Review Article

Why Metabolic Dysfunction Clusters and Diverges: A Population-Led Hypothesis of Fructokinase and Tissue Energetics

Christopher Ryan Mearns[1]

1. Independent researcher

Why does liver fat stand out in some settings, high blood pressure or kidney injury in others, and why do these problems later cluster? We propose that different diets and living conditions leave different patterns of dysfunction because they repeatedly drive fructose metabolism through fructokinase (KHK) in different tissues. The tissue most likely to falter first is the one where fructose processing repeatedly outpaces recovery. This can happen whether fructose arrives from food or is made within the body. Less sustained exposure or more time to recover may help preserve function.

We compare four potential patterns: sugary drinks with liver fat and weight gain in U.S. cohorts; sodium intake with hypertension and stroke in Japanese cohorts; repeated hot work with kidney injury in Nicaragua; and higher glycemic exposure with dementia risk. Studies of migration, food access and longevity show why these exposures should be measured rather than inferred from where people live. Experimental work gives the comparisons a common mechanistic basis: fructose can reach the liver directly from food, while high glucose and osmotic stress can stimulate its production within tissues under studied conditions.

These observed associations are the patterns to explain. The new prediction is that knowing *where* fructose flux through KHK is sustained and *how much recovery* occurs between challenges will help predict which dysfunction emerges first, what clusters later and how long function is preserved, beyond what total exposure and established risk factors already explain.

Corresponding author: Christopher Ryan Mearns, chris@liv3health.com

 doi.org/10.32388/J1GJ74

1. Why does a different problem come to the foreground?

In the Ni-Hon-San study [1], men of Japanese ancestry in Japan had lower coronary mortality than their counterparts in the U.S. cohorts, yet stroke mortality was higher in Japan among men aged 60-64. If the contrast were only one of more or less disease, why would the two causes of death point in opposite directions?

The fructose-survival hypothesis [2] already links dietary fructose and fructose made within the body to a shared energy pathway. In The KHK–Polyol Axis [3], we proposed that KHK-mediated fructose processing can impede recovery; The Conserving Cell [4] developed the idea that tissues become vulnerable when challenges recur before restoration is complete. Here we make a comparative prediction: **where repeated fructose processing outpaces recovery should help determine which dysfunction emerges first.** A pattern of sweet drinks may put the strongest early burden on the liver; a pattern of repeated heat and delayed hydration may put it on the kidney. The key is not simply how much fructose is processed in the body, but how much passes through KHK per unit time in a given tissue (its *flux*) and how far that tissue recovers before the next challenge. The model predicts a difference in the relative prominence of outcomes, potentially even under comparable total exposure. The order in which those problems emerge and later cluster is a further prediction for longitudinal studies.

Why fructokinase (KHK)? The liver offers a short answer. An experimental fructose challenge in humans [5] produced a rapid fall in liver ATP, a molecule cells use to power their work, and in inorganic phosphate. In mice given glucose [6], fructose made within the body mattered: mice unable to metabolize fructose were protected from several metabolic changes under that protocol. And in a 16-week randomized trial [7] in adults with fatty liver and type 2 diabetes, the higher dose of a KHK inhibitor reduced MRI-measured liver fat relative to placebo, without a statistically significant difference in HbA1c. Taken together, the studies give the hypothesis three footholds: an acute shift in liver energy, a route into fructose metabolism that starts with glucose, and a liver outcome that responds to KHK inhibition.

2. What changes when a food environment changes?

We chose contrasts that vary the exposure, setting, or outcome, and looked for studies that challenge the proposed connections. This is a purposive narrative synthesis, not a systematic review. The population contrasts do two jobs. They show how diet and living conditions can change within or across

communities, and they give us observed outcomes against which to check the predicted pattern in Section 4. Physiological and intervention studies test pieces of the proposed explanation.

Place changes what people eat and what they can access. In Okinawa and among people of Okinawan origin in Brazil [8], diets differed and study-defined hypertension was more common in the Brazil group, although mean measured blood pressure did not differ detectably. In the Indian Migration Study [9], rural-to-urban migrants had higher observed prevalence of obesity and diabetes than rural comparison participants. These snapshots make migration useful as a change in the whole exposure setting: habits, work, prices and access can shift together.

In São Paulo [10], rice remained a daily staple among both Japan-born migrants and their Brazil-born descendants, even as the rest of the diet differed. Income also tracked with food choices differently in the United States [11] and Chile [12]. Neither ancestry nor income tells us whether fructose arrives in a sweetened drink or as part of a meal, or how often that exposure recurs. Those are the differences this hypothesis asks us to measure.

Even the same staple can give different results. In PURE [13], the association between white rice and diabetes looked different in South Asia and China, but a regional difference was not established statistically. That is a reason to compare actual diets, including what a staple replaces, instead of treating cuisine as an exposure measure.

Sometimes access changes without anyone moving. The Gila River Indian Community's own history [14] describes how upstream diversions devastated farming and led to famine, poverty, and reliance on federally supplied processed foods. Participating First Nations in a Canadian study [15] wanted more traditional foods and described barriers such as development, regulations, and harvesting costs. A separate ten-year Sandy Lake First Nation study [16] linked a dietary pattern characterized by beef and processed foods with higher odds of developing type 2 diabetes. The exposure to explain here is a change in the food environment, including who controls access to food and water, rather than a change in any one nutrient.

The timing of exposure changes too. In Bella Coola, research on the Nuxalk food system [17] documented fresh use of some fruits in season and preservation for winter. Fresh harvests and stored foods create different rhythms of availability that a yearly average obscures. The daily rhythm raises a parallel question: gaps between meals pause new dietary fructose intake, and moderate walking after meals [18] can alter the glucose excursion. Both examples put timing on the list of things to measure.

