Ancel Keys and the Seven Countries Study:

An Evidence-based Response to Revisionist Histories

WHITE PAPER

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With emphasis on primary source material, historical records, and review/critique by *Seven Countries Study* investigators

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"The whole of anything is never told"
Henry James

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Competing Interests

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ABSTRACT

Disparagements of the methods, intentions, and conclusions of the *Seven Countries Study* are currently much in vogue. They populate books and on-line commentary, and figure prominently in prevailing dietary trends and debates. Critics frequently point out alleged flaws in the seminal study in order to contest its primary dietary finding, that saturated fat was correlated with heart disease, and call into question subsequent nutrition research. This paper was commissioned by the *True Health Initiative* to explore the historical record and address the popular contentions with primary source material and related work, and in consultation with investigators directly involved. Popular criticisms directed at the study, and the lead investigator, Ancel Keys, turn out to be untrue when the primary source material is examined.

EXECUTIVE SUMMARY

The Seven Countries Study (SCS) is an observational cohort study, started in 1958, to examine relationships among lifestyle, biomarkers, and heart disease.[1–4] The study was a massive undertaking requiring cooperation among scientists worldwide. Data collection and analysis spanned decades and were conducted concurrently with numerous groundbreaking epidemiological studies, including The Framingham Heart Study.[5] Ultimately, SCS suggested a link between dietary intake, specifically saturated fat, and heart disease. This conclusion, which corroborated other clinical and epidemiological evidence at the time, generated numerous hypotheses and has since inspired countless clinical trials.

SCS and its originator, Ancel Keys, have come under fire in recent years, particularly since Keys' death in 2004, and often in the context of popular nutrition narratives claiming that prevailing nutrition science is incorrect. Frequently, these critics believe strongly that carbohydrate, and not fat, is the source of heart disease and other illness- and do not allow for the possibility that both macronutrient classes, or specific food sources of them, might be involved. Though SCS itself never concluded that total fat intake should be restricted, writers – often bloggers – contend that the work of Ancel Keys and this study in particular are at fault for low-fat dietary trends, guidelines, and nutrition policy. As a result, modern critiques of seminal nutrition research often use SCS, and misperceptions around its methodology, as a focal point.

While continuing reanalysis of all science is part of the self-correcting process of the scientific method, it is important that these criticisms be based in fact and the documented historical record. There are, of course, limitations to SCS, which will be addressed in this paper. However, some narratives in the form of revisionist histories proposed to discredit SCS and Keys are untrue upon review of primary sources. Many of these narratives have become widely accepted by means of frequent repetition, particularly since the advent of social media. These criticisms include four primary allegations:

1. **Countries were selected and excluded based on desired outcome.**

   Keys and his team are often accused of picking only countries they believed would prove their theories and that France was purposefully excluded for this reason.

   While it is true that selection of cohorts was non-random, selection was based on practicality and dietary variation.[1–4] Allegations suggesting that SCS researchers chose locations where they already knew the outcomes are clearly false based on review of primary source material, the relevant timelines, and direct questioning of investigators.

2. **France was purposefully excluded**

   France, which had particularly poor dietary data, was not excluded from the study.[6,7] A French representative was present during the SCS pilot study in Nicotera, Italy, but ultimately researchers from France decided not to participate.[2,3,8,9]

   Critics attest that France was excluded because researchers were aware of the "French Paradox", but this concept represents an anachronism, since the information and associations being used today to allege bias were simply not available at the time the SCS was being designed and implemented.[10]

3. **Dietary data in Greece taken during Lent introduced a distortion.**

   Some critics believe that nutrient intake, particularly in Greece, was inaccurate due to dietary surveys being administered during Lent.[11]

   In fact, dietary data were purposefully collected during Lent in order to account for important seasonal variation in intake.[12] Researchers, who published average

intake of each survey period in dietary tables, found that there were no meaningful differences in macronutrient or total energy intake during Lent versus other times in the two Greek cohorts. These dietary findings from Greece were consistent with an unaffiliated dietary study completed in Crete in 1948 and published in 1953.[13,14]

4. **Sugar was not considered as a possible contributor to coronary heart disease.**

Critics contend that SCS did not appropriately address sugar intake in the analysis. Some also suggest that a later re-analysis of SCS data found sugar was more strongly associated with heart disease than saturated fat.[15]

The 1980 SCS monograph, an in-depth analysis of 10-year findings, did examine the association of sucrose and indeed found it to be associated with heart disease.[3] However, the association disappeared when saturated fat was also added into the statistical model, suggesting that sugar was associated with heart disease mostly due to its strong correlation with saturated fat in the diet. In contrast, the association between saturated fat and heart disease persisted after adjusting for sugar, suggesting it to be the primary and more significant factor. The 1999 reanalysis, contrary to one retelling, did not find that sugar was more highly associated with coronary heart disease than saturated fat; its findings were consistent with earlier SCS publications.[16]

This paper examines each of these assertions using evidence from primary sources, historical records, and observations from SCS investigators directly involved, and assesses each contention in historical and scientific context.

First, the paper provides the historical context and description of the SCS: how it was conducted, concurrent epidemiological studies, and the study findings reported through 1986. Next, the paper examines and assesses each of the most common criticisms one by one. Conclusions regarding the popular narratives (i.e., revisionist histories) are drawn

with direct reference to the relevant evidence. Limitations to the SCS are summarized as well.

Finally, in an epilogue/editorial comment, the legacy of the SCS and the lifelong work of Ancel Keys are briefly considered. What role, if any, did Ancel Keys play in the "low fat" era of nutrition policy? What conclusions were reached by Keys regarding saturated fat, dietary cholesterol, other dietary factors, serum cholesterol, components of the lipid panel (e.g., LDL, HDL) and heart disease- and how do these compare with the prevailing understanding of experts today? What is known about how Keys changed his opinions about these matters over time, and the sources used to inform such change?

This paper does not espouse or promote any dietary advice; it is intended only to present a historically accurate account of well-documented work and redress misrepresentations of that work. Further, but for brief mention in the epilogue, this paper does not address how the science and research detailed here may have been co-opted and misinterpreted by various entities in the service of various motivations not directly accountable to the epidemiologic data. Industry and government actions during this period represent a complex and contentious topic beyond the scope of this White Paper.

SEVEN COUNTRIES: AN OVERVIEW

The Seven Countries Study began in 1958 to measure dietary habits, biomarkers, and lifestyles of 12,763 men in seven countries: the United States, Italy, Finland, Greece, the Netherlands, Japan, and two nations of the former country of Yugoslavia (now Croatia and Serbia). The aim was to assess connections of both lifestyle and anthropometric measures to the risk of developing or dying from coronary heart disease.[1–4,12,17] The subjects of the research were 16 cohorts of men aged 40-59. Eleven cohorts lived in rural villages, two cohorts were railroad workers — one based in the United States and another in Rome, Italy — one cohort was comprised of Belgrade University faculty in Serbia, one was comprised of workers of an agro-industrial cooperative in Zrenjanin, Serbia, and another lived in the country town of Zutphen, the Netherlands.[1–3]

In 1957, preparation for SCS began with a pilot study in Nicotera, Italy, a town that ultimately was not to be included as a cohort in the study.[1,3,9] This is where researchers developed and tested their standardized methods for recruitment and enrollment and biomarker measurements to ensure collection would be uniform across all sites. Researchers representing all sites were present at the pilot study. Nicotera served as a dress rehearsal for the main study, which began in 1958.[3,18]

In each town, investigators enrolled eligible men and collected baseline data including blood cholesterol, blood pressure, BMI, and electrocardiograms (ECG).[2,3] They collected participants' medical and smoking histories, and they classified level of physical activity based on profession. Diet records were taken in representative subsamples of cohorts as described below.

For SCS, researchers developed new procedures to improve the accuracy and reliability of any medical diagnoses. In previous studies that relied on national disease and death data comparisons, differences in diagnostic criteria for heart disease accounted for much of the variability between countries.[10,19] To avoid this, the investigators developed strict codes for categorizing diagnosis.[3,20–22] All ECGs were sent to the

University of Minnesota for analysis and classification to reduce variability in data interpretation. The Minnesota Code was developed to reduce observer error and provide strict guidelines so type and incidence of coronary heart disease were uniformly categorized.

