EPIDEMIOLOGICAL SCIENCE

Knee osteoarthritis risk in non-industrial societies undergoing an energy balance transition: evidence from the indigenous Tarahumara of Mexico

Ian J Wallace,[1] David T Felson,[2,3] Steven Worthington,[4] Jeffrey Duryea,[5] Margaret Clancy,[2] Piran Aliabadi,[5] Geeta N Eick,[6] J Josh Snodgrass,[6] Aaron L Baggish,[7] Daniel E Lieberman[1]

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For numbered affiliations see end of article.

Correspondence to
Ian J Wallace; iwallace@fas.harvard.edu
Daniel E Lieberman; danlieb@fas.harvard.edu

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ABSTRACT

Non-industrial societies with low energy balance levels are expected to be less vulnerable than industrial societies to diseases associated with obesity including knee osteoarthritis. However, as non-industrial societies undergo rapid lifestyle changes that promote positive energy balance, individuals whose metabolisms are adapted to energetic scarcity are encountering greater energy abundance, increasing their propensity to accumulate abdominal adipose tissue and thus potentially their sensitivity to obesity-related diseases.

Objectives Here, we propose that knee osteoarthritis is one such disease for which susceptibility is amplified by this energy balance transition.

Methods Support for our hypothesis comes from comparisons of knee radiographs, knee pain and anthropometry among men aged ≥40 years in two populations: Tarahumara subsistence farmers in Mexico undergoing the energy balance transition and urban Americans from Framingham, Massachusetts.

Results We show that despite having markedly lower obesity levels than the Americans, the Tarahumara appear predisposed to accrue greater abdominal adiposity (ie, larger abdomens) for a given body weight, and are more vulnerable to radiographic and symptomatic knee osteoarthritis at lower levels of body mass index. Also, proportionate increases in abdomen size in the two groups are associated with greater increases in radiographic knee osteoarthritis risk among the Tarahumara than the Americans, implying that the abdominal adipose tissue of the Tarahumara is a more potent stimulus for knee degeneration.

Conclusions Heightened vulnerability to knee osteoarthritis among non-industrial societies experiencing rapid lifestyle changes is a concern that warrants further investigation since such groups represent a large but understudied fraction of the global population.

Key messages

What is already known about this subject?

- Non-industrial societies worldwide are experiencing rapid lifestyle changes that promote chronic positive energy balance, but the impact of such changes on knee osteoarthritis risk is unknown.

What does this study add?

- Based on data from Tarahumara subsistence farmers in Mexico, we propose that individuals in non-industrial societies undergoing an energy balance transition have a heightened sensitively to knee osteoarthritis.
- Specifically, individuals born under conditions of energetic scarcity who later encounter greater energy abundance are predisposed to accumulate abdominal adipose tissue, making them susceptible to knee osteoarthritis at lower levels of body mass index.

How might this impact on clinical practice or future developments?

- Our findings suggest that the burden of knee osteoarthritis among non-industrial societies undergoing lifestyle changes is likely greater than realised and warrants increased attention.

INTRODUCTION

Knee osteoarthritis (OA) is a major public health concern in developed and newly industrialised countries,[1] yet relatively little is known about the disease's prevalence in non-industrial societies including hunter-gatherers and subsistence farmers.[2] Although risk of knee OA is influenced by numerous factors including age, sex and certain genes, multiple lines of evidence indicate that the high burden of the disease in industrialised nations is due in large part to the obesity epidemic.[3] Obesity, defined as having a body mass index (BMI) of 30 kg/m^2 or higher, has the potential to contribute to knee OA pathogenesis by promoting chronic low-grade systemic inflammation, mechanically induced damage to joint tissues and local inflammation secondary to this damage, all of which may interact to weaken and degrade joint tissues.[3] Thus, populations with a relatively low prevalence of obesity, as has been reported for many non-industrial societies,[4,5] might be expected to exhibit proportionately low levels of knee OA.

