allowing high levels of cytokines to reach the brain.

Reducing or eliminating these adverse effects will be necessary before these drugs can be rolled out to wider populations. Curran said there simply wouldn't be enough ICU beds if therapy was made available to adult patients with solid tumors and every one of them required intensive care.

"We have to make it safer, but we don't want to reduce efficacy," he said.

Developing similar therapies for solid tumors will be more challenging.

"Solid tumors have a different tumor environment," Porter explained. "It will be harder to get [CAR-Ts] into the tumor cell."

Another substantial obstacle will be finding a way to more quickly produce CAR-T cells, which currently take weeks to manufacture from a patient's cells.

"Some patients don't have that much time," explained Porter.

A potential solution may be to develop a set of universal CAR-T cells that can be used to treat any patient, Porter and Curran agreed.

Curran is optimistic that the next generation of CAR-Ts will be able to overcome some of these challenges.

"We don't think we are done," he said. "We think there are better ways to do it."

Hope and Hype

For oncologists like Prasad, CAR-T is very promising for patients with refractory ALL. In fact, he has referred patients to ongoing trials and recommends that other physicians refer appropriate patients.

But he cautioned against the "irrational exuberance" that sometimes accompanies new cancer therapies, particularly considering the $475 000 and $373 000 price tags for tisagenlecleucel and axicabtagene ciloleucel, respectively.

"I'm excited about CAR-T," Prasad said. "It is good to be excited, but we shouldn't let our excitement cloud our critical appraisal of the benefits, [who is not benefiting], the harms, and the costs."

He noted that the price of the cells is just "the tip of the iceberg" because it doesn't include the costs associated with administering the therapy, such as potential ICU stays, or the costs of drugs to control CRS.

"It's pretty important to figure out all the surrounding costs," agreed David Rind, MD, MSc, the chief medical officer of the Institute for Clinical and Economic Review. The ICER is conducting an ongoing analysis of the comparative clinical effectiveness and cost-effectiveness of CAR-T therapies to assess their value and is collecting data from manufacturers and other sources. Rind expects an initial report in December.

However, Rosenberg points out that developing cell-based therapies that cure cancer, rather than having patients move from one expensive treatment to another, may ultimately help reduce overall costs.

"If we can develop curative treatments, then even these high price tags for the personalized therapies will save money [in the long run]," he said.

Though it's still early days in the field of CAR-T therapy, Porter expects it will have a substantial impact on cancer care.

"This isn't just a new treatment, this is a new approach to treating cancer," Porter said. "To me, the most exciting take home is that it is possible to genetically manipulate immune cells to get them to target cancer." ■

Note: Source references are available through embedded hyperlinks in the article text online.

Can Exercise Prevent Knee Osteoarthritis?

Jennifer Abbasi

A study of human skeletons housed in the vaults of US museums is providing a unique historical perspective on the prevailing wisdom that knee osteoarthritis (OA) is primarily a disease of aging and overweight, factors that are difficult if not impossible to prevent at the population level.

In the recent comparison of bones from different periods, people born in the postindustrial era were substantially more likely to have knee OA than those born earlier, confirming a widespread belief that the condition is becoming more common.

More surprisingly, however, the increase in prevalence remained even after researchers controlled for risk factors including age and body mass index (BMI). The findings suggest that the commonly accepted risk factors may be incomplete.

"At a given age, if you were born after World War II you are more than twice as likely to have OA in your knee than if you had been born earlier, regardless of your weight," said study coauthor Daniel Lieberman, PhD, chair of the department of evolutionary biology at Harvard University.

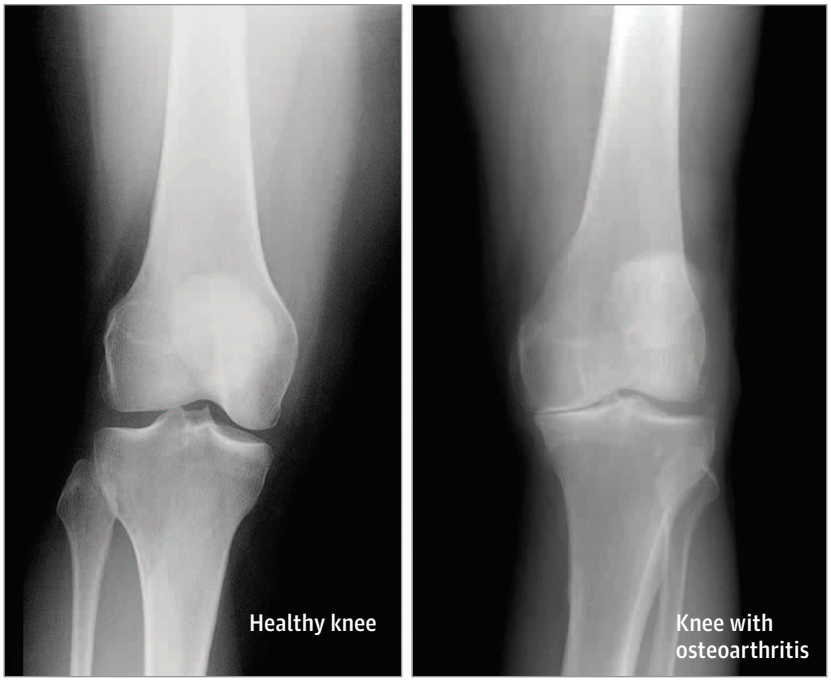
Although the study, published in the *Proceedings of the National Academy of Sciences*, was not designed to identify factors driving up cases of knee OA, experts including those not involved with the research speculate that changes in physical activity may be an explanation.