Researchers were similarly concerned with collecting consistent dietary data. In all but the US and Italian railroad cohorts, researchers collected thorough seven-day diet recall diaries;[3,4] a representative subsample of 30-50 men was chosen from each cohort to complete intensive seven-day weighed food records. Under dietitian supervision, all food and drinks consumed were weighed. In addition, duplicate samples of all foods eaten were collected, freeze dried, and sent to the University of Minnesota for chemical analysis.[4,12] Both the results from dietary recall data and weighed food sampling were published and compared in order to validate intake measures.[12,23] In the US, intake was estimated using 24-hour recalls and food frequency questionnaires. For the Italian railroad cohort, seven-day diet records and food frequency data were collected.[4]

Achieving a high follow-up rate among participants was a primary concern during study design, and the choice of measurements was made with this in mind. Oral glucose tolerance was suggested as part of an initial protocol, but was excluded due to expense and concern that participants might not return if visits lasted an additional hour.[3] Beginning in 1970, glucose tolerance tests were carried out in some cohorts, notably Zutphen, Netherlands, over the remaining course of the study.[18]

At five and 10 years, all cohorts were revisited — except the two Japanese cohorts were not examined at year 5 and the U.S. Railroad cohort, which was not examined at year 10 due to lack of funding — and biomarkers and electrocardiograms were taken again.[3] New cases of heart disease were diagnosed and death records from all cohorts, including those for the railroad workers cohort in the U.S., were carefully combed. Deceased participants' causes of death were examined and validated by the research team. Publications following up on the SCS cohorts after the 10-year mark examined coronary heart disease mortality and all cause mortality.[4,16,18]

As with coronary heart diagnoses, similar care was taken in verifying official cause of death. Death certificates for each individual, rather than official mortality statistics, were used and in more than half of deaths, researchers corroborated cause of death by interviewing a participant's family, physicians, and/or obtaining hospital records. Even when only a death certificate was available, a critical review was made to define cause of death according to standardized criteria.[18]

Three book-length study analyses were published in 1966, 1970 and 1980.[1–3] The 10-year (1980) and 15-year (1986) follow-up publications are important sources for the present paper; many other details can be found in the voluminous literature generated by the SCS.[3,4] The great number, and length, of SCS publications can prevent readers from grasping the scope and details of the study, since each paper inevitably presents only a small part of the whole story. Keys, and the large team of authors representing all of the participating nations, tracked correlations, evaluated outcomes, and determined what conclusions could be drawn from decades of evidence. SCS primarily examined the relationship among cohorts between diet and coronary heart disease, and secondarily, correlations within cohorts among lifestyle, biomarkers, and coronary heart disease.[2–4,18]

Seven Countries: Design and Main Outcomes

The Seven Countries Study is a type of observational study known as a "prospective cohort study." For a cohort study to examine outcomes such as coronary heart disease, it must enroll participants who do not possess the condition at baseline and then collect data on these participants and cohorts over time. As time goes by, researchers assess the incidence of and mortality from a given disease within and/or across the study populations. Researchers then track whether baseline measurements, like high blood pressure, are associated with differing propensities for disease development and mortality. Because researchers only observe participants and do not introduce dietary or lifestyle interventions, this is known as an "observational" study or specifically "cohort

study." A cohort study that follows participants over an extended period of time can also be referred to as "longitudinal" or "prospective."

Perhaps the most famous study of this type is The Framingham Heart Study, which followed select citizens of Framingham, MA, and was one of the first studies to show the damages caused by cigarette smoking.[5,24,25] To provide some historical context, The Framingham Heart Study was merely 8 years old at the start of the Seven Countries Study; the first major findings were published in 1957, a year before official data-collection in SCS would begin.[24]

Numerous cohort studies examining relationships between lifestyle and coronary heart disease were in their early years at the time of SCS. The Minnesota Business and Professional Men Study, also by Keys and his Minnesota colleagues, had started in 1947.[26] In a table of cohort studies predating SCS, Keys noted that on the West Coast, a cohort study in Los Angeles civil servants started in 1950 and one in San Francisco longshoremen started in 1951.[27] In Albany, NY, similar observational studies began on civil servants in 1953.[3] Other major observational studies would continue to form throughout the '50s and '60s and sample sizes would trend upward.[3]

Unlike many prospective cohort studies, which are performed in a limited geographical area, the cohorts in SCS were ecologic units. Many of the aspects of the SCS, including diet, were analyzed as an "ecological" study, meaning that Keys et al. examined correlations between the mean values of data points of the 16 geographic cohorts, as well as comparing the data from each individual.[3] An ecological study looks at the associations between exposure variables, and outcome variables, at the level of the sub-population. A semi-ecologic study also collects and analyzes data among individuals; thus, depending on the focus of study, SCS is an "ecologic" or a "semi-ecologic" study (see "Strengths and Limitations," page 48).

Selection of Countries: Diet and Diplomacy

Running a multinational cohort study in 1956 presented a series of challenges. Only a little more than a decade past World War II, there were diplomatic and practical concerns for country selection. In order to participate, funding needed to be secured for each cohort, a precluding barrier for some countries. Indeed, SCS was unable to sustain funding for its American cohort and so disease incidence of the US cohort, assessed by ECG and clinical examination, was dropped as an outcome after the five-year follow-up.[1,3]

Competency and familiarity with each region were other considerations. The University of Minnesota team attempted to work with researchers and in regions with which their international colleagues had knowledge and contacts, and where they were welcome.[3] Cooperation from village leaders and citizens was essential for adequate follow-up, which required the presence of scientists native to each of the included countries. Keys and his team benefitted from existing international contacts that assisted in scouting and suggesting locations. Many of the small communities chosen had participation rates of greater than 90%, an impressive feat requiring substantial local buy-in. The lowest participation rate for coronary heart disease incidence, still comparatively high among observational studies, was among the American railroad workers who were concerned that their jobs would be at stake if researchers discovered poor health.[3] Follow-up for total mortality was near 100% for the first 15 years.[18] Follow-up for vital status and cause of death was nearly complete for most cohorts for 25 years, and for select cohorts, for 50 years.

Selection of Countries: Statistics

Researchers carefully selected populations across a wide variation of dietary patterns, but with low variance of other characteristics to limit confounding. The rural cohorts in SCS were identical in age distribution and gender, and highly similar in level of education, socioeconomic status, and laborer lifestyle, but not in diet.[1–4] This ideally reduced confounding when comparing cohort means, while maximizing variability in cohort diets and coronary heart disease incidence.

At the time of SCS, all epidemiological studies examining health outcomes in relation to diet in single populations encountered a nearly insurmountable practical and statistical problem. The day-to-day variation in the diet of a single individual (called intra-individual variation) was of nearly the same magnitude as variation in diet between individuals (inter-individual) of the same culture.[3,28–30] In order to be reasonably confident of a difference between one person's diet and his neighbors', dietary surveys would need to have been repeated upwards of seven times.[3] This approach was impractical, prohibitively expensive and, even then, unlikely to discover major differences among individuals eating a relatively homogenous diet without a much larger sample size.

For these reasons, Keys thought it was imperative to compare disease rates where the average diets of populations varied over a wide range in order to see possible relationships between nutrient intake and chronic disease risk.[1–3,18] Consider that in a population where everyone smokes, it would be nearly impossible to find smoking associated with increased risk of lung and mouth cancers, even though true. A measurable difference in outcomes requires a discernible difference in exposure.

Hence, the choice of populations with divergent dietary patterns was crucial to the early study of possible causes of heart attack. Historically, much of the initial information that suggests diet's impact on health has come from observations of populations with outlying diets and disease incidence, including the classic observations in China and Java,

Seventh Day Adventists in Loma Linda, and smaller but more recent observations among the Maasai in Kenya and northern Tanzania, and most recently among the Tsimané of Bolivia.[31–34]

Of the seven countries, the United States and the Netherlands each provided a single cohort, the former Yugoslavia (now Croatia and Serbia) provided five, Italy three, and Japan, Greece, and Finland each contributed two.[1–4] In most cases, cohorts within each country were selected because of purported differences in eating habits, thus potentially providing dietary variation between a region's cohorts. In the analysis, comparisons were therefore made between individual cohorts as well as between countries.