In recent decades, however, non-industrial populations worldwide have been experiencing varying degrees of lifestyle change, including an energy balance transition characterised by shifts in diet and physical activity that have led to increases in BMI.[6,7] Moreover, studies of groups undergoing this energy balance transition have frequently documented a heightened sensitivity to obesity-related diseases for a given BMI relative to individuals in developed countries.[8 9] The mechanisms underlying this amplified disease risk are complex and not fully understood, but early-life environmental conditions play an important role.[10 11] Early development in energy-limited environments adapts individuals' metabolic phenotype to conditions of energetic scarcity, which may be beneficial in terms of short-term survival but potentially comes at the cost of increased susceptibility to metabolic dysregulation later in life if energy becomes more abundant.[12 13] As a result of this 'thrifty phenotype',[14] numerous populations undergoing the energy balance transition are experiencing rapidly rising rates of cardiometabolic disorders such as type 2 diabetes, hypertension and coronary heart disease,[15 16] all of which are often comorbid with knee OA,[3] implying that the threat of knee OA in non-industrial societies could be higher than perhaps expected.

Among the most salient characteristics of the metabolic phenotype of individuals born in energy-limited environments but later exposed to greater energy abundance is a propensity to preferentially accumulate and maintain visceral adipose tissue,[17 18] typically resulting in a relatively large abdomen circumference for a given body weight.[19] Excess visceral adipose tissue is a potent source of adipokines that promote chronic low-grade systemic inflammation,[20] including IL-6, TNF-α, leptin and others that may contribute to knee OA pathogenesis.[21] Moreover, experimental evidence suggests that individuals whose metabolic phenotype is adapted to energetic scarcity are not only more prone to possessing large amounts of visceral adipose tissue under conditions of energetic abundance, but their adipocytes also secrete higher concentrations of pro-inflammatory adipokines.[22 23] Therefore, it is reasonable to hypothesise that non-industrial populations experiencing the energy balance transition may not only have an enhanced susceptibility to knee OA for a given BMI, but also that abdomen size among such groups is a stronger determinant of knee OA risk than in industrialised countries.

Here, we test this model of heightened knee OA risk among non-industrial societies undergoing the energy balance transition by comparing the probability of knee OA and its association with BMI and abdomen size in two groups: the Tarahumara, an indigenous population of subsistence farmers living in the Sierra Madre Occidental of Mexico (figure 1); and a well-studied urban population of Americans from Framingham, Massachusetts.[24 25] The Tarahumara grow and eat mostly maize and beans and tend to be very physically active due to their non-mechanised farming methods, lack of motorised vehicles and the mountainous terrain in which they typically walk long daily distances to collect water, firewood and other resources.[26 27] Notwithstanding, few Tarahumara remain isolated from outside economic and cultural influences. In particular, recent expansion of the market economy in the Sierra Madre Occidental has increased the availability of inexpensive processed foods and drinks, which the Tarahumara afford by supplementing their farming with temporary paid work and government aid. As a result, Tarahumara diets have been shifting to include more high-fat, high-sugar processed foods,[28] and food preparation increasingly involves frying rather than using the more traditional methods of roasting or boiling.[29] Consequently, while anthropometric data from decades ago indicate that obesity used to be extremely rare among the Tarahumara,[30 31] recent surveys suggest it is now a growing health concern.[27 32]

This study tested four predictions: First, because the Tarahumara are still in the early stages of the energy balance transition, we predicted that they would have lower average BMIs and obesity levels than individuals from Framingham. However, second, due to early-life exposure to energy limitation, we predicted that Tarahumara experiencing the energy balance transition would tend to grow larger abdomen sizes for a given body weight compared with Framingham individuals. Third, as

Figure 1 Tarahumara subsistence farming. *Top, left*: clearing a field with a machete. *Top, right*: tilling a field with a donkey-drawn plough. *Bottom, left*: weeding a field by hand. *Bottom, right*: carrying harvested stalks of chia. Photos by David Ramos and used here with permission.

