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A falsehood that has been repeated many times becomes true, the origin of the diabesity pandemic, the most lethal of the 21st century?

Abstract

The malnutrition pandemic has reached alarming proportions in the 21st century, with nearly 860 million people suffering from obesity, almost 1.8 billion overweight, and around 900 million experiencing malnutrition due to macronutrient and micronutrient deficiencies worldwide. This issue affects over 40% of the global population, highlighting a concerning prevalence of malnutrition worldwide and its close association with chronic diseases. With eight out of 10 leading causes of global mortality being non-communicable diseases, predominantly of cardiometabolic origin, the malnutrition pandemic has become a serious threat to global health. This phenomenon has been exacerbated by the parallel increase in Type 2 Diabetes Mellitus, leading to the coining of the term "diabesity" to describe the interaction between diabetes and obesity, considered the deadliest of the 21st century. Despite nutritional interventions implemented 70 years ago, such as the Food Pyramid and the promotion of healthy lifestyles, there has been an exponential increase in interrelated cardiometabolic conditions, including cardiovascular diseases, diabetes, and cancer, dementia, and neurodegenerative diseases. This raises questions about the effectiveness of research-based recommendations over the decades, which may have been potentially flawed and deeply influenced modern life and culture, fueling sugar addiction and the pleasure of eating, and capitalizing extensively on the market economy. It is essential to make structural decisions to dismantle particularly erroneous modifications, whether nutritional or otherwise, and educate both new generations and healthcare professionals about a new paradigm of healthier and more flexible lifestyles.

This scientific essay focuses on critically reviewing the most prominent evidence supporting modern dietary and lifestyle modifications, and analyzing the historical behavior of clinical conditions that these interventions sought to modify. This allows for inferences about the potential error of research and decisions made, and sowing a new founded theory that promotes paradigm shift after rigorous research in this regard. In the context of the pandemic, these new investigations acquire even greater relevance and urgency to address the global crisis of malnutrition and diabetes.

Keywords: diabesity, metabolic syndrome, cardiovascular disease, obesity, diabetes, pandemic, dementia

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Jairo Echeverry-Raad
Department of Pediatrics & Institute of Clinical Research, National University of Colombia, Rectory Advisor, Juan N. Corpas University Foundation

Correspondence: Jairo Echeverry-Raad, Full Professor, Department of Pediatrics and Institute of Clinical Research, Faculty of Medicine, National University of Colombia, Research professor, Juan N. Corpas University Foundation, Colombia, Email jecheverryr@unal.edu.co, jairo.echeverry@juanncorpas.edu.co

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Introduction

Just before the outbreak of the COVID-19 pandemic, a worrying health panorama was revealed. Nearly 74% of the causes associated with mortality worldwide and seven of the 10 leading causes were non-communicable diseases (NCDs). These represented almost half, exactly 44%, of all deaths on the planet each year, affecting even developing nations.[1,2] NCDs, including the myriad cardiovascular conditions, are responsible, in low- and middle-income countries, for 80% of the disease burden[3,4,6–10] marking a disturbing epidemiological transition, especially in the last two decades. Despite conservative estimates dating back a few years indicating that at least two in three American adults (69%) are overweight or obese,[3] and a similar proportion suffer from cardiovascular disease, with nearly two in 10 being diabetic,[4] and eight out of 10 conditions having a cardiometabolic origin,[5] it is evident that we are facing a pandemic, the most lethal of the 21st century. Therefore, it is appropriate to propose the term "Diabesity", acronym for Diabetes and Obesity, to describe this worrying condition.

At the beginning of the 21st century, it was projected that by 2030 there would be 1 billion obese human beings in the world,[6] however reports prior to the viral pandemic already show at that time having reached that figure.[7] At present, five years from this time threshold, there are sensitive records in real time that show that, at least, we have accumulated not only almost 860 million obese people (BMI ≥ 30 kg/m2), but almost 1.8 billion overweight people (BMI between 25 and 29.9 kg/m2), and almost 900 million under nutrition due to macronutrients and micronutrients.[8] That is to say, on the verge of reaching the quarter of the century, like a pandemic,[9] a little more than 40% of the world population progressively shows some evident degree of malnutrition or metabolic problem, if not, the double burden of obesity and combined malnutrition , which, unevenly, hits countries or regions with low and middle incomes more intensely.[10] Alarming recent estimates show that only 6.8% (95% CI: 5.4% - 8.1%) of the US adult population has optimal cardiometabolic health, which has worsened significantly over the last 20 years.[11] The leading causes of age-standardized mortality worldwide, except for COVID-19 in 2020, which was fueled by them, are being occupied without change in the last 30 years, in descending order by ischemic heart disease, strokes and Chronic Obstructive Pulmonary Disease (COPD), with worrying emergence of Alzheimer's Disease and other dementias and malignant neoplasms[12] In a surprising twist, contrary to common perception, it is

estimated that 8 out of 10 current conditions related to this diabesity pandemic are directly or indirectly linked to what we introduce (or fail to introduce) into our diet, that is, The modification of the nutritional pattern should be the most important modifiable risk (or protection) factor in today's modern reality.[2]

In 2019, seven main conditions worldwide, which we know today are vascularly and metabolically interrelated with each other, caused almost 30 million deaths: Ischemic Heart Disease (9 million), cerebrovascular events (8.2 million), COPD (2.6 million), cancers of trachea, bronchi or lungs (0.85 million), Alzheimer's disease and other dementias (0.8 million), Diabetes Mellitus (0.75 million) and Kidney Diseases (0.7 million).[1,4–7] That is, before the viral pandemic, prevalent non-communicable diseases caused at least five times more deaths in a single year than all those recorded by COVID-19 to date, since its beginning in 2020.[13] Within the variety of phenotypic manifestations of "Cardiovascular Disease" (CVD) which is by far the leading cause of illness and death in the world, for example, four specific conditions stand out that constitute an overwhelming proportion of the causes of mortality in this broad category. These are Ischemic Heart Disease (49.2%), ischemic stroke (17.7%), hemorrhagic stroke (15.5%) and hypertensive heart disease (6.2%). Together, these four conditions represent approximately 90% of the fatal incidence within the general classification of cardiovascular diseases.[14] However, we find it challenging to conceive of the possibility that perhaps all, or at least 80% of the major conditions mentioned, which include cancer, dementias, neurodegenerative and autoimmune diseases, and even premature death or impaired aging of vitality, share an intermediate mechanism about which we are wrong or confused. This mechanism, possibly an effect in the long chain with primordial and distal causes, affects our genome, that is, modern conditions in a world of increasing social inequalities, could be an epigenetic effect of everything to which our genome is exposed.[15,16] As a kind of vicious circle, those people with less food security have significantly worse cardiometabolic health conditions, that is, greater overweight and obesity, high blood pressure, diabetes and acute coronary heart disease.[17]