The United States was an obvious choice because the research team was based in Minnesota.[3] Researchers and public health officials were interested in discovering factors linked to the relatively high incidence of coronary heart disease plaguing middle-aged men in the U.S.

Japan had an extremely low rate of reported coronary heart disease and a national diet uniquely low in fat, though it was unclear whether particular health outcomes reported were due to diet, the Japanese tendency to record sudden deaths as cerebrovascular, or both.[1] The Japanese cohort in Tanushimaru was a farming community, while the Ushibuka cohort was a fishing community with a diet higher in seafood.[18]

North Karelia, Finland, was known for high-fat diets and allegedly had extremely high rates of coronary heart disease. The West Finland cohort included men in two rural villages, where coronary heart disease was purportedly lower than in East Finland.[18]

The Greece cohorts in Crete and Corfu were included because they reported low mortality from coronary heart disease, but high intakes of fat, particularly olive oil.[3,18]

Sites in Croatia (former Yugoslavia) were chosen with help from a native colleague, Ratko Buzina, who provided staff for data collection in these regions.[3] This allowed

researchers to minimize costs and achieve high survey response rates. Interestingly, the five sites in former Yugoslavia were characterized by supposedly different dietary patterns. The Dalmatia cohort was known for a high vegetable Mediterranean-style diet, the Slavonia cohort had a more traditional central European diet high in animal products.[18,35] The three Serbian cohorts were chosen based on varying socioeconomic status and reportedly had similar diets; Zrenjanin included men working on an agricultural cooperative; Belgrade, the faculty at the University of Belgrade; and Velika Krsna, farmers in the rural village south of Belgrade.[18,35]

The rural regions of Italy were chosen for similar reasons: varied diets between cohorts. The Rome railroad workers provided the "Italian counterpart" to the U.S. railroad cohort. Crevalcore, in northern Italy, purportedly had a diet higher in animal fat while Montegiorgio had a diet more traditionally "Mediterranean."[18] The Netherlands was included because the Dutch government nutritionists were collegial and curious to join the pioneering comparisons among cultures.[3,36]

Notably, Keys and his team wanted to include areas with differing rates of coronary heart disease, but relied on uncertain estimates by local experts of the prevalence of disease, since government reported death rates at the time were unreliable indicators.[7]

Much of the modern criticism of the SCS is aimed at the selection or non-selection of various regions, a topic that will be covered in a later section (page 22). It's important to note that country selections aimed to include a wide range of diets so that a statistical effect *could* be measured *if* it existed. Selection was also shaped by the practical considerations of cost and connections imposed on carrying out research in any capacity. Additionally, other than preferential addition of developed nations with very diverse diets to improve the power of the study, lack of interest, preparation, or funding were the only reasons for excluding countries. Countries with willing researchers and ready funds were welcome.[8]

This paper focuses primarily on the findings reported in the 1980 and 1986 publications, which evaluated 10- and 15-year coronary heart disease incidence and mortality, as well as all-cause mortality.[3,4]

Primary Findings of the Study

Deaths from coronary heart disease were consistent with the data coming from scattered sources before the study commenced.[3] Northern Europe and America experienced a much higher incidence of and mortality rate from coronary heart disease than did men of the same age in Southern and Central Europe. Japan was characterized by very low reported coronary heart disease death rates.[3]

The finding most debated today was that the average cohort intake of saturated fat (as percent of calories or energy) was statistically significantly associated with cohort rates for coronary heart disease[3]. Total dietary fat was not associated with coronary heart disease. For example, the Greek cohorts ate about 40% of their daily calories from fat and the Japanese ate only 10% while both cohorts had very low coronary disease rates.[3,4] SCS was the first systematic study to illustrate this important dichotomy, that low rates of coronary heart disease and, in fact, of total mortality can be found with low and high total fat intakes, depending on the nature/sources of the fat and the rest of the eating pattern.[3]

Findings of Diet and Disease

Keys et al. assessed associations among cohorts using a multivariable linear regression.[3] This method was to evaluate potential ecological correlations between lifestyle and disease while controlling for potential confounding factors. Simple correlations can be found by comparing two measurements, but don't allow researchers to conclude that the correlation is specific to the dependent and independent variables examined. This is because there are other circumstances possibly associated with both major variables that are not accounted for in a simple correlation; these are known as

confounders. Adjusting for confounders does not allow researchers to overcome the primary limitation of observational studies and determine causal relationships, but can increase confidence that a correlation is valid and meaningful.[37]

A multivariable regression accounts for confounding factors by controlling for them within the statistical analysis. With this method, researchers can assess the effect of the exposure (such as a diet) on the outcome (such as coronary heart disease) including possible confounders in the equation. By including multiple factors possibly associated with coronary heart disease including weight, blood pressure, physical activity, and diet, researchers could more reliably distinguish between true correlation and coincidence. Of note, however, is that such adjustment is never perfect, and particularly in an ecological analysis does not serve to establish cause-and-effect.

Keys et al. measured the ecologic association between saturated fat and coronary heart disease controlling for total caloric intake[3]. Sugar was included in the model, which assessed the effect of saturated fat intake when adjusted for sugar intake. Saturated fat remained statistically significantly associated with heart disease in that model. The opposite circumstance did not hold true. When sugar was the independent variable, adjusting for saturated fat intake eliminated any observable association between sugar consumption and the incidence or mortality from coronary heart disease.[3,38] In other words, the analysis suggested that any variation in heart disease concurrent with sugar intake was "explained away" by variation in saturated fat intake, whereas variation in heart disease concurrent with variable saturated fat intake was not explained away by variation in sugar intake. Saturated fat emerged directly from the data analysis as the predictor variable of singular apparent importance.[3,4]

There are numerous claims, mainly on blogs, attesting that SCS did not include sugar in its statistical models; this is not the case.[3,38] However, high intake of refined carbohydrates is now considered to be a possible contributor to heart disease development;[39,40] this was not evaluated. In SCS, saturated fat intake was correlated with sugar intake and cohorts with diets higher in saturated fat also consumed more sugar.[3]

Tellingly, saturated fat intake was non-significant when serum (not dietary) cholesterol was added into the statistical model as a control variable.[3] Earlier experimental studies had clearly demonstrated that saturated fat intake caused increased serum blood cholesterol when substituted for carbohydrate or compared to supplementation with mono or polyunsaturated fatty acids.[41,42] The significant relationship between saturated fat intake and heart disease was eliminated when adjusted for serum cholesterol, which suggested that serum (not dietary) cholesterol was a key mediator.[3] To summarize: Keys et al.'s findings suggested that the correlation between saturated fat and increased coronary heart disease was due to the correlation between saturated fat intake and higher serum cholesterol levels, which subsequently affect coronary heart disease risk. Sugar was analyzed in exactly the same way as saturated fat, but did not demonstrate a significant association with relevant outcomes independently.[3]

Findings from the 1986 evaluation of coronary heart disease and all-cause mortality were consistent with those of the 1980 monograph.[3,4] Further, Keys et al. found that saturated fat intake, specifically the ratio of saturated to monounsaturated fatty acids, was significantly associated with death from coronary heart disease as well as all-cause mortality.[3,4]

Though high serum cholesterol was significantly associated with coronary heart disease outcomes, at the time of the analysis in 1980, Keys et al. concluded that there was likely a threshold under which average population cholesterol level might not be associated with increased risk.[3] Later evidence with huge samples found individual coronary heart disease risk continuous with serum cholesterol, particularly LDL, from low to high.[43]

BEGINNING THE CONTROVERSY

The SCS was one of many longitudinal observational studies in the mid 20th century that attempted to discover why coronary heart disease mortality in the United States and Northern Europe seemed high. Unlike most of those concurrent studies, Keys et al. used an ecological approach to compare the lifestyles and risk factors among entire populations and diverse regions across a wide variety of traditional eating patterns.

Why has the study become controversial? Over time, numerous arguments emerged asserting that Keys' seminal study was wrong, or worse, that data were altered or selected to reflect specific outcomes. It is possible that modern critiques of a study that began over 60 years ago led to careless handling of historical facts.