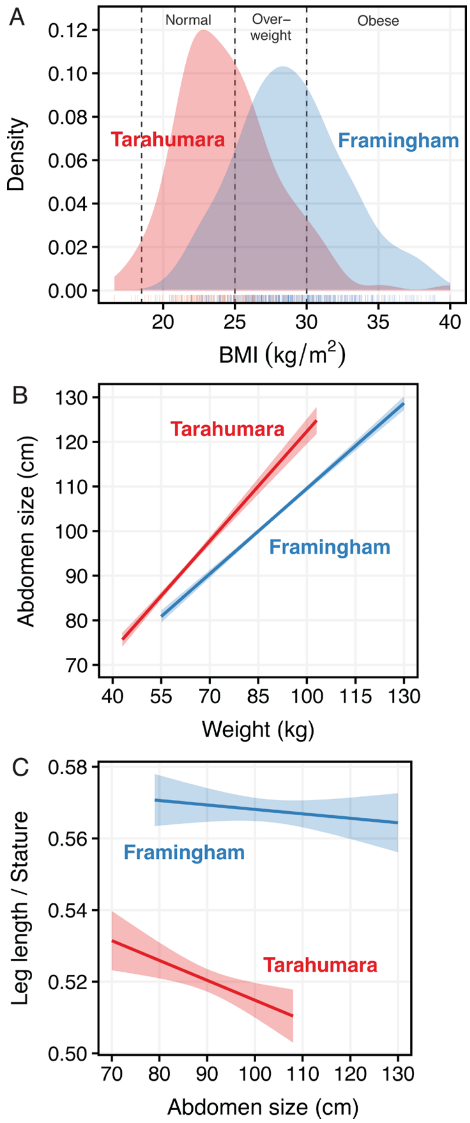

Figure 2 Anthropometric comparisons of the Tarahumara and Framingham individuals. (A) Density plot of body mass index (BMI) with thresholds for overweight and obesity indicated. (B) Association between body weight and abdomen size controlling for age. (C) Association between abdomen size and relative leg length (leg length/stature) controlling for age. Note that in (C), leg length was measured slightly differently among Tarahumara and Framingham individuals, so the difference in y-intercepts does not accurately reflect a group difference in relative leg length. Shading in (B) and (C) represents 95% CIs.

a result of this mismatch between metabolic phenotypes adapted to energetic scarcity and later-life greater energy availability, we predicted that the Tarahumara would have a higher risk of knee OA for a given BMI than Framingham individuals. Fourth and finally, we predicted that abdomen size would be a stronger predictor of knee OA risk among the Tarahumara than individuals from Framingham.

METHODS

Participants

The Tarahumara sample consists of 157 men aged 40–92 years (average±SD: 62±12 years) from the regions around the Sinforosa and Urique Canyons in the southwestern portion of the Mexican state of Chihuahua. Participants were recruited in 2015 and 2016 by word of mouth with the help of local residents and transported to clinics in the towns of Guachochi and Cerocahui where they were examined. Although our model of heightened knee OA risk among groups experiencing the energy balance transition applies as much to women as men, we were unable to collect data from Tarahumara women because of their inability to devote sufficient time to travelling to and from the clinics. To maximise participation, our research was scheduled during seasons when time devoted to farming was at a minimum, but seasonal downturns in farming activity had a greater impact on male than female workloads. The Framingham sample includes 565 white men who were members of the Offspring Cohort of the Framingham Osteoarthritis Study,[24 25] aged 40–94 years (average±SD: 66±9 years), who were examined at local clinics between 2002 and 2005. All participants were recruited without respect to knee pain or other health complaints. Basic information about participants' lifestyles obtained from questionnaires is provided in online supplementary material 1.