This intermediate mechanism manifests itself through occlusive vascular disease, affecting both large and small arteries and resulting in insufficient oxygen perfusion in the tissues, that is, prolonged tissue ischemia in a context of chronic systemic inflammation, clearly originated in metabolic stress.[18] These primary causes, mechanisms and effects are the diseases of the most lethal Pandemic of the 21st century that we point out in the title.[4] Almost 80 years ago, specifically since the end of the Second World War, the scientific community learned of the outstanding results of pioneering research based on previously unpublished cohort studies, which gave rise to the "Lipid Theory". According to this, an inappropriate diet, rich in saturated fats and low in vegetables, together with practices such as excessive smoking, excessive alcohol consumption and a sedentary lifestyle, that is, "unhealthy habits", were responsible for the formation of atheromatous plaques in the arteries and the development of arteriosclerotic vascular disease.[19] This notion extends to the present, where there is no guidance in this regard that does not proscribe or tolerate a maximum of

10% saturated fat, or limit fat consumption to less than 30% of total energy intake, but replaced by polyunsaturated fatty acids (processed vegetable oils and genetically modified margarines).[5] In that period, along with the recommendation to limit the consumption of alcohol and tobacco, the Mediterranean Diet rich in olive oil and walnuts[20] gained popularity among those wishing to reduce their cardiovascular risk,[20] which materialized in the well-known "Food Pyramid". This diet was quickly adopted by the World Health Organization (WHO), as well as by the food production policies and guidelines of the countries through their agro-industrial ministries and food marketing. Throughout the world, these guidelines influenced global health, giving rise to what today, with certain distortions, we know as the Western Standard (North American) Diet.[21] The need to reduce fat intake without losing the necessary daily energy has led to a specific configuration of the Food Pyramid. Its broad and substantial base is composed primarily of simple and complex carbohydrates, including sources such as vegetable flour products, cereals and legumes. At a higher level, although in smaller proportions, the consumption of fruits and vegetables is emphasized. Higher up, in moderate amounts, it is suggested to incorporate lean proteins. Finally, at the top, it is recommended to replace saturated fats with polyunsaturated vegetable oils and processed hydrogenated margarines.[4,5]

The marketing of this nutritional pattern has been effectively extended to the general population, even in the East, especially with regard to the proportion of daily energy coming from carbohydrates. A representative sample with a broad socioeconomic and cultural background from the five continents found that, at the dawn of the 21st century, the proportion of carbohydrates, fats and protein in the usual diet was 61%, 24% and 15% respectively.[22] Since the middle of the 20th century, after the adoption of the recommendations of this "healthy" diet, specifically, the adoption from the health systems to the homes of the aforementioned population pyramid, there has been a paradoxical and unexpected exponential increase not only in the outcomes derived mortality (which was assumed to be alleviated with this nutritional style or pattern), but the consumption of simple or complex, processed, refined, added carbohydrates was expected to increase. The linear correlation of these artificial modifications of the dietary pattern in the global concert, controlling for known risk covariates, is statistically and epidemiologically significant with the exponential growth of overweight and obesity, high blood pressure, and the constructs of Diabetes Mellitus, but also of neurodegenerative diseases, Alzheimer's and other dementias, that is, intermediate risk cofactors and clinical outcomes of modernity.[23]

The diabesity pandemic has grown throughout the world after almost 80 years of the implementation of measures to correct unhealthy lifestyles and an eating pattern designed, paradoxically, to avoid it. The prevalence of obesity in the USA grew two-fold from 13% in 1960 to 27% in 1997[24] and triple the projected rate (42%) at the end of the second decade of this century.[25,26] This exponential growth has had a linear relationship (which explains its greater variance) due to the increase in per capita consumption of carbohydrates in the standard diet[23,24] but at the same time, with a higher level of poverty and food insecurity.[17] Especially in the last decade in the USA, Diabetes Mellitus Type 2 -DM T2, has grown in its prevalence, from a confidence interval of 1.5% to 6.9% in 2004, to 12.2% in 33 % in 2016, that is, almost 5 to 10 times more, in less than 15 years, much more intense growth on the east coast of the United States.[27] That is, currently, the world is under a multiple "malnutritional" burden: overweight and obese, obese malnourished, undernourished, obese and undernourished and all their combinations or permutations,[28] and all the conditions derived from a poor cardiometabolic health that this represents.[11,17]

Despite continued efforts to reduce cigarette and alcohol consumption, encourage physical activity through fitness culture, and promote a healthy diet based on the well-known "blue zones", attempts at conservative control and the increasing use of Medications, especially statins,[29] to address risk factors for cardiovascular disease, along with the steady increase in invasive coronary therapies such as coronary catheterizations, bypasses, and stents,[30] do not appear to

be having an effective impact on the reduction in risk factors or in the prevalence of mortality during the last five decades. As an aspect that qualifies this situation, with regard to lipid-lowering drugs, it is evident that the medical community has been persuaded by the presentation of shocking statistics that exalt the benefits, minimize the frequent serious adverse effects and make it difficult to carry out an adequate and simple cost-benefit-risk.[31]