When conditions change, outcomes need not move together. In Maycoba, Mexico, stores and processed offerings expanded [19] from 1995 to 2010. Over the same period [20], obesity rose in Indigenous Pima residents and their non-Pima neighbors, but diabetes prevalence did not rise detectably in Pima men. That divergence is the point: even as the food and activity environment changed, two related outcomes did not rise in lockstep.

What might preserve function? The hypothesis makes a prediction in the other direction: less sustained KHK flux, or enough time to recover between episodes, should be associated with function lasting longer. A seasonal food pattern might allow that even when fructose intake is substantial at certain times of year. Long-lived populations give us a place to look for this pattern. In Nicoya, Costa Rica, a region often called a Blue Zone, a survival advantage among older men [21] faded across male birth cohorts [22]. Yet the earlier study found higher reported soda consumption in Nicoya, not lower. That is a challenge to any simple prediction based on reported soda consumption. How much did people drink at a time, how often, and against what patterns of physical activity? The historical comparison does not resolve whether those factors buffered exposure. It makes them questions to test, not reasons to explain Nicoya away. Even the protective pattern depends on what is measured: a Greenlandic Inuit crossover trial [23] found modestly lower daily glucose readings on a traditional marine diet, but no clear difference on the primary two-hour glucose tolerance measure.

A living comparison: Loma Linda and the wider Adventist community. In an analysis of 77,437 U.S. adults from the Adventist Health Study-2 [24], participants eating fewer ultra-processed foods reported less added sugar and fewer sweetened drinks. The adjusted mortality hazard was 14% higher at the 90th percentile of ultra-processed food intake than at the 10th. The association is with the whole food pattern. What makes this a useful counterpart to the heritage examples is that people living in a modern food environment can differ in their exposure to added sugar and sweetened drinks, and those differences sit alongside a measured difference in survival. It gives us a place to test whether the pattern of fructose exposure helps explain any of that advantage.

3. How one pathway could leave different footprints

Delivery determines where fructose arrives. The mouse gut–liver experiments [25] showed that the intestine can buffer fructose delivery to the liver under defined conditions. That gives the dietary route a concrete point of leverage: the rate and form of delivery may matter alongside the total amount.

Fructose can be made inside the tissue. Under some conditions the polyol pathway converts glucose to fructose, which can then be processed by KHK. There is direct experimental evidence for an osmotic trigger: Lanaspa, Johnson and colleagues [26] found that a salt challenge raised portal osmolality in mice, and chronic salt exposure activated the liver's osmotic-stress response and increased sorbitol and fructose. The kidney points to another setting for osmotic stress. In mice subjected to recurrent heat with delayed hydration [27], kidney injury depended on the capacity to metabolize fructose under the conditions tested. Salt and dehydration can therefore be considered as potential triggers of local fructose production, alongside their other physiological effects.

Glucose supplies another route. In eight healthy adults during a glucose clamp [28], a fructose-associated signal increased in the brain, consistent with local formation. Mouse hippocampal experiments [29] implicated KHK in a diabetic model. Johnson and colleagues' Alzheimer's hypothesis [30] takes this further: high-glycemic diets could promote fructose production within the brain, and sustained local fructose metabolism could contribute to Alzheimer's disease. The new question here is comparative: when would this route make cognitive dysfunction more prominent than the other outcomes linked to high glucose?

Tissue state can change the response. In cardiac cells and mouse models [31], stress signaling favored the KHK-C isoform, and perturbing the pathway attenuated remodeling in mice. Human cardiac biopsies showed an association. In separate mouse liver experiments [32], a different hypoxia-response factor suppressed genes involved in fructose metabolism. These separate models point in different directions. The kind of stress and where it occurs belong in the prediction.

Delivery, local production, and the capacity to process fructose help determine where the burden lands. There are two clocks: how fast fructose arrives within one episode, and how far a tissue recovers before the next. Slowing delivery during a meal changes the first clock; putting more time between comparable meals changes the second. A sustained trigger can keep the pathway engaged without distinct peaks. The tissue that struggles first may be the one with the least room to recover, even if another processes more fructose. In cultured endothelial cells [33], defined stresses reduced spare respiratory capacity with little change in baseline respiration. That experiment did not test KHK, but it shows why a normal resting measurement can miss a vulnerability. Human liver challenge results are mixed across metabolic states [34]; an acute ATP fall is not evidence that recovery failed.

A local strain can become a shared burden. Take the kidney and brain. If recurring KHK activity in the kidney contributes to sodium retention and higher pressure, a burden that begins in the kidney can reach the brain through its blood vessels, without requiring the same fructose trigger in the brain. The first step has an experimental foothold: mice with intact KHK [35] retained more sodium and developed higher pressure under the combined fructose-and-salt regimen, while KHK-deficient mice did not show that response. The downstream link has independent human support: lowering blood pressure reduced recurrent stroke risk [36]. We propose that sustained pressure can make it harder for cerebral vessels to meet recurring demands, creating a second point of vulnerability. The links are testable separately: pressure could carry a kidney-origin effect even where there is no evidence of local brain KHK engagement. This is how different starting points could lead to overlapping conditions over time.

