mechanisms underlying the response of muscle to both positive and negative stimuli.

With respect to positive stimuli, my research has studied the response to different types of exercise, both resistance exercise and aerobic exercise. My research also studies the causes of muscle atrophy in response to negative stimuli such as spinal cord injury, denervation, and disuse. For example, I have examined the effects of spaceflight on muscle for studies funded by NASA.

I became interested in muscle as an undergraduate. I majored in kinesiology, and became interested in the control of locomotion, how the nervous system activates muscles to produce movement. From this initial interest, I began looking at signaling to understand the molecular mechanisms that determine how muscles respond to different stimuli.

What are some of the accomplishments that you are proudest of?
I am proud of the research that my lab has published over the years. Our research has had a significant impact on the field, many of our findings in preclinical animal models have been shown to translate to humans. It is always exciting when preclinical findings can be translated.

I am also proud to have served as a role model for young scientists, particularly young women. When I was teaching an undergraduate course in exercise physiology in the mid-2000s, young women would tell me how much they appreciated having a woman scientist as a professor.

Finally, I am deeply grateful and proud to have had the opportunity to influence so many students at different phases of their careers and to advocate for my graduate and postdoctoral students.

What are some of the barriers that you faced in your career?
Like many women, I have certainly had the experience of not having my voice heard. I have also worked in some environments that were not supportive of women or that had different expectations for promotion for men and women. Fortunately, I have been able to succeed, despite encountering such barriers, but it has not always been easy.

What advice would you give to fledgling scientists or students considering a career in science?
First, I would emphasize that running a laboratory is like running a small business; however, most graduate students do not receive sufficient training in how to run a laboratory. Hiring good people is essential.

Second, from a research perspective, I tell my students to not be afraid to challenge dogma. Do not exclusively pursue incremental advances. Instead, take risks and conduct studies that can have a big impact.

Third, many programs now provide mentoring committees for young faculty, and finding mentors is certainly good advice for young scientists. But I would also recommend finding an advocate, somebody who will advocate for your career, nominate you for awards. Advocates are different from mentors, and they do not necessarily have to work at the same institution as you.

And finally, I would stress the importance of finding your scientific community. It may be local, perhaps in your department, but it can also be broader. For me, I have found my scientific community in scientific societies. I have served as an active member of the American Physiological Society (APS) and recently became the President-elect. APS provided me with a scientific home and a network of people outside of my local community to interact with and rely upon.

NEWS AND EVENTS

The 9th Annual Vivian W. Pinn Symposium Spotlights Advances in Data Science and Women's Health

On May 15, 2025, ORWH held its 9th annual Vivian W. Pinn Symposium, "Advancing Data-Driven Innovation for the Health of Women". The symposium, which honors the first full-time director of ORWH, Vivian Pinn, M.D., is held every year during National Women's Health Week. The 9th annual symposium focused on advances in data science and women's health. ORWH Director Janine Austin Clayton, M.D., FARVO, gave the opening remarks. Raquel Hill, Ph.D., Chair and Professor of Computer and Information Sciences and Professor at Spelman College, gave the capstone address, "Advancing Data Innovations for Health Improvements: Possibilities and Pitfalls." A recording of the event is available on the symposium's event page.

Simultaneous Treatment of Male Partners Reduces Recurrence of Bacterial Vaginosis

(Original research by L. A. Vodstrcil, et al., DOI: 10.1056/NEJMoa2405404)

Bacterial vaginosis is the most common vaginal infection in reproductive age women. It occurs when a shift occurs in the vaginal microbiome. Symptoms can include itching, irritation, burning during urination, and changes in vaginal odor and discharge, but some women with bacterial vaginosis do not experience any symptoms. Even in the absence of symptoms, bacterial vaginosis increases women's risk of developing pelvic inflammatory disease and of contracting sexually transmitted infections, such as gonorrhea and HIV.[18] During pregnancy, bacterial vaginosis raises the risk of premature labor.[19]

Bacterial vaginosis is typically treated with oral antibiotics. Unfortunately, women experience very high rates of recurrence after treatment—approximately 60% will experience a recurrence within a year.[20] Whether sexual transmission from male partners contributes to the high rates of recurrence has been controversial.[18] Early trials of co-treatment of male partners with oral antibiotics did not find a benefit.[18] In addition, men do not experience symptoms of bacterial vaginosis.[18]

Now, however, a randomized clinical trial published in the *New England Journal of Medicine* has provided strong evidence that male partner co-treatment for bacterial vaginosis reduces the risk of recurrence.[21] Lenka A. Vodstrcil, Ph.D., Senior Research Fellow at the Melbourne Sexual Health Centre, and colleagues randomly assigned women with bacterial vaginosis and their partners either to first-line antibiotic therapy for the women only or to first-line antibiotic therapy for the women in combination with oral and topical antibiotic therapy for her male partner. The trial was ended early because of efficacy: By 12 weeks after treatment, women whose partners were co-treated had approximately half the rate of recurrences (35%) versus women whose partners were not treated (63%).[21]

In an accompanying editorial, Christina A. Muzny, M.D., M.S.P.H., of the University of Alabama at Birmingham and Jack D. Sobel, M.D., of Wayne State University in Detroit Michigan, argue that the trial results provide strong evidence that bacterial vaginosis can be sexually transmitted, particularly in the context of a regular sexual partnership, and that clinicians need to consider co-treatment of male partners as part of standard of care for this common condition.[18]

Childhood Adversity Is Linked with Different Health Impacts for Men and Women in Midlife