Anthropometry, knee radiographs and pain assessment

Each participant's stature, body weight and abdomen circumference were measured. In addition, measurements of leg length from a subset of participants in each group (n=101 Tarahumara; n=88 Framingham individuals) were available from prior research.[33 34] Leg length was measured as greater trochanter height and umbilical height among the Tarahumara and Framingham individuals, respectively. Relative leg length, calculated as the ratio of leg length to stature, is a well-established surrogate measure of an individual's energy availability during prenatal and early postnatal development, with a short relative leg length being indicative of an energetically limited early-life environment.[35 36]

A single weight-bearing posteroanterior fixed-flexion radiograph of both knees was obtained from all participants using a SynaFlexer x-ray positioning frame following a standardised protocol.[37] Radiographic features of the knees were assessed using the Kellgren/Lawrence scale[38] of 0–4 based on the presence of osteophytes, joint space narrowing, sclerosis and cysts. Presence of radiographic knee OA was defined as having a Kellgren/Lawrence score of 2 or greater in one or both knees.

All participants were asked in Rarámuri (the native language of the Tarahumara), Spanish or English the following question: "On most days, do you have pain in your knee?" Individuals were considered to have symptomatic knee OA if they had both knee pain and radiographic knee OA in one or both knees.

Statistical analyses

Data from Tarahumara and Framingham participants were compared using generalised linear models, from which we report unstandardised point estimates and 95% confidence intervals (CIs). An alpha level of 0.05 was set for statistical significance and all tests were two-tailed. Analyses were performed in R v 3.5.1. Further details on the statistical models, results of model goodness-of-fit tests and summary statistics for raw data are reported in online supplementary material 2.

RESULTS

Across all participants (n=722), after controlling for age, Tarahumara BMIs (adjusted mean, 24.3 kg/m^2; 95% CI 23.8 to 24.9 kg/m^2) were, on average, 17% lower (95% CI 15% to 20%; $p<0.0001$) than those of Framingham individuals (adjusted mean, 29.4 kg/m^2; 95% CI 29.0 to 29.8 kg/m^2) (figure 2A). After controlling for age, the probability of obesity (BMI ≥30) among