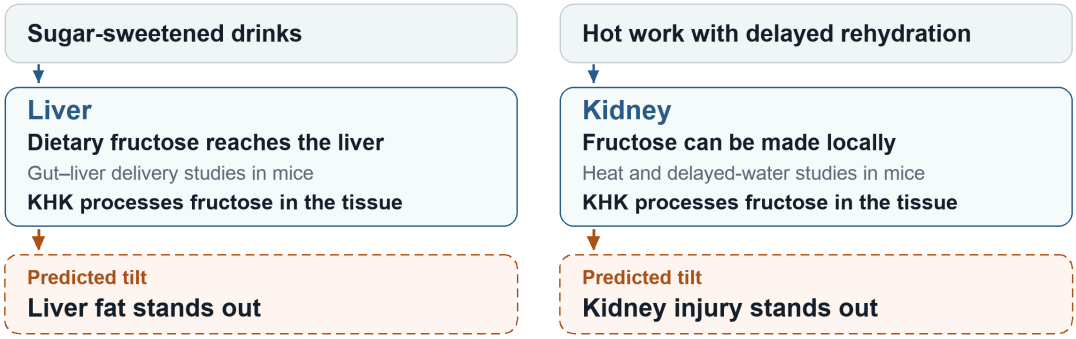
The model's two components are shown together in Figure 1: where the burden lands and how much time the tissue has to recover.

Figure 1 / Conceptual model

Where fructose is processed and when tissues recover

These two factors may shape which dysfunction stands out.

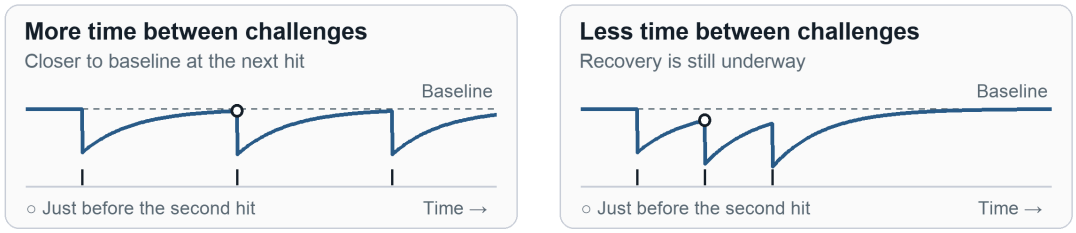
A Where the burden lands



The outcome most likely to stand out is the one linked to the tissue that keeps getting hit before it has recovered.

B Why spacing matters

Same number and size of challenges. Schematic curves, not measured data.



Distinguishing test: did the repeated hits change recovery itself?

Use the single-hit recovery curve and compare at equal time after the last hit.

Figure 1. Where fructose is processed and when tissues recover.A. Dietary fructose delivery to the liver and local fructose production under heat with delayed rehydration are distinct routes to KHK. The route evidence shown here comes from mouse studies [25][27]. The predicted outcomes describe relative prominence, not exclusive effects. A possible route to later clustering is kidney strain contributing to higher blood pressure and, in turn, to strain on cerebral vessels [35][36]. **B.** Identical schematic disturbances use the same recovery kinetics on both timelines. The open circles mark the moment before the second challenge. Closer spacing leaves greater residual disturbance at that point; the curves are not measured data and do not assume slower recovery or permanent damage.

doi.org/10.32388/J1GJ74

4. One pathway, different starting points

The table puts the observed patterns next to what the model adds. These are comparisons of measured exposures and outcomes in specific populations, not rankings of countries. The same trigger can affect more than one organ: the prediction is a *tilt* toward one outcome relative to others, which should vary with where flux is sustained and how much recovery occurs.

Exposure pattern	What stands out in the observed data	What the hypothesis predicts	A test that distinguishes the explanation
Frequent sugary drinks	U.S. cohorts: more incident fatty liver in older Framingham participants [37]; greater weight gain among women who increased intake in Nurses' Health Study II [38].	Frequent, rapid fructose delivery tilts the profile toward liver fat relative to early kidney injury.	At comparable intake, does shorter spacing leave poorer hepatic recovery and a stronger liver signal, and does verified KHK inhibition narrow the gap?
Repeated high-sodium exposure	Japan: higher estimated sodium intake associated with incident hypertension [39]; higher dietary sodium-to-potassium ratio associated with stroke mortality [40].	Where salt repeatedly drives endogenous fructose production in pressure-regulating tissues, pressure-related outcomes become more prominent.	At comparable sodium intake, does verified KHK inhibition reduce the pressure response? A direct vessel-wall effect would also have to show up at similar pressure.
Repeated hot work	Nicaragua: hotter days associated with acute kidney injury visits [41]; longer sugarcane work associated with incident chronic kidney disease [42].	When rehydration is delayed, repeated osmotic stress with incomplete recovery should tilt the profile toward kidney injury.	At matched heat, workload and hydration, does verified KHK inhibition reduce the tilt toward kidney stress relative to liver stress?
Repeated high glucose or high dietary glycemic load	Higher average glucose in a U.S. cohort [43] and higher estimated glycemic load in UK Biobank [44] were associated with dementia.	Where glucose repeatedly feeds local brain fructose production, cognitive dysfunction could stand out. This is the exploratory branch.	Does a brain-relevant measure of KHK engagement add information beyond systemic glucose and vascular risk?

Sugary drinks: why start with the liver?

In Framingham [37], frequent sugary-drink consumption was associated with about 2.5 times the adjusted odds of incident CT-defined fatty liver in the older cohort; the association was inconsistent in

the younger cohort. A randomized child beverage trial [45] found less weight gain with a sugar-free drink, but changed calories as well as fructose exposure.

Is fructose itself the distinguishing exposure? The FRUITLESS trial [46] found a modest additional reduction in liver fat when fructose was replaced by equal calories from glucose; a separate feeding trial [47] did not find that separation. In another randomized overfeeding study [48], saturated fat and simple sugar both increased liver fat, with different metabolic responses. Liver fat is therefore a useful expected outcome to test, but cannot identify the route that produced it.

Heat and exertion: why look to the kidney?