The main burden of morbidity and mortality is notably evident in the five most densely populated countries and, eventually, with the greatest potential economic growth and development: China, India, Russia, the United States and Indonesia, which lead in the total number of annual deaths due to cardiovascular disease in the world,[14] as if they were victims of some type of punishment inherent to modernity, progress or civilization, specifically, of the diet that is exaggeratedly enriched in carbohydrates and ultra-processed, industrialized polyunsaturated transgenic fats, in all ages, races, lengths and latitudes of the world, in the last 60 or 70 years.[32–34] But until a decade ago, aggregative studies of serious clinical trials[35] found (modest) potential utility in reducing saturated fat and replacing it with polyunsaturated fatty acids. Since the beginning of the COVID-19 viral pandemic, the most vulnerable population for its severe forms, but also for hospitalization, admission to intensive care, mechanical ventilation, death, sequelae or prolonged forms of the disease, were precisely * It was estimated that in 2019, the turnover for cardiac artery interventions (catheterizations, bridges or coronary stents) worldwide was approximately 7.7 billion US dollars, a market with a sustained compound annual growth of 4.7%.[30] Those individuals who coincidentally showed in extremis, the coronary risk factors previously mentioned, especially the inflammatory state and immune deregulation, the metabolic syndrome-obesity or diabesity (actually the insulin resistance syndrome), in elderly individuals, polymedicated for this.[36] In one of the most surprising findings in the epidemiology of the viral pandemic, an estimated 131 million (126 to 137) people died worldwide from all causes in 2020 and 2021, of which 15.9 million (14 .7 to 17.2), that is, 12%, could be attributed to the COVID-19 pandemic but that, during those two years, contrary to what happened in 80 countries, mortality from all causes in 20 countries was lower during the pandemic than expected based on historical trends.[13]

Previous works that coincide with the first epidemic peak are consistent in showing that, in addition to age and the aforementioned cardiovascular risk cofactors, the low levels of the Vitamin D hormone present in animal fat, less than 25 ng/dl, are responsible for a large part of the variance in outcomes after SARS-CoV2 infection and other respiratory viral infections[37,38] which is explained by the deprivation in vitamin D levels caused by diabesity, dietary restriction or pharmacological reduction of cholesterol, as well as its poor activation in the winter months at the end of the year with little sun, which preceded and promoted the rise of the pandemic.[39] That is, the most prominent viral pandemic so far in the 21st century is of malnutritional-metabolic origin, rather than infectious viral. Malnutrition of macro and micronutrients due to excess and defect. This eating pattern, the Food Pyramid, which places intense emphasis on the intake of carbohydrates and prohibits the intake of saturated fats, has intensely permeated the food culture from health systems to homes, not only in the USA but throughout the world,[22] which was supported by the lipid theory, derived from population ecological studies in the USA and Europe, since the middle of the 20th century, according to which a large intake of saturated fats led to an increase in "bad" cholesterol, which produces obstructive or thrombogenic atheromatous plaques in the proximal arteries of noble organs.[40] However, over the past four decades, there has been an unprecedented increase in the risk factors and negative conditions that this nutritional intervention was expected to control. The progressive growth has spread exponentially to the main scourge of humanity, cardiovascular disease, but also to the unprecedented appearance as a public health problem of metabolic syndrome, a harbinger of hyperglycosis and insulin resistance, conditions that in turn have been associated with the increase in cancer, dementia and neurodegenerative diseases.[4,6,7] Cutting-edge aggregative research leaves no room for doubt: sugar consumption, even in small doses and in any form, presents a clinically and statistically significant increase in all pathological conditions, regardless of their nature or affected organ system. This element, which may seem insignificant, accounts for a considerable attributable fraction of the global burden of disease and mortality.[41]

The diabesity pandemic is only in its initial phase, threatening to soon undermine healthcare systems and national finances. Although it does not have a specific vaccine, it is paradoxical that it is possibly completely preventable. The key to stopping its advance lies in correcting the errors rooted in the lifestyles adopted in our modern civilized society. These errors, motivated by the search for comfort, comfort and quality of life from a hedonistic perspective, that is, the search for sensory pleasure through food and other exposures,[42] prioritizing immediate enjoyment over nutritional or health considerations, which is strongly supported by to sugar addiction and deeply rooted in the capitalist world of the market economy, makes it a complex and big problem, and only by correcting these trends, with simple (but difficult) actions, knowing what we are facing, will we be able to effectively contain this growing threat.

The theory then arises that a nutritionally and metabolically regulated immune system is highly resistant to most toxic or infectious exposures, such as SARS CoV2, as well as serious diseases resulting from them. This goes against the prevailing paradigm, which maintains that in 8 out of every 10 patients or deaths, even from COVID-19, the primary cause is dys-nutritional and dystrophic metabolic stress on the connective tissue of the macro- and microcirculation causing tissue hypoxia. Therefore, we have been lost and confused when pursuing control of the final or intermediate effects in the pathogenic chain, such as endothelial dysfunction of arterial circulation and microcirculation. Even in their genesis, these dysfunctions could be a protective mechanism against imminent death that we will see later.[15] Faced with the stubborn ineffectiveness of preventive measures of all kinds, aimed mainly at reducing the intake of saturated fats or at pharmacologically reducing cholesterol levels, as well as cardiovascular risk factors, and their meager impact on the growing rates of morbidity and global mortality,[42,43,70–76] it is necessary and urgent to go beyond reflection in structural decision-making, especially in the education or re-education of new generations of human beings and health workers within the framework of a new paradigm, contained but broad and flexible, of lifestyles.

Faced with the stubborn ineffectiveness of preventive measures of all kinds aimed mainly at reducing the intake of saturated fats or pharmacologically reducing cholesterol levels, as well as cardiovascular risk factors, and their meager impact on the growing rates of morbidity and mortality at a global level, it is necessary and urgent to go beyond reflection,[43] in making structural decisions, especially in the education or re-education of new generations of human beings and health workers within the framework of a new paradigm, contained but broad and flexible, of lifestyles. Is it possible that the paradigm of lifestyles, particularly modern nutritional and food marketing, based on lipid theory and the culturally accepted and practiced "healthy" lifestyle habits that derive from it, are found wrong or confused?

This scientific essay is framed as a Theoretical Review, in the classification proposed by Paré and collaborators,[44] with the aim of addressing the question posed. To this end, a comprehensive integrated review of the global burden of "diabesity" and its associated conditions was carried out, considering changes that have occurred over time. The scientific and conceptual literature is analyzed comprehensively, although selectively, especially during the last 70 years, a period in which nutritional and nutritional patterns have been artificially manipulated lifestyles. The purpose is to offer an alternative causal unified theory and, consequently, to explore possible solutions that require rigorous evaluation.