A Missing Link

Lieberman decided to study osteoarthritis of the knee while writing a book on what he calls "mismatch diseases." These conditions, like heart disease and diabetes, are more common or severe today "because our bodies are inadequately or imperfectly adapted to modern environmental conditions," he explained.

While compiling a table of major mismatch diseases for the book, he had a realization: Although numerous epidemiological studies have indicated that knee OA is highly prevalent today, and that older age and obesity are strong risk factors, whether the disease's prevalence can be explained by an ever-aging population and increasing obesity has never been tested.

"Because people are, on average, living longer today than they were a century or so ago, and because obesity has only become a public health crisis within the past few decades, many clinicians assume that knee OA is highly prevalent today because people are living longer and are more commonly obese," said Ian J. Wallace, PhD, a postdoctoral researcher in Lieberman's laboratory and first author of the new study. "Because there is an assumption that these are the risk factors that best explain the current prevalence of the disease, little



attention is paid to prevention since aging is unavoidable and the obesity epidemic has been extremely difficult to tackle."

To investigate these assumptions about risk factors, Wallace and academic collaborators documented cases of knee OA in more than 2000 skeletal remains of people who died between 1905 and 1940 during the early industrial era and between 1976 and 2015 during the modern postindustrial era. They also examined 176 skeletons from prehistoric hunter-gatherers and early farmers who lived between 6000 to 300 BP (before present, or years prior to 1950). To diagnose knee OA in cadaver collections from around the country, they looked for knee eburnation, a bone-on-bone polishing of the femur, tibia, and patella that occurs when cartilage is worn down in the late stages of degenerative joint disease.

All of the study subjects were at least 50 years old when they died, based on death records or age-related changes on the surface of their hip bones, and BMI was available from death records for most early industrial (84%) and postindustrial (64%) samples.

Knee OA has previously been documented in human fossils, and the new research confirmed that it's an ancient ailment: 8% of prehistoric individuals in the study had the condition. It also appears to have become more common over the past century. Prevalence was 16% among the 819 postindustrial samples but only 6% in the 1581 early industrial samples.

On average, postindustrial individuals in the study were older and heavier when they died than preindustrial individuals, and age and BMI were positively associated with knee OA in these groups. But even after controlling for age and BMI, as well as sex and ethnicity, prevalence was still 2.1 times higher for people who died between 1976 and 2015 than for those who died between 1905 and 1940.

"I think that we all have in the back of our minds that it's not just aging and obesity that is causing the increase in arthritis," said Brian M. Grawe, MD, an orthopedic surgeon and assistant professor of sports medicine at the University of Cincinnati Academic Health Center, who was not involved with the work. "They basically proved that there is a missing link."

The Fitness Factor

For now, the researchers can only speculate on what that missing link—or, more likely, links—could be. Experts agree that knee OA is almost certainly multifactorial, and Lieberman and his coauthors suggest plausible modern-day contributors ranging from inflammatory diets to hard pavements to the advent of footwear.

At the top of their suspect list is the shift toward more sedentary lifestyles. Research suggests that exercise can help prevent knee OA. According to David Felson, MD, a coauthor on the new study, physical activity within a certain range likely promotes the growth and maintenance of knee cartilage, ligaments, and bones, and strengthens muscles to appropriately distribute loads across the joint.

Felson is a professor of medicine and epidemiology at Boston University School of Medicine, where his research focuses in part on causes of osteoarthritis. "The absence of activity, the sort of sedentary lifestyles many of us have fallen into, may not be so healthy for our joints," he said. "I think it's a reasonable idea."

Jeffrey Geller, MD, chief of the division of hip and knee reconstruction at Columbia University Medical Center, points to the fact that knee cartilage in adults has no blood supply other than that promoted by physical activity.

"Activity and weight-bearing forces the nutrients in the joint fluid to diffuse into knee cartilage, and that is its main source of nutrition," he said. "There's no formal mechanism other than the sort of pumping action of the mechanics of the knee."

On the other end of the spectrum, physical activity-related knee injuries, like anterior cruciate ligament and meniscal tears, are a well-established precursor to knee OA, and could also be contributing to the increase in prevalence.