The kidney puts the other route to the test. Local fructose production makes it possible for the pathway to matter even when a fructose-rich diet is not the starting point. In the same Nicaraguan plantation setting [41], higher environmental heat was associated with more hospital visits for acute kidney injury. That matches the *direction and organ* suggested by the heat and delayed-hydration mouse experiments. The human pattern extends beyond acute visits: in two community cohorts in Nicaragua [42], each additional year of sugarcane work was associated with a higher rate of developing chronic kidney disease. Together, these results point to the kidney over two timescales. The next comparison is whether KHK contributes beyond the effects of workload, renal blood flow and hydration.

Overlap: context may change the response to the same exposure. A small crossover during hot exercise [49] found worse acute kidney markers with a caffeinated high-fructose soft drink than with water. A more closely matched sports-drink comparison [50] found no difference between drinks with 55% and 50% fructose shares. The contrast suggests the experiment to run next: **does background heat change where the same fructose exposure leaves its strongest mark?** That calls for varying heat while holding the drink constant.

Blood pressure: how a local effect could travel

The kidney–brain example in Section 3 starts with a specific question: can KHK alter the pressure response to an exposure? The Japanese cohort findings give this prediction an epidemiological target: sodium exposure tracks with new hypertension in one cohort, and the sodium-to-potassium balance tracks with stroke mortality in another. In mice [35], combined fructose and high salt raised systolic pressure and reduced sodium excretion in wild-type animals but not in KHK-deficient animals. A human salt challenge [51] found that pressure and osmolality rose together, while a human dietary

crossover [52] found differences in sodium excretion and 24-hour pressure under different comparisons. A direct human test needs to vary salt and fructose independently and follow osmolality and pressure over the same time course.

Separate blood pressure from the vessel wall. A human feeding study [53] found impaired arterial dilation under higher sodium without a detectable rise in pressure. Another study [54] detected increased albumin escape after acute IV salt loading but not after higher dietary sodium. Dilation, barrier function and stiffness are different outcomes; the evidence does not establish a common KHK-mediated vascular effect.

The clinical countercheck is straightforward: both salt substitution [55] and blood-pressure medication [36] produced numerically larger estimates of benefit for recurrent hemorrhagic than ischemic stroke, without establishing a subtype difference. The pattern is compatible with ordinary blood-pressure lowering. A human KHK inhibitor trial [7] also found no clinically meaningful pressure difference in safety assessments, although it did not test a salt challenge. The sharper question is whether KHK contributes to the pressure response under particular exposures, or to a separate vessel-wall effect at comparable pressure.

Cognition: how far does the hypothesis reach?

Higher average glucose was associated with incident dementia in the Adult Changes in Thought cohort [43], even among participants without diabetes. A separate UK Biobank analysis [44] linked the upper range of estimated dietary glycemic load with dementia. Neither measured glucose peaks or brain KHK. In ACCORD MIND [56], more intensive glucose lowering did not improve the primary cognitive test at 40 months. And in CARDIA [57], midlife liver fat did not clearly predict five-year cognitive decline.

These studies make cognition an outcome to watch, but they do not establish that it precedes other dysfunction. The distinction is between the direct route Johnson proposes, in which fructose is made and processed in the brain, and an indirect route, in which dysfunction elsewhere reaches the brain through its blood supply. A brain-relevant measure of pathway engagement would need to add information beyond systemic glucose and cerebral perfusion to support the first route.

The liver is the human anchor, and heat-related kidney injury gives the clearest contrasting tissue and trigger. The pressure branch tests whether a local effect can spread through the circulation. The cognitive

branch asks whether the brain can also be a starting point in its own right. The strongest test will compare outcomes in the same people, rather than infer their order from separate cohorts.

5. What would change our minds?

Would the broad pattern recur? Compare prespecified outcomes in the same people across different measured exposure patterns, then ask whether the contrast recurs as diets or living conditions change. Record dose, delivery rate, frequency and spacing separately, and keep definitions and observation periods comparable. Test whether those exposure features improve prediction beyond total intake or burden before attributing any added signal to KHK. The clearest test is to measure both exposures and both outcomes in the same participants. The model predicts that frequent sugary-drink intake will track more strongly with liver fat than with kidney injury, while repeated heat strain will shift that balance toward kidney injury. Choose the kidney measure and the scales for comparing associations before analysis, and account for co-exposure to heat and sugary drinks. A precise result in the opposite direction would weaken the prediction; estimates too imprecise to distinguish the patterns would leave it unresolved. This first population test asks which outcome stands out, not which started first or what caused the difference. Testing the order of onset, later clustering and preservation of function requires longitudinal measures of those outcomes.

Would KHK explain any of the difference? Ask whether tissue-relevant engagement measures improve predictions of the outcome mix and later within-person clustering beyond established risks. Separately, a paired liver–kidney experiment could test whether heat shifts an early response toward the kidney under comparable fructose exposure, and whether selective perturbation with verified engagement in both tissues weakens that shift. An unchanged shift under verified perturbation would weaken the KHK explanation in that setting. Lack of added prediction beyond later blood pressure or glycemia would limit practical value, but would not by itself rule out a pathway acting through those factors.

Start where human measurement is feasible. In a small human crossover study [58], phosphorus-31 magnetic resonance spectroscopy tracked the liver's response to oral fructose. KHK inhibition suppressed the phosphomonoester signal consistent with fructose-1-phosphate accumulation and the accompanying fall in inorganic phosphate. That gives us a way to check hepatic engagement in a controlled challenge. Serial ATP and phosphate measurements could track return toward baseline, alongside a prespecified measure of liver function. These readouts do different jobs: the first is a marker of engagement, the second tracks energetic recovery, and the third tests whether recovery matters for

what the liver does. A comparable KHK-specific readout has yet to be validated for the other tissues discussed here.