(Original research by J. Alley and J. Gassen et al., 2025. Brain, Behavior, and Immunity. DOI: 10.1016/j.bbi.2024.07.019)

Childhood adversity is a well-established risk factor for chronic disease later in life.[22,23] Stressors experienced during childhood include financial distress, emotional, sexual, or physical abuse, emotional or physical neglect, witnessing of domestic abuse or violence, household member imprisonment, living with someone who is abusing alcohol or drugs, or living with someone who is mentally ill or suicidal. More than half of American adults report experiencing one or more these stressors in childhood, and one-fifth report experiencing at least three—making the lasting health impacts of early life stress a major public health concern.[24]

To examine how early life stress might affect health later in life, Jenny Allen, Ph.D., Jeffrey Gassen, Ph.D., of the University of California, Los Angeles, and their colleagues examined how stressors during childhood related to 25 biomarkers of inflammation, metabolism, and stress, and 20 major health conditions among approximately 2,000 participants of the Midlife in the United States (MIDUS) Study—a nationally representative, longitudinal study funded by NIH. They observed several sex differences. The associations of childhood stressors with metabolic biomarkers (e.g., insulin, cholesterol, and triglycerides) in midlife were generally larger for women than men; however, emotional abuse and neglect were associated with more pronounced detrimental health effects among men, particularly for thyroid issues, blood disorders, and mental and behavioral health problems. Both men and women who experienced emotional abuse during childhood had elevated risks for cancer and respiratory issues in adulthood. Notably, severity of early life stress, regardless of type, was the strongest predictor of later-life chronic disease for both men and women.

These findings highlight the importance of research on the mechanisms through which early life stress may affect later life health, and how these mechanisms might vary by the extremity and type of stressors experienced and by biological sex.

Exercise May Help Protect Against Brain Aging Through Multiple Mechanisms

(Review by A.R. Tari and T.L. Walker et al., 2025. Lancet. DOI: 10.1016/S0140-6736(25)00184-9)

Aging is linked with cognitive decline and an increased risk for dementia. Regular exercise, particularly exercise that improves cardiorespiratory fitness, may help slow the rate of this decline and lower individuals' risk for dementia. For example, super-agers, or individuals who exhibit little to no cognitive decline late in life, typically engage in higher than average levels of physical activity.[25] High levels of physical activity are associated with a 28% lower risk of dementia.[26] Notably, cardiorespiratory fitness

is more tightly linked with longevity than physical activity alone.[27] In a recent prospective study, maintaining or improving cardiorespiratory fitness over time was associated with a 40% lower risk for developing dementia.[28]

In a March 2025 *Lancet* review, Atefe Rafiee Tari, Ph.D., of the Norwegian University of Science and Technology, and Tara L. Walker, Ph.D., of the Queensland Brain Institute at the University of Queensland, and colleagues describe the multiple mechanisms by which physical activity may slow cognitive aging and lower the risk for dementia.[29] Physical activity reduces the risk for diseases linked with higher risks of dementia, including hypertension and type 2 diabetes. It has also been linked with reductions in many of the so-called hallmarks of aging (signs of cellular and physiological dysfunction that increase with age), including reducing chronic inflammation and circulating markers of cellular senescence, improving cellular waste removal, and enhancing structural and functional connectivity in the brain. Physical activity increases brain-derived neurotrophic factor, which may protect against age-related neurotoxic changes related to calcium-ion homeostasis and mitochondrial dysfunction. In rodents, exercise enhances neurogenesis (the growth of new neurons) and synaptogenesis (the growth of new connections between neurons), both of which play key roles in learning and memory.

Several of the brain-relevant changes induced by physical activity appear to differ by sex, suggesting that it is important to examine its impacts in both sexes. For example, exercise alters microRNA (a type of RNA that regulates gene expressions) in the blood, but the microRNAs associated with cardiorespiratory fitness differ in men and women. Similarly, exercise modifies DNA methylation (the chemical tagging of DNA that alters gene expression), but with greater modifications in females than males.

The review underscores the diversity of mechanisms by which physical activity may exert neuroprotective effects. Based on their review, the authors call for more precise exercise studies that use carefully controlled and repeated exercise regimens, and for more widespread public communication of the brain benefits of high-intensity physical activity.

UPCOMING EVENTS

63rd Meeting of the Advisory Committee on Research on Women's Health (ACRWH)	June 17, 2025, 9:00 a.m.–2:30 p.m. EDT
Small Business Opportunities for Innovative Women's Health Research	June 25, 2025, 11:00 a.m.–1:00 p.m. EDT
NIH Women's Health Research Roundtable: Vaginal Microbiome and Implications for Women's Health	July 17, 2025, 3:00 p.m.–4:00 p.m. EDT
64th Meeting of the Advisory Committee on Research on Women's Health (ACRWH)	October 7, 2025, 9:00 a.m.–4:00 p.m. EDT
Specialized Centers of Research Excellence (SCORE) on Sex Differences 2025 Annual Meeting Keynote and Capstone Addresses	November 3, 2025, 8:00 a.m.–5:00 p.m. EST
Building Interdisciplinary Research Careers in Women's Health (BIRCWH) Annual Meeting	November 4, 2025, 8:00 a.m.–5:00 p.m. EST

FUNDING OPPORTUNITIES

Women's Health Research (NOT-OD-24-079) Applications due by November 5, 2027

Interventions to expand cancer screening and preventive services to ADVANCE health in populations that experience health disparities (R01, Clinical Trial Required) (PAR-25-098) Applications due by January 8, 2027

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