"That's always been there and I'm sure that explains why some of the fossils we see that have OA got OA," Lieberman said. But, he added, "people might be more susceptible to injury today because they're weaker or they do more abnormal things, like skiing. We did not evolve to ski, I can tell you that as an evolutionary biologist."

Although Felson agrees that sports factor into knee OA, "probably only about 10% of knee OA in older adults is related to recognized sports injuries from earlier in life. It's not as big a factor as you might think," he said.

But the extreme fitness trend of the past decade or so could create more knee OA cases—and knee replacements—down the line. "Things like CrossFit… I see people injuring themselves all the time that have no business doing these activities," Grawe said. "It's leading to a lot of injuries of the knee and ultimately it can lead to arthritis."

There are already around 700 000 knee replacements every year in the United States,

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Geller said, and orthopedic surgeons estimate there may be a need for more than 2 million per year by 2025, potentially outpacing the supply of knee surgeons. Most of the increase will come from the growing aging population, according to Geller, but some may be related to other factors, such as obesity or physical activity levels.

Geller advises joint-friendly exercises. "Things like a stationary bike or an elliptical … are probably the best form of exercise because the impact on a joint is minimal," he said.

Lieberman's team is now looking at prevalence of knee OA in living populations from different parts of the world who have different lifestyles and levels of physical activity. Because physical activity and overweight influence each other, the researchers will try to control for both variables independently in these studies to parse their individual contributions to knee OA. The researchers are also focusing on the effects of physical activity on joints in general and cartilage in particular using animal models in the laboratory.

In the end, having a happy medium of physical activity may turn out to be a reasonable approach to warding off knee OA, along with maintaining a healthful diet and weight to reduce joint-damaging inflammation and abnormal load bearing.

"To me, what's important about the paper is that it suggests that OA is much more preventable than we often assume," Lieberman said. ■

Note: Source references are available through embedded hyperlinks in the article text online.

The JAMA Forum

Five Ethical Values to Guide Health System Reform

Lawrence O. Gostin, JD

The US health system is so mired in politics, with positions hardened by rigid ideologies, that we can't even seem to talk with one another civilly about difficult tradeoffs. If the polity could agree on core ethical values to guide discourse, we would make hard health system choices based on *which* values we prefer and *why*. Herein, I offer 5 critical values for health system reform—universal access, equitable access, affordable access (cost), quality, and choice—explain the tradeoffs, and provide reasons why certain values should take priority. There will be disagreement across the political spectrum, but alternative visions should be justified by reasoned argument.

Universal Access

Health is foundational to life's joys and opportunities—reproduction, family, work, play, and creativity, to name a few. If a person is ill, injured, or in pain, having access to health care that is affordable, accessible, culturally and linguistically appropriate, and of good quality is of high value. There is no "right to health" in the United States. Even absent a domestic legal entitlement, however, universal access should represent a core ethical value precisely because every individual would choose health care as a personal priority and for family members.

Equitable Access

Vast inequalities exist across multiple spheres, which animates compelling political debates. Fairness is a strong value in the United States but so are economic freedom, individual striving, and entrepreneurship. It is unlikely that quality health care services will be distributed equally across all populations. Yet fairness requires a reasonable allocation of quality services according to need, irrespective of ability to pay.

Popular support for Affordable Care Act guarantees—no exclusions for preexisting conditions or lifetime caps on coverage—is testament to the value of equity. Equity requires that the lived experiences of individuals in access and quality of health services are not inordinately different based on wealth, geography, race, or religion. Tolerating some differences may be acceptable to many, but widely disparate treatment—marked tiers in access and quality—appears unjust.

Cost: Affordable Access

In theory, everyone understands that cost is important in any societal decision. Resources are limited, and the polity will accept only so much taxation. The line between public services and revenue raising, and the public's tolerance for increased public debt, are quintessentially political questions. But somehow in health care, attempts to constrain costs are shrouded in partisan accusations of rationing. Many US consumers are suspicious of national, single-payer health systems, such as the United Kingdom's National Health Service and Canada's single payer system, and associate them with rationing of care—yet think highly of Medicare, even though it, too, is a single-payer system. Private health insurance, of course, also rations care but on a different basis, based on the cost of premiums, co-payments, and deductibles. It is widely known that the United States spends nearly double per capita on health care than other countries. Yet US health indicators (eg, life expectancy and child and maternal mortality) rank low compared with those of Organisation for Economic Co-operation and Development nations.

Given scarce resources, the World Health Organization (WHO) recommends the following priorities: maximizing population health, prioritizing the worse off, and shielding people from health-related financial risks. Allocation of health care resources should give marked preference to clinical evidence of cost-effectiveness. The WHO, and many countries, have evidence-based medicines lists, indicating what will and will not be paid for. The National Institute

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