The origin of the confusion and the possible light at the end of the tunnel

The concern for a healthy lifestyle, within the framework of the so-called "sleep "American" or modernity, has its origins especially in the aftermath of the Second World War, supported since that date by ecological and observational epidemiological studies originating in the USA and Europe, with significant follow-up times and clinically important, unpublished outcomes. Up to that point, and that evaluated the effects of diet, body movement and, among many others, certain consumption habits (alcohol, cigarettes), on clinical outcomes and mortality from these causes.[4,5,40] This series of investigations was led by the renowned "Seven Countries Study" -SCS- an epidemiological study of 15 years of follow-up, by Ancel Keys and collaborators,[46] carried out with samples obtained in Japan, the United States, Canada and four countries. Europeans, capriciously selected it must be said, which was extended in a follow-up for more than 40 years by the European countries involved.[47] This initiative, collected by science and the community in its paradigmatic findings, was accompanied, to mention the most representative, by others such as the Framingham study, begun in 1948, which, with cardiovascular emphasis in the Framingham Heart Study, identified arterial hypertension, high cholesterol and electrocardiographic evidence of left ventricular hypertrophy, as its clear risk factors and, after an initial 6 years of follow-up, made its first indexed publication in 1961.[48] At that time (1966), also in the existing nutritional paradigm, the US CDC began to develop the nutritional database using a structured survey as a source, the National Health and Nutrition Examination Survey (NHANES)[49] and a little later, the accumulated information from the cohort of US Nurses and Health Workers.[50] In parallel, from the National Institute of Health of the USA, in 1991, by government design, the national long-term health study was undertaken, which focused on prevention strategies for coronary heart disease, breast cancer, color -rectal and osteoporosis in postmenopausal women, with the respective nutraceutical intervention arms, of the so-called Womens Health Initiative or WHI study.[51]

The a priori suspicion of serious methodological errors in biased populations in terms of exposure factors and outcomes, of the Seven Countries Study and in all those of that line and subsidiaries in the following 50 years, and a posteriori, the lack or poor response to nutritional and risk factor control measures derived from said information in the global disease burden, not only in the USA but throughout the world, suggests that these studies could have been confused or distorted in their results. . But, disconcertingly, it is not explained how the world has not emerged from its state of obtundation or anesthesia regarding this and the implications for our modern life and, especially for our future within the framework of an aspiration for a long life, with potential, vitality and quality of life. Would it not be at least, from both an epistemological and pragmatic perspective, appropriate to consider the eventual uncertainty in which we find ourselves regarding its causality, and with the aim of controlling or even suppressing ("flattening the curve") these incremental pandemics, conceive a new integrative, common or unified causal chain? This chain would allow, following the Pareto Principle, to focus on the 20% of the causes that generate 80% of the effects.[52]

This alert and this question, perhaps, gave rise to a new breed of epidemiological, experimental and ecological, primary and aggregative research, which has tried to find the truth of this great problem, the nutritional and lifestyle problem in health, human morbidity and mortality. Conspicuously, the barrage of results and publications of these investigations, which surprisingly contested the paradigm installed in "healthy" lifestyles to date, gave their warnings at the dawn of the 21st century,[53] but especially during the five years that preceded the start of the COVID-19 viral pandemic.[3,4,15,34,35,54–60] Given its magnificent workmanship, from our perspective, we must highlight here the Prospective Urban and Rural Epidemiological study or PURE study, a kind of bastion of truth, sponsored by the PHRI (Population Health Research Institute) of McMaster University in Canada. It explicitly attempted to address the same questions about risk factors and health outcomes asked by the preceding large epidemiological studies, attempting to correct errors incurred in sampling (making it truly representative), in measuring exposures, in analyzes and adjustments, and in the outcomes that, in addition to the cardiovascular, extended to those that are secularly taking the lead in the global burden of disease such as cancer, dementia and neurodegenerative diseases. Implicitly, it sought to evaluate the impact of urbanization (by having rural controls) and Western lifestyles, as "intermediate" risk promoters (nutritional changes, physical activity, among others), and "proximal" risk factors for metabolic syndrome that is, obesity, high blood pressure, dysglycemia, dyslipidemia[4] and, among others, the habit of smoking and other behaviors, on the prevalent outcomes referred to.

It was designed in 2002 and will extend until 2030, with an initial threshold of 20 years of follow-up of a sample of approximately 225,000 participants, urban and rural with proportional affiliation, in 58 sites in 27 countries (Argentina, Brazil, Canada, Chile, Colombia, Ecuador, Peru, Uruguay, Bangladesh, China, India, Iran, Kazakhstan, Kyrgyzstan, Malaysia, Pakistan, Palestine, United Arab Emirates, Pilipinas, Poland, Sweden, Turkey, Russia, Saudi Arabia, South Africa, Tanzania, and Zimbabwe), contemplating the entire socioeconomic and cultural spectrum of the five continents.[61] With more than 120 articles published to date, derived from different geographical cohorts and for different outcomes, the first of them, as was scientifically essential, focused on instrumental validations, such as those that are difficult to validate, or cross-culturally adaptable, eating questionnaires.[62]

It is pertinent, due to its relevance and significance for the aforementioned diabesity pandemic, but also due to the historical milestone in epidemiological research that it represents, to make here a critical judgment of one of its publications from 2017, by Mahshid Dehgan and collaborators of the PURE initiative.[22] With the purpose of assessing the impact of the usual diet on total mortality and the appearance of cardiovascular disease events, emulating the study of the seven countries, it attempted to correct its errors in sampling, selection, measurement, analysis and adjustments, it is That is, it tried to optimize both its internal and external validity, considering to begin with a wide spectrum of sites, regions and countries in the sample, with undernutrition and overnutrition, from the five continents.[63]

Its primary objective was to evaluate the possible association between the intake of both fats (total, saturated, unsaturated) and carbohydrates, in their impact on total mortality and cardiovascular events and, as secondary objectives, the same between these nutrients

and specific clinical conditions: Acute Myocardial Infarction –AMI-, Cerebrovascular Accident –CVA-, mortality from cardiovascular disease and non-cardiovascular disease. The cohort finally recruited, between January 2003 and March 2013, after the incompleteness of measurement and registration data of 3.2% of the original cohort, 143,934 individuals of varied socioeconomic and cultural status, sampled by their living households, with ages between 35 and 70 years of age and with feasibility of follow-up. This sample came from 18 countries (of the initial 27 participants), three high-income (Canada, Sweden and the United Arab Emirates), 11 middle-income (Argentina, Brazil, Chile, China, Colombia, Iran, Malaysia, Occupied Palestinian Territory, Poland, South Africa and Turkey), and four low-income countries (Bangladesh, India, Pakistan and Zimbabwe).