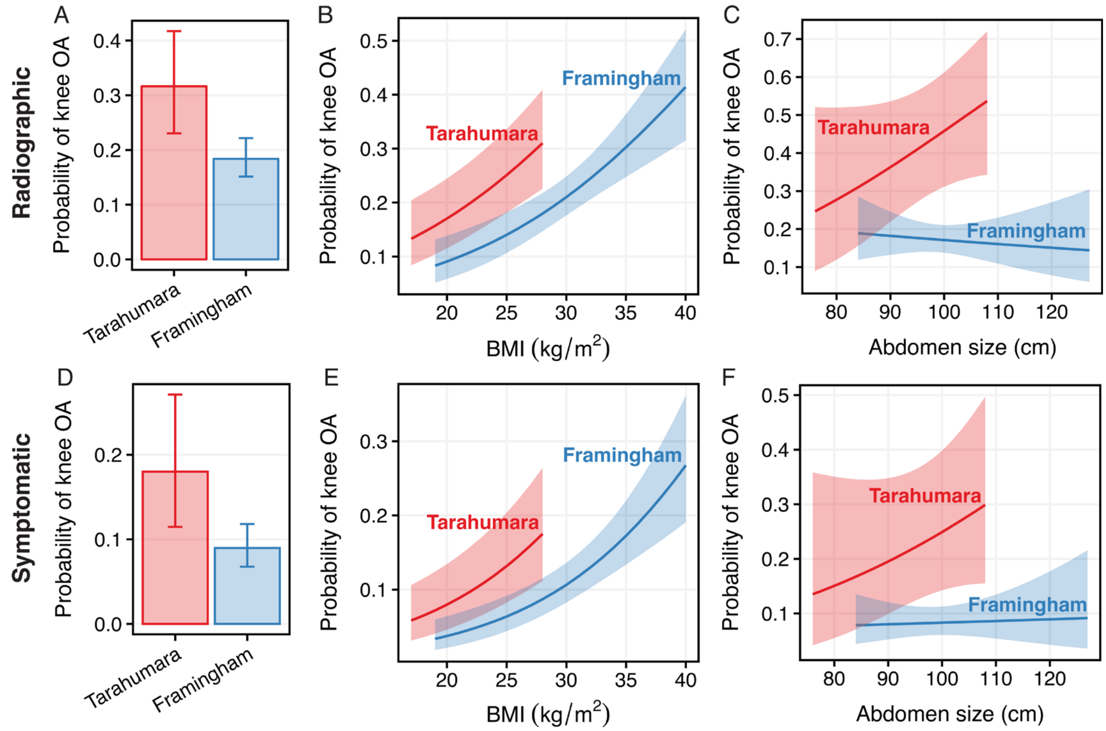

Figure 3 Comparison of knee osteoarthritis (OA) probability and its association with body mass index (BMI) and abdomen size among the Tarahumara and Framingham individuals. (A) Probability of radiographic knee OA controlling for BMI and age. (B) Association between radiographic knee OA probability and BMI controlling for age. (C) Association between radiographic knee OA probability and abdomen size controlling for age and body weight. (D) Probability of symptomatic knee OA controlling for BMI and age. (E) Association between symptomatic knee OA probability and BMI controlling for age. (F) Association between symptomatic knee OA probability and abdomen size controlling for age and body weight. Whiskers in (A) and (D) and shading in (B), (C), (E) and (F) represent 95% CIs.

the Tarahumara (6%; 95% CI 3% to 11%) was 35% lower (95% CI 26% to 41%; $p<0.0001$) than among Framingham individuals (41%; 95% CI 37% to 45%). The probability of being overweight ($25\leq$BMI<30) was 13% lower (95% CI 1% to 24%; $p=0.023$) among the Tarahumara (32%; 95% CI 25% to 39%) than Framingham individuals (45%; 95% CI 41% to 49%) after controlling for age. However, controlling for body weight and age, Tarahumara abdomen circumferences (adjusted mean, 109.3 cm; 95% CI 107.6 to 111.0 cm) were larger ($p<0.0001$) than those of Framingham individuals (adjusted mean, 99.4 cm; 95% CI 98.8 to 99.9 cm) (figure 2B; see also online supplementary material 3). Controlling for age, abdomen size was negatively associated with relative leg length among the Tarahumara ($p=0.0042$) but not among Framingham individuals ($p=0.38$) (figure 2C).

Radiographic knee OA was present in 24% (38/157) of the Tarahumara participants and 24% (135/565) of Framingham individuals. The probability of having radiographic knee OA increased with BMI and age across all participants ($p<0.0001$ for both variables), but after controlling for BMI and age, radiographic knee OA probability among the Tarahumara (32%; 95% CI 23% to 42%) was 13% higher (95% CI 1% to 27%; $p=0.0057$) than among Framingham individuals (18%; 95% CI 15% to 22%) (figure 3A,B). Among the Tarahumara, the probability of radiographic knee OA increased more markedly with greater abdomen circumference than among Framingham individuals (group×abdomen size interaction: $p=0.041$) after controlling for age and body weight (figure 3C).

Symptomatic knee OA was diagnosed in 13% (21/157) and 13% (71/565) of the Tarahumara and Framingham participants, respectively. BMI and age were positively associated with symptomatic knee OA probability ($p<0.0001$ for both variables across all participants), but after adjusting for BMI and age, symptomatic knee OA probability among the Tarahumara (18%; 95% CI 11% to 27%) was 9% higher (95% CI 0% to 20%; $p=0.0092$) than among Framingham individuals (9%; 95% CI 7% to 12%) (figure 3D,E). Controlling for age and body weight, symptomatic knee OA probability tended to increase more markedly with greater abdomen size among Tarahumara than Framingham individuals (figure 3F), but not significantly so (group×abdomen size interaction: $p=0.27$).