Does the spacing effect depend on KHK? Hold the number of exposures and each episode's dose, form and delivery rate constant; vary the interval between episodes. The prediction is that with closer spacing, a prespecified function in the target tissue will be further from its pre-exposure baseline just before the next challenge. Measure the recovery trajectory after a single challenge first, then compare repeated schedules both before the next challenge and at the same elapsed time after the last one. That separates ordinary carryover from a lasting change in recovery. If KHK contributes, the difference between the two schedules should shrink when KHK is selectively suppressed and suppression is verified in that tissue. If the difference persists despite verified suppression, the KHK explanation for it weakens. If recovery is indistinguishable with KHK active and the estimate rules out a meaningful difference, the spacing prediction itself weakens.

Track pathway engagement separately from functional recovery. A smaller ATP drop on the next exposure does not establish recovery, and inhibition can narrow a spacing difference simply by making each challenge smaller. A change in recovery itself should be visible after accounting for the size of the initial disturbance. Nor does an early recovery gap establish later damage. Seasonal availability motivates the question, but does not show that spacing has the same effect across timescales. Test the duration of a continuous challenge separately.

Conclusion

We propose that the first weak point is the tissue where repeated KHK flux most consistently outpaces recovery. What that tissue passes on to others may then help determine what clusters later. If the hypothesis is right, the timing and location of fructose metabolism should help explain why populations with different diets and living conditions develop different mixes of dysfunction, and why some retain function longer.

Statements and Declarations

Funding

This work was carried out as an independent research project with no specific external grant. The author funded the work personally.

Potential Competing Interests

Christopher Ryan Mearns is the founder and an owner of LIV3 Health, a company that develops nutritional protocols and dietary supplements, including SugarShield. This commercial interest is relevant to the topic. This article does not evaluate commercial products or establish their efficacy or KHK-inhibitory activity in humans.

Ethics

This article synthesizes published literature and proposes future research. It reports no new research with human participants or animals and uses no identifiable individual-level data.

Data Availability

No new datasets were generated or analyzed for this article. The materials supporting the synthesis are cited in the references.

Author Contributions

Christopher Ryan Mearns conceived and developed the hypothesis, directed the literature synthesis and manuscript revision, and takes responsibility for the work.

Use of Generative AI

ChatGPT and Codex assisted with literature research, drafting, editing and reference preparation under the author's direction. The author is responsible for the accuracy and integrity of the final text.

References

1. ^*Worth RM, Kato H, Rhoads GG, Kagan A, Syme SL (1975). "Epidemiologic Studies of Coronary Heart Disease and Stroke in Japanese Men Living in Japan, Hawaii and California: Mortality." Am J Epidemiol.* **102***(6):481–490. doi:10.1093/oxfordjournals.aje.a112186.*
2. ^*Johnson RJ, Lanaspa MA, Sanchez-Lozada LG, Tolan D, Nakagawa T, Ishimoto T, et al. (2023). "The Fructose Survival Hypothesis for Obesity." Philos Trans R Soc Lond B Biol Sci.* **378***(1885). doi:10.1098/rstb.2022.0230.*

3. ^Mearns CR, Gross P (2026). "The KHK–Polyol Axis as a Convergent Energetic Bottleneck in Chronic Disease Persistence." Qeios. doi:10.32388/r2nfg9.
4. ^Mearns CR (2026). "The Conserving Cell: A Unified Hypothesis of Metabolic Restoration and Fragile Systems." Qeios. doi:10.32388/5rwzcm.2.
5. ^Boesiger P, Buchli R, Meier D, Steinmann B, Gitzelmann R (1994). "Changes of Liver Metabolite Concentrations in Adults with Disorders of Fructose Metabolism After Intravenous Fructose by 31P Magnetic Resonance Spectroscopy." Pediatr Res. **36**(4):436–440. doi:10.1203/00006450-199410000-00004.
6. ^Lanaspa MA, Ishimoto T, Li N, Cicerchi C, Orlicky DJ, Ruzycki P, et al. (2013). "Endogenous Fructose Production and Metabolism in the Liver Contributes to the Development of Metabolic Syndrome." Nat Commun. **4**: 2434. doi:10.1038/ncomms3434.
7. a, b^Saxena AR, Lyle SA, Khavandi K, Qiu R, Whitlock M, Esler WP, et al. (2023). "A Phase 2a, Randomized, Double-Blind, Placebo-Controlled, Three-Arm, Parallel-Group Study to Assess the Efficacy, Safety, Tolerability and Pharmacodynamics of PF-06835919 in Patients with Non-Alcoholic Fatty Liver Disease and Type 2 Diabetes." Diabetes Obes Metab. **25**(4):992–1001. doi:10.1111/dom.14946.
8. ^Mizushima S, Moriguchi EH, Nakada Y, Biosca MDG, Nara Y, Murakami K, et al. (1992). "The Relationship of Dietary Factors to Cardiovascular Diseases Among Japanese in Okinawa and Japanese Immigrants, Originally from Okinawa, in Brazil." Hypertens Res. **15**(1):45–55. doi:10.1291/hypres.15.45.
9. ^Ebrahim S, Kinra S, Bowen L, Andersen E, Ben-Shlomo Y, Lyngdoh T, et al. (2010). "The Effect of Rural-to-Urban Migration on Obesity and Diabetes in India: A Cross-Sectional Study." PLoS Med. **7**(4):e1000268. doi:10.1371/journal.pmed.1000268.
10. ^Cardoso MA, Hamada GS, Souza JMD, Tsugane S, Tokudome S (1997). "Dietary Patterns in Japanese Migrants to Southeastern Brazil and Their Descendants." J Epidemiol. **7**(4):198–204. doi:10.2188/jea.7.198.
11. ^Baraldi LG, Steele EM, Canella DS, Monteiro CA (2018). "Consumption of Ultra-Processed Foods and Associated Sociodemographic Factors in the USA Between 2007 and 2012: Evidence from a Nationally Representative Cross-Sectional Study." BMJ Open. **8**(3):e020574. doi:10.1136/bmjopen-2017-020574.
12. ^Crovetto M M, Uauy R, Martins AP, Moubarac JC (2014). "Disponibilidad de Productos Alimentarios Listos Para el Consumo en los Hogares de Chile y su Impacto Sobre la Calidad de la Dieta (2006-2007)" [Household Availability of Ready-to-Consume Food and Drink Products in Chile: Impact on Nutritional Quality of the Diet]. Rev Med Chil [Medical Journal of Chile]. **142**(7):850–858. doi:10.4067/s0034-98872014000700005.
13. ^Bhavadharini B, Mohan V, Dehghan M, Rangarajan S, Swaminathan S, Rosengren A, et al. (2020). "White Rice Intake and Incident Diabetes: A Study of 132,373 Participants in 21 Countries." Diabetes Care. **43**(11):26