The SCS, like all scientific endeavors, was not without limitations, which will be summarized below. But attempts to paint the study as "corrupt" or "cherry-picked" lack merit.

To demonstrate this, we critically examine claims frequently made including:

1. *That Keys, et al. selected countries with a specific outcome in mind; that SCS had data from 22 countries but highlighted only seven.*
2. *France was deliberately excluded because the SCS research team was aware of the "French Paradox."*
3. *That dietary surveys made in Greece were invalid because they occurred during Lent.*
3. *That an analysis of SCS data published in 1999 proved that sugar, and not saturated fat, was associated with coronary heart disease.*

Authors referred to primary literature as well as communication with original members of the SCS research team to evaluate claims that have become popular on blogs and in diet books. The authors note that this effort illustrates "Brandolini's Law:"

"The amount of energy needed to refute [misinformation] is an order of magnitude bigger than to produce it."[44]

Addressing Cherry-picking Accusations: History of the 6-Country Graph

Many critiques start with a cherry-picking argument: Keys had data from 22 countries and chose only the seven that fit his hypothesis.[45] This accusation is startlingly pervasive, yet demonstrably false.

Where does this argument come from? Misrepresentations of the source of the data are years old; Keys himself responded to critics who incorrectly thought SCS data came from national statistics.[46] Speakers, bloggers, journalists, and other detractors of SCS frequently cite this graph:[47]

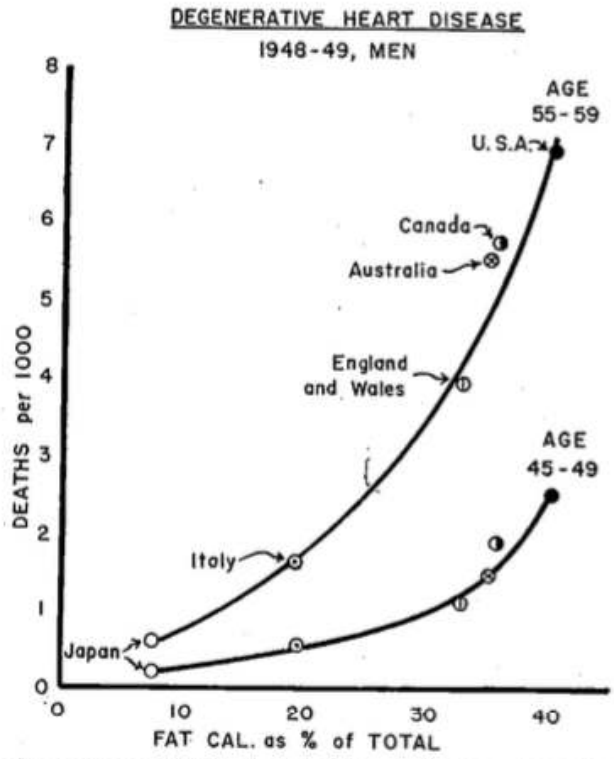

FIG. 2. Mortality from degenerative heart disease (categories 93 and 94 in the Revision of 1938, categories 420 and 422 in the Revision of 1948, International List. National vital statistics from official sources. Fat calories as percentage of total calories calculated from national food balance data for 1949 supplied by the Nutrition Division, Food and Agriculture Organization of the United Nations.

Figure 1: From "Atherosclerosis: A problem in newer public health," Journal of the Mount Sinai Hospital, 1953. This image has been reproduced from widely available reproductions accessible online. Permission to reproduce the original has been sought from the publisher, and a response is pending at this time.

And then this one:[6]

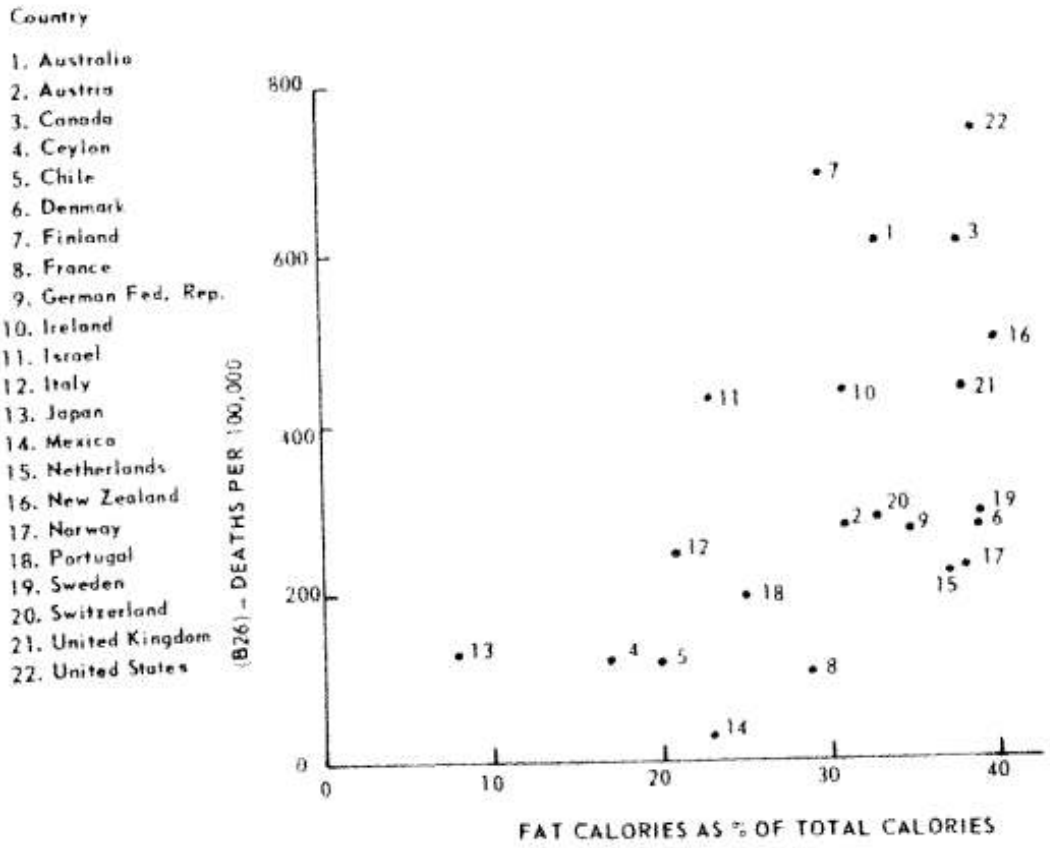

FIG. 3. Mortality from arteriosclerotic and degenerative heart disease (B-26) and fat calories as per cent of total calories in males fifty-five to fifty-nine years. Calculated from national food balance data by F.A.O. (see text for definition).

Figure 2: From "Fat in the diet and mortality from heart disease: A methodologic note," 1957, New York State Journal of Medicine. Permission to reprint granted by the publisher.

The first graph is from a paper by Ancel Keys, showing a correlation between fat in the diet, calculated from national disappearance data, and World Health Organization (WHO) data on heart disease in six countries.[47] The second, from a paper by statisticians Jacob Yerushalmy and Herman Hilleboe, shows the same relationship but with 22 countries.[6] Many critics suggest that the second graph eliminates the correlation between fat intake and heart disease. Though it is easy to see that the positive correlation between fat intake and heart disease remains in this version, it does appear weaker.

The seemingly stark contrast of these graphs side-by-side has become an enduring argument for the inaccuracy of, and alleged "cherry-picking" of countries for — the SCS. But **neither of these graphs** is from the SCS.

The first graph of six nations is from an earlier paper by Ancel Keys in 1953, more than a decade before the first publications from SCS.[47] The second is from a paper published in 1957, nearly a year before baseline data collection began in SCS cohorts.[6] Clearly, neither of these graphs uses the same data as the SCS.

The first graph is often mistakenly attributed to SCS, and critics of the study are not fastidious about correcting the mistake. The incorrect assertion that SCS started with 22 nations and pared down to the seven that fit Keys' hypothesis even made it to the Wikipedia entry for SCS for a time.[45] A cursory examination of the primary source material reveals it to be a false proposition.