At baseline, and in the third, sixth and ninth year of follow-up of each individual since their inclusion, sociodemographic variables (sex, age, education, employment, economic income), lifestyles were established using validated formats and instruments. (smoking habit, physical activity, alcohol consumption), health history, medications and biological variables (Weight, Height, Blood Pressure, Body Mass Index, Waist Perimeter, Hip Perimeter, Waist/Hip Ratio). Of particular interest in the exhibition, the Food Frequency Questionnaire (FFQ-) was used, validated,[22,64] plus translations into languages other than English, adaptations and cross-cultural validations [65], where this was necessary.[64,66–69] From the caloric intake, the percentage of the intake represented by the three macronutrients was calculated categorically for each individual. Of note for internal validity, in the conversion of food to nutrients, a specific database for each country was designed based on 43 available macro or micronutrients. On the other hand, a validated physical activity questionnaire was used,[70] which finally summarized said variable in Metabolic Equivalent of Task (MET-) minute per week, which was stratified into low (< 600 MET). min per week), Moderate (600 to 3000 MET min per week), and High (> 3000 MET min per week).

The research ensured that there was telephone contact or a person-to-person interview at least once a year with each individual included, in which a median observation of the outcomes of 7.4 years (IQR 5.3 -9.3 years) could be ensured which varied depending on the entry of each country into the cohort. In the multivariate analyzes of the relative risk of the outcomes over time (Hazard Ratio -HR-), the models took into account a priori for adjustments, geographical region, age, sex, education, smoking habit, physical activity, waist/hip ratio, history of diabetes and urban or rural origin, and the comparison of dietary patterns such as high in carbohydrates and low in fat and vice versa. Despite criticisms of the validity and applicability of ecological cohort studies, in which it is very difficult to adjust for changes over time in exposures in repeated measures, omit measurement of new or unknown exposures, the fragility of measuring instruments65], even validated as the FFQ, and the risk of loss as the follow-up time increases, this study, from our perspective and from the point of view of its internal validity, possibilities of generalizability and level of evidence it provides, is a better standard than any of the studies preceding this date and therefore, its results and applicability have exceptional importance in the culture of nutrition, body movement and current health. In the need of contrast for the translation of this evidence, we allow ourselves below to display the baseline characteristics of the participants in the study, accompanied by a comment regarding the possible variation in the seven regions of analysis (China, South Asia, Europe and Canada, South America, the Middle East, Southeast Asia, and Africa).

The sample was slightly predominantly female (58.3%), with regional ranges ranging from 68.1% in Africa and 54% in Europe and Canada, and an average age of approximately 50 years (3 years older in Europe and 2 years less in other regions), who lived in a little more than half of the cases (52.7%) in urban areas. Education varies slightly, being mostly up to the secondary level, but being higher in the Middle East for the pre-secondary level (60.2%) and in China, for secondary education (52%). Physical activity varies with 44.5% of participants reporting high physical activity, with the highest rate in Europe and Canada (59%). One-fifth of the sample (21.1%) were regular smokers, with a highest prevalence in Africa (30.3%) and a lowest in Europe and Canada (15.2%). The waist/hip ratio of 0.87, with a standard deviation of 0.08, although not adjusted for sex, suggests a low tendency towards abdominal prominence (an indicator of consolidated metabolic syndrome). Even so, there is a trend towards slight systolic arterial hypertension (130.9 mm Hg), especially in Africa (139 mm Hg) and a surprising 7.1% of participants with a history of diabetes, being highest in Southeast Asia (13.5%). and lowest in Africa (5.1%).

Carbohydrate intake constituted 61.2% of dietary energy, being highest in China (67%). Fat intake was 23.5%, being highest in Europe and Canada (30.5%) and in Southeast Asia (30.3%). Importantly, in South Asia and Africa, but also in low- and middle-income countries, two-thirds of the population studied consumed at least 60% and up to 77% of their daily energy in the form of carbohydrates, mainly represented by white rice and white bread. Protein intake was 15.2%, being lowest in South Asia (11.6%). Saturated fat intake was 8%, being highest in Europe and Canada (10.9%) and in Southeast Asia (10.2%). Monounsaturated fat intake was 8.1%, being lowest in South America (7%). Polyunsaturated fat intake was 5.3%, being highest in the Middle East (7%). The regions of South America, Canada and Europe, and the Middle East, showed the lowest proportion of vegetables as a source of protein in the diet and the sample coming, especially, from Southeast Asia and Africa, showed slightly different basal levels of cardiovascular risk, in especially higher systolic pressure, smoking habit, sedentary lifestyle and history of diabetes.

In the results, after a median follow-up of 7.4 years, the baseline cumulative risk of dying in the entire cohort was 4.3% and of suffering a major cardiovascular event was 3.5%. Two thirds (66%) of the deaths were associated with a non-cardiovascular cause, 29% with a cardiovascular cause, and 6% with trauma. Among non-cardiovascular deaths, the most common cause was cancer, followed by chronic respiratory diseases, except in Africa where infectious diseases lead, and followed by respiratory disease. Within cardiovascular events, stroke with 47% and acute myocardial infarction with 45% represented the overwhelming majority.

All multivariate analyzes were performed after controlling or adjusting for the other measured risk factors. In this sense, the two most striking results show that high carbohydrate consumption increased the risk of dying from any cause by 28% (HR: 1.28 95% CI 1.12-1.46) and the risk of death by 36%. die from a non-cardiovascular cause (HR:1.36 95% CI 1.16- 1.60) but high consumption of total fats reduced the risk of dying from any cause by 23% (HR:0.77 95% CI 0.68-1.00], 18% the risk of stroke and 30% the risk of dying from cardiovascular causes (HR:0.82 95% CI 0.60-0.82], and a higher protective attributable fraction to a higher consumption of saturated fat (HR:0.80 95% CI 0.69-0.93). In the most illustrative aspect of the true background to our uncertainty, all the risks of dying or suffering cardiovascular and non-cardiovascular events, which in their linear trend are reduced to the extent that total fat intake and its subtypes increase, are They are attenuated when total carbohydrate consumption exceeds the 60% threshold, reversing the trend and increasing risks when carbohydrate consumption exceeds 70%.

Conspicuously, high total protein consumption reduced the risk of dying from any cause by 12% (HR: 0.88 95% CI 0.77-1.00), and reduced the risk of dying from non-cardiovascular causes by 15% (HR: 0.85 95% CI 0.73-0.80).