43–2650. doi:10.2337/dc19-2335.

14. ^ *Gila River Indian Community. "History." Gila River Indian Community. https://www.gilariver.org/index.php/about/history.*
15. ^ *Batal M, Chan HM, Fediuk K, Ing A, Berti P, Sadik T, et al. (2021). "Importance of the Traditional Food Systems for First Nations Adults Living on Reserves in Canada." Can J Public Health. **112**(S1):20–28. doi:10.17269/s41997-020-00353-y.*
16. ^ *Reeds J, Mansuri S, Mamakeesick M, Harris SB, Zinman B, Gittelsohn J, et al. (2016). "Dietary Patterns and Type 2 Diabetes Mellitus in a First Nations Community." Can J Diabetes. **40**(4):304–310. doi:10.1016/j.jcjd.2016.05.001.*
17. ^ *Lepofsky D, Turner NJ, Kuhnlein HV (1985). "Determining the Availability of Traditional Wild Plant Foods: An Example of Nuxalk Foods, Bella Coola, British Columbia." Ecol Food Nutr. **16**(3):223–241. doi:10.1080/03670244.1985.9990863.*
18. ^ *DiPietro L, Gribok A, Stevens MS, Hamm LF, Rumpler W (2013). "Three 15-min Bouts of Moderate Postmeal Walking Significantly Improves 24-h Glycemic Control in Older People at Risk for Impaired Glucose Tolerance." Diabetes Care. **36**(10):3262–3268. doi:10.2337/dc13-0084.*
19. ^ *Chaudhari L, Begay R, Schulz L (2013). "Fifteen Years of Change in the Food Environment in a Rural Mexican Community: The Maycoba Project." Rural Remote Health. doi:10.22605/rrh2404.*
20. ^ *Esparza-Romero J, Valencia ME, Urquidez-Romero R, Chaudhari LS, Hanson RL, Knowler WC, et al. (2015). "Environmentally Driven Increases in Type 2 Diabetes and Obesity in Pima Indians and Non-Pimas in Mexico Over a 15-Year Period: The Maycoba Project." Diabetes Care. **38**(11):2075–2082. doi:10.2337/dc15-0089.*
21. ^ *Rosero-Bixby L, Dow WH, Rehkopf DH (2014). "The Nicoya Region of Costa Rica: A High Longevity Island for Elderly Males." Vienna Yearb Popul Res. **11**:109–136. doi:10.1553/populationyearbook2013s109.*
22. ^ *Rosero-Bixby L (2023). "The Vanishing Advantage of Longevity in Nicoya, Costa Rica: A Cohort Shift." Demogr Res. **49**:723–736. doi:10.4054/demres.2023.49.27.*
23. ^ *Lewis JI, Lind MV, Møller G, Hansen T, Pedersen H, Christensen MMB, et al. (2023). "The Effect of Traditional Diet on Glucose Homoeostasis in Carriers and Non-Carriers of a Common TBC1D4 Variant in Greenlandic Inuit: A Randomised Crossover Study." Br J Nutr. **130**(11):1871–1884. doi:10.1017/s000711452300106x.*
24. ^ *Orlich MJ, Sabaté J, Mashchak A, Fresán U, Jaceldo-Siegl K, Miles F, et al. (2022). "Ultra-Processed Food Intake and Animal-Based Food Intake and Mortality in the Adventist Health Study-2." Am J Clin Nutr. **115**(6):1589–1601. doi:10.1093/ajcn/nqac043.*

25. ^ a b Jang C, Wada S, Yang S, Gosis B, Zeng X, Zhang Z, et al. (2020). "The Small Intestine Shields the Liver fro m Fructose-Induced Steatosis." Nat Metab. **2**(7):586–593. doi:10.1038/s42255-020-0222-9.

26. ^ Lanaspa MA, Kuwabara M, Andres-Hernando A, Li N, Cicerchi C, Jensen T, et al. (2018). "High Salt Intake C auses Leptin Resistance and Obesity in Mice by Stimulating Endogenous Fructose Production and Metaboli sm." Proc Natl Acad Sci U S A. **115**(12):3138–3143. doi:10.1073/pnas.1713837115.

27. ^ a b Roncal Jimenez CA, Ishimoto T, Lanaspa MA, Rivard CJ, Nakagawa T, Ejaz AA, et al. (2014). "Fructokinas e Activity Mediates Dehydration-Induced Renal Injury." Kidney Int. **86**(2):294–302. doi:10.1038/ki.2013.492.