Legitimate confusion on the topic is likely due to the passage of time and failure to review the full historical record. The historical context behind the development of each graph readily clears up the controversy surrounding this mistaken assertion.

The six-country graph

In 1953, Ancel Keys' presentation at a symposium, "Recent Advances in Therapy," at Mt. Sinai Hospital included the first graph displaying six countries.[47] This presentation was then published as a paper the same year, titled, "Atherosclerosis, a problem in newer public health."[47] In it, Keys presented a wide-ranging review of the evidence available at that time, suggesting that atherosclerosis was not simply a natural consequence of aging and that diet might be related to heart disease outcomes. What was revolutionary about this was the idea that heart disease could be preventable. This was an intuition Keys could not prove at the time, though his future work and that of many others, have proven him right.[39,40,47,48]

In the paper, Keys pointed out that diagnosis of cardiovascular disease, which he referred to as "degenerative diseases of the heart," varied greatly but seemed to share common biological pathways.[47] His second point was to show that serum cholesterol tended to be higher in people with heart disease than in people without it. And thirdly, he reviewed previous experimental evidence in humans showing that altering the amounts of fat and dietary cholesterol in the diet affected serum cholesterol levels.[47]

This, along with the six-country graph, was meant to posit the following thought process. The mortality for middle-aged men in the United States was higher than in similarly developed countries; this mortality difference seemed to be due to higher mortality from coronary heart disease. A higher fat intake was associated with a greater incidence of heart disease in some countries. His conclusion was to suggest that fat intake was correlated with coronary heart disease through serum cholesterol level, but that type of fat might also matter.[47]

Keys said at the time: "Whether or not cholesterol, etc., are involved, it must be concluded that dietary fat is somehow associated with cardiac disease mortality, at least in middle age." It is interesting to note that at this time, in 1953, Keys primarily posits that change in risk may be attributable to total fat, rather than saturated fat, in the diet.[47] He would later refine his thinking on this topic with data from his own work in human cross-over dietary experiments, clinical trials, and in SCS, where only saturated fat proved to be associated with an increase in risk.[3,4,41,42] This, according to Keys' many co-investigators, was his consistent pattern; he would methodically test the hypotheses he formed on the basis of provisional data, and evolve his thinking in accord with the data and findings.[49]

The six-country graph appeared in a research paper that ran more than 20 pages and included tables and results from numerous comparative studies showing the differences in mortality, coronary heart disease mortality, and food disappearance data among multiple countries, results of experimental data on diet and serum cholesterol, and observational comparisons of average serum cholesterol in populations with and without

heart disease.[47] None of this was decisive proof of cause-and-effect, but was the start of a line of research still yielding new insights, and the basis for Keys' hypotheses at the time.

Why did Keys choose only six countries for the particular graph? According to Keys, these six countries represented those that had the most reliable dietary and vital statistics at the time, in 1952.[47] A consistent principle in the *Laboratory of Physiological Hygiene* (Keys' Department at the University of Minnesota) at the time and for many years later was: *the data you talk about have to be of the highest caliber, valid, reliable, and most relevant to the scientific question*.[50] Additionally, numerous scientists had noticed that WWII had changed not just total mortality statistics, but coronary heart disease death rates as well, and that countries occupied by Germany during the war experienced significant upheavals to traditional diets that altered their risk factors for heart disease. "In Norway," Keys pointed out, "the public health and vital statistics records were well maintained and it is clear that not long after the national dietary change began, there was a marked decline in mortality from circulatory disease, particularly arteriosclerotic heart disease."[47]

Though the paper was published in 1953, the data used by Keys in the graph (and likely the most recent data available) were from 1949, only four years after the end of the war. Dietary changes in Germany and the countries it occupied lasted longer than the end of the war and could possibly have introduced bias into a simple correlation.[51] In a later paper, Keys noted "the prolonged influence of the war and its aftermath on the diets of many countries cannot be ignored."[7,52,53]

Yerushalmy and Hilleboe's response

In 1955, Keys presented to atherosclerosis experts in Geneva the same information, in a talk that was published as "The relationship of the diet to the development of atherosclerosis in man."[6,54] Two public health professionals, Jacob Yerushalmy and Herman Hilleboe, were in attendance. They were not impressed by what they interpreted as Keys' confidence that dietary fat was causally linked to heart disease; they felt there

was not substantial evidence to make a causal claim.[6] Yerushalmy and Hilleboe chided Keys for altering his "cautiously observed" correlation in 1953 to the more strident assertion he made in 1955:

"The analysis of international vital statistics shows a striking feature when the national food consumption statistics are studied in parallel. Then it appears that for men aged forty to sixty or seventy, that is, at the ages when the fatal results of atherosclerosis are most prominent, there is a remarkable relationship between the death rate from degenerative heart disease and the proportion of fat calories in the natural diet. A regular progression exists from Japan through Italy, Sweden, England and Wales, Canada and Australia to the United States. No other variable in the mode of life besides the fat calories in the diet is known which shows anything like such a consistent relationship to the mortality rate from coronary or degenerative heart disease."[6]

Yerushalmy and Hilleboe, concerned that Keys was overstating a simple correlation, decided to investigate these claims.

Four years after Keys' initial paper was published, Yerushalmy and Hilleboe published a critique in July of 1957, featuring a 22-country graph showing Keys' correlation substantially weakened.[6] In September of 1957, Hilleboe published another 19-page paper focused on the same topic covering similar points.[55] Of the 15 tables and graphs included in Keys' 1953 paper, which relied on a thorough history of clinical, experimental, and observational evidence, Yerushalmy and Hilleboe's July 1957 paper chose to focus on a single piece of evidence, the six-country graph.[6]

They took issue with Keys' selection of countries, since they noted that data on dietary intake and heart disease mortality existed for 22 countries.[6] Yerushalmy and Hilleboe, however, failed to consider that food intake and heart disease incidence were probably influenced by the war and Nazi occupation. In fact, numerous countries included in their graph — Germany, Norway, the Netherlands, France, Denmark, and Greece — experienced atypical food availability and intake in the years prior to and directly after the war, the effects of which had been mentioned in Keys' 1953 paper.[7,47,51]

Yerushalmy and Hilleboe's criticisms of Keys' 6-country correlation graphic were to some extent valid, though the graph represented only a fraction of Keys' larger argument.[6] First, they pointed out that any simple correlation by itself could not prove a causal link between an exposure and an outcome, thus introducing the criteria for causal inference from correlations. In fact, Keys had not claimed causation.[47]

Next, they questioned the quality and accuracy of heart disease diagnoses among countries. Some countries were more precise with their diagnoses of heart disease, while other countries were more likely to file deaths under a broader category of heart-related deaths.[6] These imprecisely categorized deaths were not included in Keys' initial 1953 six-country assessment, and Yerushalmy and Hilleboe criticized the omission, though it's possible Keys considered quality of diagnosis in his selection of the six countries with "fully comparable dietary and vital statistics."[47] Further, Yerushalmy and Hilleboe had found another dietary factor more significantly associated with heart disease than fat: animal protein.[6]

They took care to point out that their observation shouldn't suggest animal protein was truly correlated with increased heart disease since an "apparent association often proves to be the result of non-pertinent extraneous factors."[6] They intended only to point out that multiple dietary correlations could be made and that scientists can't rely on single associations to assume cause. In fairness, neither of Keys' previous papers had relied on a single correlation; they included the results of multiple observational and experimental studies.[47] Nor was causality asserted; Keys simply hypothesized in accord with the findings, and these hypotheses, in part, were the basis for the SCS.