Three additional aspects emerge as significant in the translation of this evidence for decision making:

The first at the micro level is that, theoretically, the replacement of just 5% of total carbohydrate intake with polyunsaturated fatty acids is associated with a relative reduction of 11% in the risk of mortality (HR: 0, 89 95% CI 0.82-0.97) and, if this replacement is made with saturated fat, the risk of stroke is reduced by 20% (HR: 0.80 95% CI 0.69-0.93]. The second aspect in this same order is that, in the step wise of the multivariable models, by including the educational level of each individual, the estimators are smaller in their magnitude of association, which gives this aspect an opportunity for effective intervention. But especially, from the epistemological perspective of science, it is confirmed that the previously accepted theory on the relationship between saturated fats and cardiovascular disease was confused by the presence of another factor, the true causal agent: the increasing and predominant consumption of sugar in the standard Western diet. This revelation represents a valuable lesson about the nature of knowledge and the scientific method.

Hans Reichenbach, recognized for his contributions to logical empiricism in the first half of the 20th century, formulated the principle of common cause.[71] This principle maintains that, if two variables are correlated, such as Saturated Fat (SF) and Cardiovascular Disease (CVD), one could be a cause of the other (GS→CVD). Otherwise, there is a third variable that causes both, known as variable confounding. From Reichenbach's work he derived another central principle of causality and control of confounding variables in epidemiology. By controlling the 'confounding' variable, in this case, incremental sugar consumption (ISC), the association between GS and CVD disappears. This demonstrates that the association between GS and CVD is due to ISC, which in turn causes both rather than being a sign of a genuine causal relationship between the two, a phenomenon known as 'conjunctive fork'. As a concrete manifestation of the central problem, if the studies carried out by Ancel Keys and his collaborators had considered the consumption of sugar, both natural and added in the diet, as an adjustment variable, they would have reached the same results as later studies, such as those carried out by Dehghan and his collaborators. The latter demonstrated that the causal relationship between the consumption of saturated fats and cardiovascular diseases was a spurious association, confused by the true toxin: sugar, which, without euphemisms, has been responsible for the most lethal epidemic of the 21st century (Table 1).

Table 1 taken from Dehghan et al.,[22]

Variable	Subgroup	subgroup	Baseline global trend (n 135,335)	Comment on geographic extreme values
Age (years, SD)			50.29 (9.92)	3 more years (Europe), or 2 years less, in the regions
Female sex			58.3%	68.1% (Africa), 54% Europe and Canada
Urban			52.7%	
Tens. Art. Sisto. (mmHg)			130.9	
Waist/Hip Ratio (SD)			0.87 (0.08)	
Currently smokers			21.1%	30.3% Africa, 15.2% Europe and Canada
Education	Pre-secondary		42.6%	Highest 60.2% in Middle East
	Secondary		38.3%	Highest 52% in China
	Post-secondary		19.1%	Highest 61.2% Europe and Canada
	Low		17.5%	Highest 35.2% Southeast Asia
Physical activity	Moderate		38%	Highest 46.6% and 45% in Middle East and Africa respectively
	high		44.5%	Highest 59% Europe and Canada
History of diabetes			7.1%	Highest 13.5% Southeast Asia
Energy from:	Carbohydrates		61.2%	Highest, 67% in China
	Fats		23.5%	Higher, 30.5% and 30.3% in Europe and Canada and the Southeast Asian respectively
	Proteins		15.2%	Lower, 11.6% in South Asia
	protein source	animal floors	6.4% 8.8%	Lowest, 1.6% in South Asia and highest, 10.5% in South America
	saturated fat		8%	Higher, 10.9% and 10.2% in Europe and Canada and the Southeast Asian respectively
	monounsaturated fat		8.1%	Lower, 7% in South America
	polyunsaturated fat		5.3%	Highest 7% in Middle East

A unified primary causal theory that explains the bulk of the world's disease burden

So, following a prominent error in historical epidemiological research, which was confounded by sugar consumption, and supported by accumulated evidence, both observational and experimental, as well as evolutionary biology, it is shown that, at least, the High-quality fats, such as saturated fats from non-artificially processed animals, are not only safe, but essential for human health. They are the main macronutrient necessary for maximum survival, longevity and vitality, especially in the absence of carbohydrates, and are essential

for the subsistence of our species.[72–76] Therefore, as an alternative theory diametrically opposed to the Lipid Theory, excess sugar and, especially, deficiency of other macronutrients and micronutrients essential for life and health, are involved in the initial and intermediate stages of pathogenic promotion of cardiovascular diseases and diabetes.[4] These factors would, in turn, be closely interrelated with other problems possibly of similar origin, such as high blood pressure, cancer, autoimmune diseases and neurodegenerative conditions, which are increasing worldwide, especially in vulnerable communities due to poverty and social inequalities.[77–80]

Considering the concept and going back to the beginning of the epidemiological transition of the currently predominant epidemics, a disproportionate increase in the intake of carbohydrates in the daily diet of adults is evident. Just 100 years ago, this percentage did not exceed 25%, while today it represents a little more than 60% of the calories consumed daily. This increase has occurred deliberately and in contrast to human evolution and physiology,[4,15,21] after its genetic manipulation and industrial processing in the forms of fruit juices, cereals, flours of plant origin and their derivatives, alcohol and even with the addition of empty calories from sweeteners.[81] A recurrent intake of these rapidly absorbed simple carbohydrates generates intense blood glucose peaks (hyperglycosis) and consequently insulin and counter-regulatory peaks, which inexorably culminate in the saturation or resistance of their cellular receptors.[4] Insulin receptor resistance is associated with alterations in a wide range of biological actions, to highlight lipid and protein glycation, with an increase in cardiovascular risk lipoproteins, accumulation of visceral, abdominal and vascular fat and increase in uric acid.[82]

The disproportionate increase in the intake of sugar and ultra-processed foods in the standard world diet,[83] has also taken on the tinges of a true addiction, like that of any psychoactive substance, which has made and will therefore make its control very difficult.[84] Along these lines, those individuals with an excessive total intake of sugar (in the upper quartile) have a 19% greater risk of developing Alzheimer's disease (AD), than those with the lowest sugar consumption (lower quartile) with a hazard ratio [HR] of 1.19 (95% CI: 1.05-1.34, p = 0.01). An estimated 10 g/day increase in total daily sugar intake (about 2.4 teaspoons) is associated with a 1.3% to 1.4% increased risk of AD.[85]