DISCUSSION

Previous research has demonstrated that individuals born in energy-limited environments who are later exposed to greater energy abundance often have a heightened sensitivity to obesity-related diseases including type 2 diabetes, hypertension and coronary heart disease.[10–13] Building on this work, we have proposed a model of heightened knee OA risk among non-industrial societies undergoing the energy balance transition and tested predictions of this model by comparing the probability of the disease and its association with BMI and abdomen size among an indigenous group of subsistence farmers in Mexico, the Tarahumara, relative to urban Americans from Framingham, Massachusetts. Overall, the results support four key predictions of our model. First, as expected for a population still in the early stages of the energy balance transition, the Tarahumara were found to have lower average BMIs and obesity levels than individuals from Framingham. Nevertheless, second, the Tarahumara tended to have larger abdomens for a given body weight than Framingham individuals, indicating relatively greater abdominal adiposity, a potent source of adipokines that promote chronic low-grade systemic inflammation.[20 21] Moreover, abdomen size among the Tarahumara was negatively associated with relative leg length, an established biomarker of early-life nutritional environment,[35 36] suggesting that larger abdomen sizes among the Tarahumara derived from the interaction between scarcity-adapted metabolisms and later-life energy abundance. Third, in association with this relatively low-BMI, large-abdomen phenotype, the Tarahumara exhibited a heightened susceptibility to radiographic and symptomatic knee OA for a given BMI compared with Framingham individuals. In addition, fourth, proportionate increases in abdomen size in the two groups were associated with greater increases in radiographic knee OA risk among the Tarahumara than individuals from Framingham, implying that the abdominal adipose tissue of the Tarahumara was a more potent stimulus for knee tissue degeneration. These findings suggest that risk of knee OA among non-industrial populations undergoing the energy balance transition is likely greater than would be expected based on the prevalence of obesity alone. Instead, our findings suggest that knee OA is yet another obesity-related disease to which risk is enhanced by mismatches between early-life and later-life energy availability.

Although our model emphasises the contribution of chronic low-grade systemic inflammation to knee OA pathogenesis, another factor that often plays an important role is mechanically induced joint tissue damage.[39] Since physical activity is the most common source of knee loading, it is important to consider to what extent the Tarahumara's relatively high activity levels might have affected their risk of knee OA. Routine activity engendering knee loads within the normal physiological range is not inherently harmful to knee tissues,[3] as illustrated by the fact that habitual long-distance runners are not more prone to knee OA than non-runners.[40 41] Nevertheless, activities that expose knees to abnormal, supraphysiological loads undoubtedly have the potential to damage joint tissues, explaining the strong association between traumatic injuries and knee OA.[39] It is thus notable that during examinations, all participants in this study were asked whether they had ever experienced a knee injury that limited their ability to walk for more than 3 days, and only 18% (7/38) of the Tarahumara with radiographic knee OA reported ever having had such an injury, compared with 30% (40/135) of Framingham individuals with radiographic disease (Fisher's exact test: $p=0.22$). Also, among Tarahumara and Framingham participants who were not diagnosed with knee OA, we measured knee joint space width (a proxy for cartilage thickness) from radiographs using an established protocol[42] and found that while joint space width declined with age in both groups (online supplementary material 4), age-related joint space thinning was not more rapid among the Tarahumara than Framingham individuals (general linear model, group×age interaction: $p=0.98$). Therefore, the Tarahumara's active lifestyles do not appear to have distinctly predisposed them to either injury-related knee OA or generally greater joint tissue degeneration throughout life. Ultimately, based on available evidence, if Tarahumara activity patterns influenced susceptibility to knee OA, we speculate that it was not primarily because the loads their knees sustained were abnormally high, but that due to the energy balance transition, knee loading in many individuals occurred in the context of chronic low-grade systemic inflammation that weakened their joint tissues.