While Yerushalmy and Hilleboe accurately pointed out the liability of inferring causation from correlation, their paper was not without major flaws of its own. After the papers published in July and September of 1957, Keys responded with an editorial in the Journal of Chronic Disease that November.[7]

According to Keys, Yerushalmy and Hilleboe had used dietary and health data irrespective of quality; this is something Keys felt could affect results. Secondly, Keys pointed out that in some of the included countries, dietary data could not possibly reflect coronary heart disease data because some countries' populations included had a large percentage of recent immigrants whose diets were affected by their culture and country of origin. The dietary data, then, were not reflective of the population being measured and, thus, could not accurately be correlated with disease incidence.[7]

Most importantly, Keys pointed out that Yerushalmy and Hilleboe suffered from a chronological problem – something that would later be codified in the Bradford Hill criteria.[7,56] In his September 1957 paper, Hilleboe used dietary data primarily from 1954 to analyze the relationship with earlier coronary mortality data from 1950-52.[55]

Keys points out that the foundations of coronary heart disease start years before disease mortality. It is more likely that a country's average diet in the mid- to late 1940s would show an accurate correlation with heart disease deaths in the 1950s than would concurrent dietary data, and implausible that a country's average diet after recorded disease mortality could be a true correlation, particularly if dietary patterns had changed over time.[7]

It is also important to note that dietary data of the mid-1950s were not reflective of dietary data a decade previously in many of these European countries that were gravely affected by World War II.[7] Keys points out that this is particularly the case with the Netherlands:

"*In the data as tabulated by Dr. Hilleboe and Dr. Yerushalmy, the most striking departure from a good correlation between dietary fat in 1954 and mortality in 1950-1952 is the case of the Netherlands… There are no reliable records for the war years, but it is known that food fats available in the Netherlands were greatly reduced from 1940-1944, that the diet was at the near starvation level… In no case is it proper to suggest that the deaths in 1950-1952 should reflect the diet of the surviving population in later*

years."[7] This comment by Keys was in direct response to a related paper published singly by Hilleboe.[55]

Inferring causality

Those well-versed in epidemiology will recognize the applicability of Bradford Hill's criteria governing the inference of causation from correlation, but it is important to point out that these criteria, taken for granted today, were not published until the mid 1960s.[56] That is over a decade after this debate on saturated fat, and indeed after the Surgeon General's Report on Smoking (1964) that largely relied on epidemiological evidence to infer causation between smoking and lung cancer.[57] The academic debates on how epidemiology should be used to influence public health policy, so eloquently summarized in the Bradford Hill criteria, had their genesis in debates that took place in the 1950s, including this one between Keys, and Yerushalmy and Hilleboe.[58]

The effects

Yerushalmy and Hilleboe, intentionally or otherwise, distorted Keys' original point by citing a single piece of data and critiquing it as if it were the basis for his entire line of reasoning. However, in doing so, they made several good — if pedantic — points about the limitations of observational evidence for inferring causal relationships.[6,55]

By the time Yerushalmy and Hilleboe's paper was published, SCS was already underway incorporating procedures designed to avoid the exact traps Yerushalmy and Hilleboe highlighted.[3] SCS would standardize the way diet and heart disease were measured in cohorts. Rigid protocols eliminated much of the variability in local infrastructure and diagnosis. In-depth surveys and chemical analysis of food samples increased the exactitude of dietary data compared to relying on a country's food availability data. SCS would also tailor methodology to control for what Yerushalmy and Hilleboe called the "non-pertinent extraneous factors" that create false correlations.[3,6] The SCS team selected locations that allowed entire towns to be sampled and enrolled

mostly men of the same age and socioeconomic status, which ensured that sampled populations would be largely similar except with regard to diet and lifestyle, the independent variables of interest. The study's prospective design allowed it to enroll subjects before disease began and carefully tracked the representative diet of each cohort; giving it a great deal more validity than using national or FAO statistics.[3]

In conclusion, **the famous six-country graph had nothing to do with the Seven Countries Study** and was produced from an earlier analysis that used unrelated and less robust data. Further, the epidemiological debate between Ancel Keys and Yerushalmy and Hilleboe concerned issues about the specificity of correlations, which were controlled for in the later and more precise and extensive data obtained in the SCS. The presentation of graphs of 6 and 22 countries, juxtaposed to claim cherry-picking in the SCS, is a popular falsehood; the graphs were not produced in the same study, and NEITHER was from the Seven Countries Study.[3,6,47]

The Exclusion of France

Another popular criticism, similar to the first, is that Keys excluded countries that didn't fit his hypothesis. Namely, France was purportedly excluded due to the "French Paradox."

The "French Paradox" rests on the assumption that people in France tend to eat a diet higher in saturated fat than people in other developed nations, yet experience lower rates of heart disease.[10] Critics believe that Keys was aware of this paradox and intentionally left France out of the SCS. This, like the cherry-picking accusation, is demonstrably incorrect.

France was not excluded

Missed by most revisionists is the fact that **France was indeed invited to participate in the Seven Countries Study**. As previously mentioned, the SCS team wanted local scientists from included countries to lead the project in their respective regions.[3] Countries with willing, capable researchers, interest, and funds were welcome to join. Some countries opted out due to lack of interest or resources; Sweden and Spain declined for these reasons, respectively.[8]

Representatives from France had been included and Dr. Jacques Carlotti, a physician from Paris, was part of the pilot study team in Nicotera, Italy.[1,3,9] Ultimately, representatives from France decided not to participate, possibly due to lack of desire, lack of funding, or both. **There was no explicit intent on the part of the American SCS researchers to include or exclude France**.

The "French Paradox" did not yet exist

The first reference to the now ubiquitous "French Paradox" in the literature was in 1981, making the concept a modern one. Pierre Ducimetière pointed out that the term was

first used in a paper by French epidemiologist J. L. Richard describing heart disease incidence in French policemen.[10] While it may have been noted that the French had rich diets, it was not until the major diet cohort studies like Framingham and SCS were published that the concept of France as a heart disease exception took hold.[10] In fact, the data available in the early and mid 1950s about the French diet did not suggest that people of France had either an atypical diet or heart disease profile.[6] Quite simply, even if Keys and colleagues had been inclined to act on bias, there would have been no basis at the time for a bias against the participation of France. All evidence regarding the SCS suggests very much the contrary regarding Keys and colleagues, that they took pains and went to great lengths to avoid bias in their methods.

The lack of French diet data

France was one of the many European countries occupied by Germany during World War II, and thus experienced an extended period of dietary deprivation.[7,51,53] As in much of Europe, staple foods including animal foods and dairy were rationed and supplies decreased throughout the war, in both Vichy and occupied France. Rationing was stopped only in 1949 as France — like much of occupied Europe — struggled to recover after the war's end.[51,52,59] Perhaps unsurprisingly, the food availability data for France in the late 1940s and early 1950s was not of the highest quality.

In fact, the Yerushalmy and Hilleboe paper of July 1957 inadvertently provides evidence that international data for food availability and consumption in France were poor.[6] Of all 22 countries with varying qualities of dietary data, only France had no available estimates for fats derived from animal and vegetable sources (proxies for saturated and unsaturated fats).

The study record therefore belies the claim that Keys purposefully excluded France from SCS due to concerns that France's high saturated fat intake and low heart disease rate would upset his hypothesis. There was little reliable dietary information available, and none to foster any such inference. Further, the study's design specifically included

countries with high fat intake and unknown levels of heart disease, such as Greece, in order to test the relationship between total fat intake and coronary heart disease.[3] Ultimately, SCS concluded that there was no observed relationship between the two; only saturated fat showed a strong correlation.[3]

The French Paradox in the 1950s: Poor records and poor diagnoses

The scant evidence available in the early 1950s during the planning phase of SCS did not show a French Paradox.

For example, see the 22-country chart from Yerushalmy and Hilleboe's 1957 paper[6] (page 23, page 35). France is represented by #8 on the chart. France does appear to have extremely low heart disease rates, but it is also listed as having a total fat intake of less than 30% of calories, an intake consistent with the often maligned initial dietary guidelines of the United States.[6] Few people who point to France to advocate the safety of diets high in saturated fat encourage total fat intake this low.

Additionally, Yerushalmy and Hilleboe's paper argued that the appearance of low coronary heart disease mortality in France was a façade; due more to different diagnostic criteria than to a truly lower mortality rate from heart disease.[6] And so again, critics of Keys from a half-century ago wind up refuting a popular claim among critics today.