Almost without a doubt for more than a decade, a paradoxical 180-degree turn from the prevailing paradigm has been observed: a significant increase in the total intake of sugars, rather than fats, has emerged as the main trigger of the main dyslipidemias. This includes elevated triglyceride levels, alterations in the apolipoprotein B (ApoB)/apolipoprotein A1 (ApoA1) ratio, and an increase in levels of low-density LDL cholesterol, all intensely atherogenic particles.[86,87] Simultaneously, this intake causes a reduction in HDL cholesterol levels, which is protective or antiatherogenic. Furthermore, dietary sugar levels have been found to be associated with increased blood pressure.[88] In summary, the predominant hyperglycidic diet is positioned as the main link in the pathogenic chain not only of cardiovascular disease, but of practically all diseases correlated with modern life.[18] Then the metabolic stress of hyperglycosis, for which human biology is not ancestral or genetically designed, causes that after the insulin resistance that occurs, all the biochemical and metabolic pathways of regulation and "control" of the excess are triggered, with the consequent glycation of circulating fats and proteins[89] and their deposition in the viscera, especially in the liver and abdomen in the form of triglycerides and eventually, atherogenic cholesterols in the medial layers of the great vessels that have an important systolic kinetic impact.[15,90] But fats do not primarily cause vascular obstruction unless there are elevated levels of circulating sugar.[18] At the level of microcirculation, dyskinesia of the precapillary sphincters mediated by the sympathetic nervous system causes tissue hypoperfusion that compensatorily determines Arterial Hypertension. Macro and microvascular abnormalities and abnormal deposits of metabolic origin together make up the increasingly prevalent connatural condition of modernity: the pleomorphic cerebro-cardio-nephro-immuno-metabolic syndrome of Diabesity.[18,91]

We can speculate, extrapolating local or regional data,[92,93] that approximately one third of the world's population suffers from essential arterial hypertension, with the main reason for outpatient consultation being,[94] whose pharmacological control can modestly reduce acute vascular events. Especially by attenuating systolic hypertension. But this prevalence seems really meager compared to the burden of the condition we are examining, since it is very possible that the rise in blood pressure is a neurovegetative response to ischemia and tissue hypoxia induced by vasoconstriction caused by the associated glycemic and insulin imbalance to the metabolic stress of diabesity. That is, the 'silent disease,'[4] as it has been called, is more a homeostatic cry for help to restore tissue perfusion than a "pathology." Therefore, like a kind of puzzle that is completed, the close relationship between obesity, diabetes, high blood pressure, cardiovascular diseases and sleep apnea or hypopnea, another contemporary challenge, is logical.[95,96] Therefore, at the current time, in the most lethal pandemic of the 21st century, we are facing a serious problem of chronic malnutrition (Obese & Malnourished), due to an excess of a macronutrient is not essential†: glucose, and large deficiencies of saturated fat and micronutrients that overwhelm our ancestral biology. But it is still possible that the common root cause of the diseases of the modern pandemic is yet to be discovered, which forces us to begin expeditions in search of it and we are committed to that. Although it is still necessary to exhaust the criticism of all the available evidence, given these PURE findings and those referred to in the preceding scientific argument, we could assure that the causal lipid theory of cardiovascular disease is diametrically wrong and that the invention of the food pyramid that currently known, derived from said protuberant error, has been the cause of the most lethal pandemics of the 21st century.

It is very strange that even though it was recognized more than half a century ago,[97–99] it is not an episteme of medical training, the condition of evolutionary ancestral deficiency, which is crucial in the genesis, mechanism and pathogenesis of diseases. promoted by hyperglycosis and that would provide logical support for an alternative unified causal theory not only of the cardiometabolic disease but also of the associated and correlative conditions of the hyperglycemia-hyperinsulinemia peaks that are a faithful of the same,[15,100] but also, of imperative needs given their significance of their experimentally rigorous evaluation.[101]

Eons ago, not in other animals, guinea pigs and primates, of course humans, we experienced a genetic mutation in the GULUP gene, which codes for the production of the enzyme L-Gulonolactone Oxidase.[102] This enzyme plays an indispensable role in the last step of the synthesis of vitamin C (Ascorbate), a fundamental substance for the consolidation and maturation of the collagen structure wherever there is mesenchymal matrix or connective tissue.[103] As a result of this mutation,[104] human beings are born with an innate "public" error in the metabolism of ascorbic acid, known as Hypoascorbemia,[105] which will become anascorbemia in case of lack of dietary replacement or competitive inhibition in the cellular receptors.

This genetic error makes vitamin C an "essential" substance for the body and requires regular intake under penalty of deficiency disease.[103] With an essential nutrient for our metabolism is any xeno-tropho-biotic factor (chemical, physical, mechanical, biological, etc.) that must be ingested or to which the living being must be regularly exposed, in Minimum Necessary Daily Doses, for normal organic functioning and that our biology is incapable of synthesizing or producing de novo. In this sense, Carbohydrates are not essential macronutrients since they can be produced de novo by gluconeogenesis, by the transformation of fats and proteins in the liver.[4,15,100]

Given our inability to produce or reconstitute Vitamin C de novo from other hexoses, the restriction of its exogenous supply, as sailors suffered during long periods on the high seas, leads to the connective tissue disease we know as Sailors' Scurvy. This disorder was treated serendipically with oranges and lemons by James Lind, who carried out what has been recognized as the first formal controlled clinical trial in history, published in 1753.[106] However, adequate doses of vitamin C (a hexose) intake enter into allosteric and stereochemical competition with the excessive levels of glucose (other hexose),[99,100] present in exaggerated quantities in the modern diet, competing with cellular receptors,[107] displacing it and leading to cellular depletion and developing subclinical forms of scurvy. These subclinical forms manifest, among other aspects, especially in the skin, joints and in the sub-endothelial collagen of the arteries and arterioles. These deficiencies cause alterations in the entire mesenchymal economy, but with a critical effect at both the microvascular and macrovascular levels. In the microcirculation, structural and functional abnormalities are generated that generate interstitial edema and difficulties in cell perfusion, resulting in poor tissue oxygenation, which commonly triggers compensatory arterial hypertension. At the macrovascular level, especially in the central arteries, given the weakening of the connective tissue of the arterial wall, continuity solutions are generated, a kind of fenestrations in the endothelium, through which the blood content tries to escape and, from there, the tendency to bleeding, made protuberant in clinical Scurvy.