This study has important limitations. First, we were able to collect data only from a relatively small sample of Tarahumara men and no women, and thus the degree to which the vulnerability to knee OA of the participants in this study is representative of the overall Tarahumara population is unclear. Second, our model assumes that the effect of the energy balance transition on abdominal adiposity (and hence knee OA risk) depends on an individual's energy status during early development, yet we lack direct information on this. Nevertheless, our finding that relative leg length was negatively associated with abdomen size among the Tarahumara provides indirect support for our model.[35 36] Third, while our model assumes that the primary pathway by which greater abdominal adiposity affects knee OA risk is through higher levels of chronic low-grade systemic inflammation, logistical difficulties prevented us from collecting data on most biomarkers of inflammation from the Tarahumara. We were able, however, to measure C-reactive protein (CRP) levels from dried blood spots using an established protocol[43] in a subset of the Tarahumara, and as would be expected, CRP levels were found to be positively associated with abdomen size (general linear model, $p=0.013$) after controlling for age and body weight (online supplementary material 5). Although CRP is a non-specific marker of inflammation that is associated with knee OA pain but not radiographic disease,[44] these data underscore the link between abdomen size and systemic inflammation levels. Fourth, differences in anthropometry and knee OA risk between Tarahumara and Framingham individuals are interpreted as being primarily due to environmental factors, but we cannot rule out that genetic variation was partly responsible for some of the patterns detected between groups. Even so, at least in terms of knee OA risk, we would expect any influence of genetics to have been limited given that alleles affecting disease susceptibility have relatively small effect sizes.[45] Moreover, the vast majority of genetic diversity among humans is accounted for within populations,[46] and there is currently little evidence that alleles affecting knee OA risk are biased towards the small fraction of genetic diversity that exists between populations.

Finally, the results of this study provide further evidence supporting the hypothesis that knee OA represents an example of a 'mismatch disease' that is caused in part by human bodies being inadequately or imperfectly adapted to novel features of modern environments.[2] However, whereas prior discussions of this hypothesis have focused on the extent to which knee OA stems from deleterious interactions between modern environments and the genes we inherited from ancient ancestors who evolved in markedly different environments,[2 3] this study highlights the potential contribution to knee OA risk by another form of mismatch, one which reflects processes operating on a much shorter timescale, within just a single generation.[12 13] Ultimately, more data are needed from the Tarahumara and other non-industrial groups to determine more precisely the magnitude and mechanisms of heightened knee OA risk faced by individuals born in energy-limited environments who later experience greater energy abundance. In all likelihood, both evolutionary and developmental mismatches play important roles in the growing burden of knee OA worldwide, yet the potential impact of mismatches between early-life and later-life energy availability is especially alarming and warrants special attention, as non-industrial societies undergoing the energy balance transition comprise a large fraction of the global population[47] and typically receive little attention from health and prevention services.[48]

Author affiliations
[1]Department of Human Evolutionary Biology, Peabody Museum, Harvard University, Cambridge, Massachusetts, USA
[2]Rheumatology Section, Boston University School of Medicine, Boston, Massachusetts, USA
[3]NIHR Manchester Musculoskeletal Biomedical Research Centre, Manchester University Hospitals NHS Foundation Trust, Manchester, UK

[4]Institute for Quantitative Social Science, Harvard University, Cambridge, Massachusetts, USA
[5]Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA
[6]Department of Anthropology, University of Oregon, Eugene, Oregon, USA
[7]Cardiovascular Performance Program, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

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Contributors IJW, DTF, SW and DEL designed research. IJW, DTF, JD, MC, PA, GNE, JJS, ALB and DEL performed research. IJW and SW analysed data. IJW, DTF, SW and DEL wrote the paper.

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