In Keys' 1953 review paper, he compared the dietary data of six countries using mortality statistics from *WHO Annual Epidemiological and Vital Statistics* category "B-26: Arteriosclerotic and degenerative heart disease."[6,47] Mortality from heart disease was categorized as deaths per 100,000 people. In France, there were only 102 such deaths ascribed to code B-26 from the 1951-1953 data, much lower than the United States' number of 739. But Yerushalmy and Hilleboe point out that there is also the catch-all heart disease category of "B-27: Other diseases of the heart." In the United States, only 35 deaths per 100,000 were assigned to this category, while France had 180 per 100,000.[6] If one were to combine deaths in France from B-26 and B-27, France would still have a

somewhat lower heart disease rate than the United States, but not impressively so, and by no means "paradoxical."

Below is the chart of 22 countries with France added back showing total deaths from B-26 and B-27 included. The adjusted number is represented by the red dot.

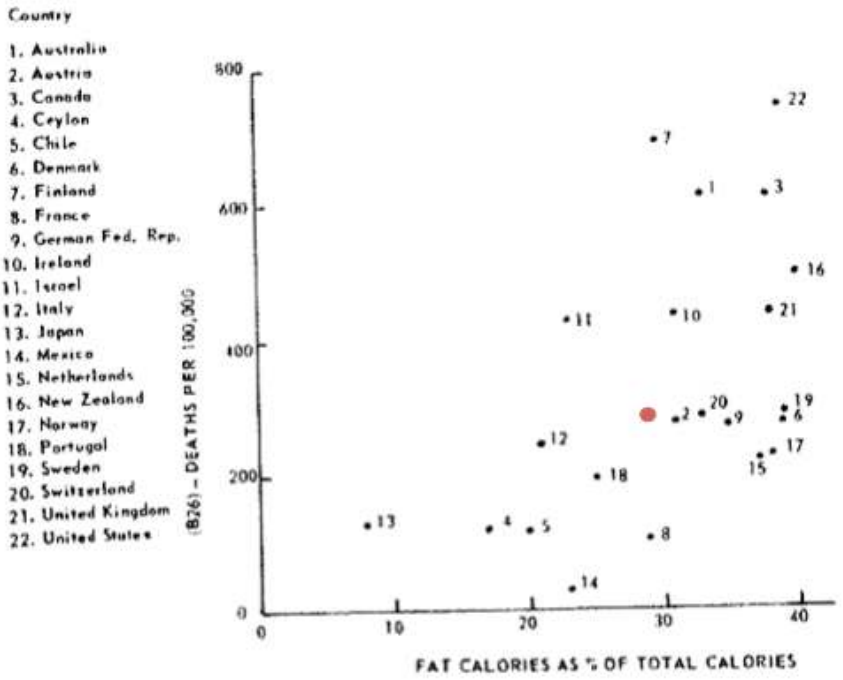

FIG. 3. Mortality from arteriosclerotic and degenerative heart disease (B-26) and fat calories as per cent of total calories in males fifty-five to fifty-nine years. Calculated from national food balance data by F.A.O. (see text for definition).

Figure 3: Adapted from "Fat in the diet and mortality from heart disease: A methodologic note," 1957, New York State Journal of Medicine. Permission to reprint granted by the publisher.

If the deaths categorized as "B-27: Other diseases of the heart" are included in the coronary heart disease mortality data, it is clear that France falls into line with an upward slope demonstrating a correlation between fat intake and heart disease. Indeed, later research has also brought to light the fact that inter-country variability in nationally reported mortality data is a major weakness in ecological studies and may be responsible for part of what we now think of as "The French Paradox."[10,19] Later epidemiological

studies on coronary heart disease across Europe showed that heart disease risk in France is consistent with the geographic gradient seen in SCS that showed lower incidence in southernmost regions and higher incidence moving north.[60,61] Clear evidence describing lower rates of coronary heart disease, but not all-cause mortality, in French men disproportionate to what would be predicted based on traditional risk factors were not defined until the 1980's.[62,63]

SCS would go on to control for variability in cause-of-death diagnoses by using study-specific researchers and standard and objective criteria to categorize and determine official cause of death for the study data across all participating sites.[3]

In conclusion, **the argument that The Seven Countries Study excluded France due to knowledge of the French Paradox is false and anachronistic**. The concept of the French Paradox did not exist until decades after SCS was launched. Further, WHO and FAO data available around the time of the start of SCS gave no reason for researchers to think that the French ate a richer diet or experienced significantly less heart disease than other similar countries in Europe.[6] Finally, France was not excluded from SCS at all, but was invited- and French researchers declined to participate.[8]

The Seven Countries Study: Dietary Data in Greece

Critics of SCS often cite concerns with methodology in addition to country selection. One criticism, predominantly featured in the book *Big Fat Surprise,* was that one of the dietary surveys conducted in Crete took place during Lent.[11] Because Lent requires fasting among adherent Orthodox Greek Catholics, the author concluded that saturated fat and animal food intake were significantly underestimated in SCS. How would this have impacted the findings? Following this argument, it's possible that the Greeks were eating a moderate or even high saturated fat diet that went undetected by researchers. If true, this would weaken the argument that saturated fat intake was significantly associated with incidence of and mortality from heart disease, since both Greek cohorts had an extremely low incidence. However, this critique overlooks several key points.

First, the SCS researchers were aware some dietary recalls occurred during Lent.[3,12] Statistical comparisons were done and there were no differences in intake between Lenten and non-Lenten sampling periods. Sampling during Lent, rather than being a researcher oversight, was a purposeful choice. If diet was significantly different during this time, it was important for researchers to capture those data accurately.[3,8] Additionally, the findings of SCS in Greece were consistent with an earlier and unaffiliated dietary intake study in Greece, suggesting that Keys et al. did collect accurate data.[3,13,14]

Dietary differences during Lent

There were two cohorts examined in Greece: Crete, and Corfu. These cohorts were unique due to the extremely low levels of heart disease these participants experienced, and also their high fat intake (around 40% of calories in Crete).[1,3] Dietary intake was measured via in-depth, seven-day, precisely weighed food records: two in Corfu and three in Crete. To validate the findings, a representative subsample of each cohort was chosen and followed for a week. Throughout this week, all food eaten by participants was

weighed and measured by researchers, and proportional physical samples of all food were taken, freeze-dried, and shipped back to the lab for chemical analysis. Then "food tables" based on seven-day weighed food records and chemical analyses were created.[12]

When all the data for dietary intake in Greece were compared, researchers found little variation in total intake between different dietary surveys.[3] The February survey in Crete and part of the March-April survey in Corfu were taken during Lent. In a 1968 monograph containing all of the dietary survey and chemical analysis methodologies, researchers made a specific note: "*The Greek Orthodox rules are much more strict than those of the Roman Catholic Church and the 'fasting' period of eight weeks should, theoretically, have a major impact on the total diet for the year. However… actual practice is different from Church prescription*." Total caloric intake was "substantially unaffected," and the proportion of energy intake from the macronutrients was similarly unaffected.[12]

From the same paper, researchers broke down food intake by percent of energy from specific foods and percent energy from macronutrients. **The argument that including Lent in the survey would lower the percent of calories coming from saturated fat — often simplified as animal fat in dietary tables — is effectively moot**. As shown below in Figure 4 from the 1968 monograph, "Dietary studies and epidemiology of heart diseases," the same animal fat intake was observed during Lent in Corfu and a slightly *higher* intake of animal fat during Lent in Crete.[12]

Similarly, it can be seen below in Figure 5, a table from the same paper, that there was little difference in total macronutrient intake between seasons.[12] Below, researchers aligned dietary intake measured by seven-day surveys next to corresponding values found by chemical analysis. Generally, chemical analysis slightly underestimates fat intake. In the monograph, den Hartog et al. theorize that this was likely due to fat from foods adhering to the sides of collection tubes.[12] (Readers with any experience using bomb calorimetry for high fat foods like fast food or snack chips have likely experienced this frustrating phenomenon.)

Table 3. Sources of calories in the diets of the men in Crete and Corfu

Calories estimated from tables of food composition applied to the weighed quantities of all foods and alcoholic beverages consumed by each individual in 7 consecutive days. Means and, in parentheses, standard deviations.