To counteract this innate deficiency that is consolidated by insufficient exogenous contributions and especially by competition from the hyperglycosis of modern life, the body tries to seal the emerging and growing cracks in the arteries with a kind of pavement composed of activated lipoprotein A (LpA) by platelets, which also deposit calcium and form atheromatous plaque. This pavement adds calcium, foam cells and other conspicuous elements that looked exotic before the industrial age. There is a perverse parallel between the diseases of modernity, civilization and development, the consumption of fossil fuel and, especially, the production of plastic, which accumulates overwhelmingly and everywhere without degradation, which is estimated to grow exponentially and will become unmanageable in the year 2050.[108] A recent cohort study of acceptable methodological accuracy, carried out in 304 patients who underwent carotid endarterectomy for asymptomatic carotid disease, followed for almost three years, found that in more than half of the patients (58%), particles were detected. of polyethylene in their removed atheroma plaques, with an average concentration of 21.7 ± 24.5 µg per mg of plaque and also polyvinyl chloride in 12.1% with an average concentration of 5.2 ± 2.4 µg per mg of plaque. The most alarming aspect is that those patients in whom micro or nano plastic particles were detected within their atheroma plaques had almost five times the risk of suffering from a non-lethal acute myocardial infarction, a non-lethal cerebrovascular event or dying from any cause. (HR, 4.53; 95% CI, 2.00 to 10.27; P<0.001).[109]

Returning, the plaques, which eventually become unstable, bleed, thrombose, and can acutely obstruct the arteries, actually represent an initial rescue mechanism to prevent massive internal bleeding caused by chronic vitamin C deficiency. This is the great pathogenesis that it is necessary to validate through randomized controlled experiments in individuals with vasculopathy.[110–112] Given this panorama, returning to the theory and proposal of Linus Pauling and collaborators,[111,112] the plausible option arises of administering large doses of micronutrients, especially vitamin C, Vitamin D, Selenium and Zinc, in the treatment and rehabilitation of cardiovascular disease associated with hyperglycemia.[110,113] Furthermore, sugar suppression added to the diet can be consolidated as a fundamental pillar in the rehabilitation of modern pandemics. However, from a broader perspective, recent evolutionary scientific evidence about the human being paradoxically contradicts the need for comfort or the search for comfort in modernity and the immediate satisfaction of biological and emotional needs. That is, any exhibition should not be hedonistic in principle. Instead, it suggests that everyday living conditions that respect and align with circadian or circannual cycles,[114,115] and that generate traumas, stimuli or challenges to the systemic economy, of small and medium intensity, what we call exotrophic stimuli , can trigger hormetic or adaptive responses associated with maximum longevity.[116,117]

Among the aspects that should be the subject of urgent experimental research (at least natural) to understand the optimal interaction of our genome, they preferably include when our social relationships are complete, balanced, sufficient and adequate, a restful sleep, exposure to in the sun, the daily performance of short but intense and conscious physical efforts, breathing for tissue saturation, the practice of intermittent fasting, calorie restriction through a narrow daily eating window or deep fasting, increasing the proportion of animal fat in relation to dietary protein, supplementation of vitamins and trace elements, and, above all, the maximum possible reduction in the intake of simple processed carbohydrates, processed vegetable oils and synthetic consumer products that are ingested, inhaled or applied on the skin.[118,119] These current attitudes and practices, which must have had their idiosyncratic adjustments and those typical of our ancestors, have proven to be more effective than any modern medicine, intervention or artificial activity, designed by man for his "well-being", but which should be pursued to achieve of extreme longevity and vitality that at least reaches the expectations of the human species.[114,120]

Conclusion

An exponential growth has been observed in cardiovascular diseases and other chronic conditions associated with cardio-neuro-nephro-metabolic syndrome, derived from a recurrent state of hyperglycemia (hyperglycosis), accompanied by an equally recurrent activation of insulin and exhaustion or resistance of their cellular receptors.

This phenomenon shows a clear causal correlation with the deliberate decision to increase the intake of sugars and carbohydrates in the standard diet, which currently constitutes approximately 65% of the total daily intake, as established in the Food Pyramid. This dietary modification was justified at the time as a way to obtain an economical and efficient source of energy, quickly available, and to compensate for the reduction in the consumption of animal fats considered "atherogenic", a strategy that has permeated from health systems to homes around the world. However, these decisions were based on scientific research that has subsequently been distorted as biased, confused, and diametrically wrong. The damage caused

Because of these decisions, it is deeply rooted in modern culture, and it is imperative to begin urgent measures to dismantle the pedestal on which the consumption of sugars and carbohydrates has been placed, discouraging their intake from early childhood and encouraging consumption instead of healthy fats. In a context where it is recognized that a significant proportion of the results published in the biomedical field are erroneous[121] and that the tools intended for health professionals to use evidence in decision making have been subverted,[122] it is It is now, more than ever, essential and unavoidable to identify the authentic evidence that supports a new paradigm in terms of healthy lifestyles. To achieve this, it is essential to train a leading and independent group of health professionals in the search, critical evaluation and application of the vast information available.

In this process of education and paradigmatic transformation, it is essential to carry out a critical and exhaustive review of the existing information to determine the most effective measures to control addiction to sweet taste, which affects a large proportion of the population and is deeply rooted on palatability, low cost and the commercial interests of the food industry. Therefore, it is imperative to move from reflection and analysis to concrete action, especially through preventive education aimed at new generations of teachers and students. This involves raising awareness about the importance of what is ingested, inhaled or applied to the skin, as well as the impressions of our senses, spirituality and relationships with others in the ecosystem. These aspects, which we propose to be called together 'Exposome', have the potential to modify our genome and should be the subject of priority attention, research and application. This must be framed in the notion that any exposure factor in our biology cannot be generalized if it is not idiosyncratic, that is, it is necessary to establish, for each individual or population group in particular, the appropriate, necessary or sufficient doses to progress, since the doses and effects of said exposure have a J-shape, that is, as bad as its absence, but sometimes, its excess is even worse.[123,124] These actions are essential to reverse the alarming trend of diet-related chronic diseases and to protect the survival, health, well-being and longevity with quality of life of future generations.

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Conflicts of interest

The author declares that there are no conflicts of interest.

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