28. ^ Hwang JJ, Jiang L, Hamza M, Dai F, Belfort-DeAguiar R, Cline G, et al. (2017). "The Human Brain Produces Fructose from Glucose." JCI Insight. **2**(4). doi:10.1172/jci.insight.90508.

29. ^ Li Y, Jiang T, Du M, He S, Huang N, Cheng B, et al. (2023). "Ketohexokinase-Dependent Metabolism of Cere bral Endogenous Fructose in Microglia Drives Diabetes-Associated Cognitive Dysfunction." Exp Mol Med. **5 5**(11):2417–2432. doi:10.1038/s12276-023-01112-y.

30. ^ Johnson RJ, Tolan DR, Bredesen D, Nagel M, Sánchez-Lozada LG, Fini M, et al. (2023). "Could Alzheimer's D isease Be a Maladaptation of an Evolutionary Survival Pathway Mediated by Intracerebral Fructose and Ur ic Acid Metabolism?" Am J Clin Nutr. **117**(3):455–466. doi:10.1016/j.ajcnut.2023.01.002.

31. ^ Mirtschink P, Krishnan J, Grimm F, Sarre A, Hörl M, Kayikci M, et al. (2015). "HIF-Driven SF3B1 Induces KH K-C to Enforce Fructolysis and Heart Disease." Nature. **522**(7557):444–449. doi:10.1038/nature14508.

32. ^ Eberhart T, Schönenberger MJ, Walter KM, Charles KN, Faust PL, Kovacs WJ (2020). "Peroxisome-Deficienc y and HIF-2α Signaling Are Negative Regulators of Ketohexokinase Expression." Front Cell Dev Biol. **8**:566. doi:10.3389/fcell.2020.00566.

33. ^ Dranka BP, Hill BG, Darley-Usmar VM (2010). "Mitochondrial Reserve Capacity in Endothelial Cells: The I mpact of Nitric Oxide and Reactive Oxygen Species." Free Radic Biol Med. **48**(7):905–914. doi:10.1016/j.freer adbiomed.2010.01.015.

34. ^ Bril F, Forbes SC, Kalavalapalli S, Cusi K (2026). "Patients with MASLD Exhibit in Vivo Changes in Hepatic Response to Oral Fructose Consumption." J Clin Endocrinol Metab. **111**(9):2620–2629. doi:10.1210/clinem/dg ag125.

35. ^ a b c Hayasaki T, Ishimoto T, Doke T, Hirayama A, Soga T, Furuhashi K, et al. (2019). "Fructose Increases the Activity of Sodium Hydrogen Exchanger in Renal Proximal Tubules That Is Dependent on Ketohexokinase." J Nutr Biochem. **71**:54–62. doi:10.1016/j.jnutbio.2019.05.017.

36. ^ a b c Chapman N, Huxley R, Anderson C, Bousser MG, Chalmers J, Colman S, et al. (2004). "Effects of a Perin dopril-Based Blood Pressure–Lowering Regimen on the Risk of Recurrent Stroke According to Stroke Subty

pe and Medical History." Stroke. ***35****(1):116–121. doi:10.1161/01.str.0000106480.76217.6f.*

37. ^ a, b *Park WY, Yiannakou I, Petersen JM, Hoffmann U, Ma J, Long MT (2022). "Sugar-Sweetened Beverage, Die t Soda, and Nonalcoholic Fatty Liver Disease Over 6 Years: The Framingham Heart Study." Clin Gastroenter ol Hepatol.* ***20****(11):2524–2532.e2. doi:10.1016/j.cgh.2021.11.001.*

38. ^ *Schulze MB, Manson JE, Ludwig DS, Colditz GA, Stampfer MJ, Willett WC, et al. (2004). "Sugar-Sweetened Beverages, Weight Gain, and Incidence of Type 2 Diabetes in Young and Middle-Aged Women." JAMA.* ***292*** *(8):927–934. doi:10.1001/jama.292.8.927.*

39. ^ *Takase H, Sugiura T, Kimura G, Ohte N, Dohi Y (2015). "Dietary Sodium Consumption Predicts Future Bloo d Pressure and Incident Hypertension in the Japanese Normotensive General Population." J Am Heart Assoc.* ***4****(8):e001959. doi:10.1161/jaha.115.001959.*

40. ^ *Okayama A, Okuda N, Miura K, Okamura T, Hayakawa T, Akasaka H, et al. (2016). "Dietary Sodium-to-Pot assium Ratio as a Risk Factor for Stroke, Cardiovascular Disease and All-Cause Mortality in Japan: The NIP PON DATA80 Cohort Study." BMJ Open.* ***6****(7):e011632. doi:10.1136/bmjopen-2016-011632.*

41. ^ a, b *Hansson E, Jakobsson K, Glaser JR, Wesseling C, Chavarría D, Lucas RAI, et al. (2024). "Association Betwe en Acute Kidney Injury Hospital Visits and Environmental Heat Stress at a Nicaraguan Sugarcane Plantatio n." Workplace Health Saf.* ***72****(4):131–142. doi:10.1177/21650799241235410.*

42. ^ a, b *Gonzalez-Quiroz M, Heggeseth B, Camacho A, Oomatia A, Al-Rashed AM, Zhang Y, et al. (2023). "Popula tion-Level Detection of Early Loss of Kidney Function: 7-Year Follow-up of a Young Adult Cohort at Risk of Mesoamerican Nephropathy." Int J Epidemiol.* ***53****(1). doi:10.1093/ije/dyad151.*

43. ^ a, b *Crane PK, Walker R, Hubbard RA, Li G, Nathan DM, Zheng H, et al. (2013). "Glucose Levels and Risk of De mentia." N Engl J Med.* ***369****(6):540–548. doi:10.1056/nejmoa1215740.*

44. ^ a, b *Novau-Ferré N, Mateu-Fabregat J, Papagiannopoulos CK, Chalitsios CV, Panisello L, Markozannes G, et a l. (2025). "Glycemic Index, Glycemic Load, and Risk of Dementia: A Prospective Analysis Within the UK Biob ank Cohort." Int J Epidemiol.* ***54****(6). doi:10.1093/ije/dyaf182.*

45. ^ *de Ruyter JC, Olthof MR, Seidell JC, Katan MB (2012). "A Trial of Sugar-Free or Sugar-Sweetened Beverages and Body Weight in Children." N Engl J Med.* ***367****(15):1397–1406. doi:10.1056/nejmoa1203034.*

46. ^ *Simons N, Veeraiah P, Simons PIHG, Schaper NC, Kooi ME, Schrauwen-Hinderling VB, et al. (2021). "Effects of Fructose Restriction on Liver Steatosis (FRUITLESS); A Double-Blind Randomized Controlled Trial." Am J Clin Nutr.* ***113****(2):391–400. doi:10.1093/ajcn/nqaa332.*

47. ^ *Johnston RD, Stephenson MC, Crossland H, Cordon SM, Palcidi E, Cox EF, et al. (2013). "No Difference Betwe en High-Fructose and High-Glucose Diets on Liver Triacylglycerol or Biochemistry in Healthy Overweight*

Men." Gastroenterology. ***145****(5):1016–1025.e2. doi:10.1053/j.gastro.2013.07.012.*

48. ^*Luukkonen PK, Sädevirta S, Zhou Y, Kayser B, Ali A, Ahonen L, et al. (2018). "Saturated Fat Is More Metabol ically Harmful for the Human Liver Than Unsaturated Fat or Simple Sugars." Diabetes Care.* ***41****(8):1732–173 9. doi:10.2337/dc18-0071.*

49. ^*Chapman CL, Johnson BD, Sackett JR, Parker MD, Schlader ZJ (2019). "Soft Drink Consumption During and Following Exercise in the Heat Elevates Biomarkers of Acute Kidney Injury." Am J Physiol Regul Integr Com p Physiol.* ***316****(3):R189–R198. doi:10.1152/ajpregu.00351.2018.*

50. ^*Tourula E, Heikkinen ME, Regester A, Owen MG, Hess HW, Spence L, et al. (2026). "Hydrating with a Highe r-Fructose Sport Drink Does Not Worsen Acute Kidney Injury Risk During Simulated Work-Related Heat Stre ss." Am J Physiol Regul Integr Comp Physiol.* ***331****(2):R127–R146. doi:10.1152/ajpregu.00047.2026.*

51. ^*Kanbay M, Aslan G, Afsar B, Dagel T, Siriopol D, Kuwabara M, et al. (2018). "Acute Effects of Salt on Blood P ressure Are Mediated by Serum Osmolality." J Clin Hypertens.* ***20****(10):1447–1454. doi:10.1111/jch.13374.*

52. ^*McMillan RK, Stock JM, Romberger NT, Wenner MM, Chai SC, Farquhar WB (2025). "The Impact of Dietar y Sodium and Fructose on Renal Sodium Handling and Blood Pressure in Healthy Adults." Physiol Rep.* ***13*** *(6). doi:10.14814/phy2.70284.*

53. ^*DuPont JJ, Greaney JL, Wenner MM, Lennon-Edwards SL, Sanders PW, Farquhar WB, et al. (2013). "High Di etary Sodium Intake Impairs Endothelium-Dependent Dilation in Healthy Salt-Resistant Humans." J Hyper tens.* ***31****(3):530–536. doi:10.1097/hjh.0b013e32835c6ca8.*

54. ^*Rorije NMG, Olde Engberink RHG, Chahid Y, van Vlies N, van Straalen JP, van den Born BJH, et al. (2018). "Microvascular Permeability After an Acute and Chronic Salt Load in Healthy Subjects." Anesthesiology.* ***12 8****(2):352–360. doi:10.1097/aln.0000000000001989.*

55. ^*Ding X, Zhang X, Huang L, Xiong S, Li Z, Zhao Y, et al. (2025). "Salt Substitution and Recurrent Stroke and Death." JAMA Cardiol.* ***10****(4):343. doi:10.1001/jamacardio.2024.5417.*

56. ^*Launer LJ, Miller ME, Williamson JD, Lazar RM, Gerstein HC, Murray AM, et al. (2011). "Effects of Intensive Glucose Lowering on Brain Structure and Function in People with Type 2 Diabetes (ACCORD MIND): A Ran domised Open-Label Substudy." Lancet Neurol.* ***10****(11):969–977. doi:10.1016/s1474-4422(11)70188-0.*

57. ^*Gerber Y, VanWagner LB, Yaffe K, Terry JG, Rana JS, Reis JP, et al. (2021). "Non-Alcoholic Fatty Liver Disease and Cognitive Function in Middle-Aged Adults: The CARDIA Study." BMC Gastroenterol.* ***21****(1). doi:10.1186/s1 2876-021-01681-0.*

58. ^*Koene EJC, Buziau AM, Cassiman D, Cox TM, Bons J, Scheijen JLJM, et al. (2025). "Safety and Efficacy of Ph armacological Inhibition of Ketohexokinase in Hereditary Fructose Intolerance." J Clin Invest.* ***135****(6):e18737*

6. doi:10.1172/jci187376.

Declarations

Funding: No specific funding was received for this work.

Potential competing interests: Christopher Ryan Mearns is the founder and an owner of LIV3 Health, a company that develops nutritional protocols and dietary supplements, including SugarShield. This commercial interest is relevant to the topic. This article does not evaluate commercial products or establish their efficacy or KHK-inhibitory activity in humans.