Item	Crete			Corfu	
Period	1960 Sept.	1962 May-June	1965 Feb.	1961 Sept.	1963 Mar.-April
Number of men	32	34	30	40	34
% Cal., bread	28.9 (7.1)	28.1 (6.6)	22.6 (7.9)	38.1 (7.0)	40.8 (6.8)
% Cal., olive oil	32.6 (6.8)	33.0 (6.5)	28.5 (7.2)	25.7 (6.0)	22.1 (5.5)
% Cal., animal protein	2.6 (1.6)	2.8 (2.8)	4.0 (1.6)	3.3 (2.1)	3.2 (1.7)
% Cal., animal fat	5.5 (3.8)	5.8 (2.8)	6.7 (3.3)	3.9 (3.2)	3.9 (2.3)
% Cal., alcohol	2.1 (2.7)	5.2 (6.8)	5.7 (5.5)	8.4 (5.7)	7.2 (5.2)
All other sources	28.3	25.1	32.5	20.6	22.8

Figure 4: From "Dietary studies and epidemiology of heart disease," 1968, Stichting tot wetenschappelijke Voorlichting op Voedingsgebied. Permission to reproduce granted by the publisher.

Table 4. Men in Greece, 7-day survey data, means and standard errors

Area	Date	No. Men	Cal./Day Tables	Cal./Day Chem.	% Protein Cal. Tables	% Protein Cal. Chem.	% Fat Cal. Tables	% Fat Cal. Chem.
Crete	Sept. 1960	30	2769 ±78	2654 ±91	10.2 ±0.2	10.6 ±0.4	41.8 ±1.2	35.7 ±1.2
Crete	May-June 1962	33	2848 ±97	2781 ±97	9.8 ±0.3	9.2 ±0.3	41.8 ±1.0	37.9 ±1.1
Crete	Feb. 1965	30	2626 ±98	2566 ±82	11.6 ±0.4	9.6 ±0.3	37.4 ±0.9	34.6 ±0.9
Corfu	Sept. 1961	40	2796 ±89	2632 ±90	11.2 ±0.4	10.3 ±0.4	34.2 ±0.9	26.2 ±0.9
Corfu	Mar.-April 1963	34	2877 ±62	2712 ±116	11.5 ±0.2	10.0 ±0.2	31.2 ±0.9	28.2 ±0.9

Figure 5: From "Dietary studies and epidemiology of heart disease," 1968, Stichting tot wetenschappelijke Voorlichting op Voedingsgebied. Permission to reproduce granted by the publisher.

Far from overlooking the problems inherent with collecting dietary data during a time of religious fasting, researchers actively sought to see a difference.[3,12] In the Greek Orthodox church, adherent practitioners can have between 180-200 annual days of religious fasting, a sum that makes up at least half the year.[64] It would be irresponsible not to include days of ritual fasting in populations with high adherence since this would

affect the average dietary intake of people over a calendar year, though adherence does not appear particularly strict in this case.

Averaged, researchers determined that men in both Corfu and Crete consumed 7% and 8% of their daily calories from saturated fat respectively, with the other fats coming from monounsaturated fat, and very small amounts from polyunsaturated fat.[3] Total fat intake in Corfu was estimated at 33% and in Crete at 40%, which is consistent with the values represented in Figure 5.[12]

The Rockefeller Foundation Study

Some concerns have been expressed that the dietary survey data aren't accurate for other reasons, such as a small subgroup sample size. If this were the case, data reliability could be examined by comparing dietary data collected by SCS with the summary of data from any other dietary studies or food availability data at the same time. Inaccuracy could be suspected if the SCS findings were to show values significantly different from those of other dietary surveys.

In her paper on the history of the Mediterranean diet concept, Marion Nestle pointed out that in 1948, three years past ravages of World War II, the Greek government was interested in improving health and quality of life for citizens. It therefore enlisted the help of scientists and funding from the Rockefeller Foundation to measure lifestyle factors.[14] Among other measurements, this study also did seven-day weighed dietary surveys among a sample of Greek citizens in Crete. The study, led by epidemiologist Leland Allbaugh, compared the results of their dietary survey with FAO availability data and energy available based on household food stores.[13]

Data were collected in 1948 and results were published in 1953. The results are shown below (concurrent U.S. food balance is included for comparison).[13,14]

TABLE 3
Percent of total energy contributed by major food groups in the diet of Crete compared with their availability in the food supplies of Greece and the United States in 1948–1949[1]

Food group	Crete: 7-d record	Greece: food balance	US: food balance
Energy			
(MJ/d)	10.6	10.4	13.1
(kcal/d)	2547	2477	3129
Foods (%)			
Cereals	39	61	25
Pulses, nuts, and potatoes	11	8	6
Vegetables and fruits	11	5	6
Meat, fish, and eggs	4	3	19
Dairy products	3	4	14
Table oils and fats	29	15	15
Sugar and honey	2	4	15
Wine, beer, and spirits	1	—[2]	—

[1] Adapted from reference 15.
[2] Data not available.

Figure 6 From "Mediterranean diets: historical and research overview," 1995, American Journal of Clinical Nutrition. Permission to reproduce original figure granted by the author.

Though the table is organized differently, it is clear that the results, published 15 years before the 1968 monograph, largely agree with the data of SCS. Oils and fats are 29% of total energy while animal foods are 4% and dairy is 3%.[13] Animal foods plus dairy make up 7% of the 1953 findings, while the combination of animal protein and animal fats (which are comprised of roughly the same foods) made up 8.1%. If any major difference appears, it is that the later dietary survey of SCS finds Greek men consuming slightly more total calories.[12] This makes sense, considering that the first survey was conducted only three years after WWII and only one in every six families reported having satisfactory diets.[13,14] Participants generally stated that they would prefer to have more food, particularly meat and other animal foods.

There is little evidence that Greek citizens were eating higher amounts of saturated fat and animal foods that were not picked up in either dietary survey.

In conclusion, insinuations that Greek dietary data in SCS were inaccurate, negligent, or unrepresentative are unfounded. Sampling during Lent was purposeful in order to ensure accurate average intakes in Crete and Corfu. Further, the dietary findings showed that Greek citizens did not significantly alter dietary intake during Lent. These dietary data are consistent with earlier, high quality, independent dietary surveys undertaken in Crete in the late 1940s.

Sugar vs. Saturated Fat in Heart Disease

Multiple sources have reported that SCS neglected deleterious effects of sugar on health in favor of promoting a low-fat agenda.[11,15] One accusation is that the regression analyses used in SCS did not adjust for sugar as a possible confounder.[65] Still another stated that a later 1999 reanalysis of SCS data found that sugar was more highly correlated with heart disease than saturated fat, proving that sugar, and not saturated fat, was a culprit.[11,15]

Like the other arguments addressed in this paper, these criticisms do not withstand scrutiny with attention to primary sources and historical documents. Sugar was adjusted for in the multivariable analysis, as was discussed in the findings section above.[3] The 1999 reanalysis did not upend the findings of the 1980 SCS publication; in fact, findings remained consistent.

Adjusting for sugar

Summaries are quick to state that SCS did not consider sugar when statistical analyses were performed searching for relationships between diet and heart disease. Had these correlations been done, critics attest, it would be clear that sugar correlates as well as or better than saturated fat with the incidence of heart disease.

The SCS investigators found and reported that sugar did correlate with heart disease.[3] However, Keys et al. did not find that sugar was significantly related to heart disease when the model was adjusted for saturated fat. This was consistent with experimental findings at the time that failed to show a physiological mechanism directly connecting sugar intake and heart disease.[66] Ultimately, sugar received only a few paragraphs in the 1980 SCS publication not because there was something to hide, but because there was nothing to show. Sugar was analyzed in the same way as saturated fat, and the findings that resulted were the findings reported.[3]

Mechanistic involvement in heart disease

John Yudkin, a professor of nutrition in London, posited in the 1960s that heart disease could be related to hyperinsulinemia caused by a high sugar diet.[66] In his 1971 paper, "Sugar Intake and Coronary Heart Disease," A.R.P. Walker explained the history and state of nutrition science regarding sugar intake and heart disease. He included descriptions of Yudkin's human trials, which were published more than 12 years after the start of SCS.[66] During the four-week trials, participants consumed up to 40% of their daily calories from sucrose for two weeks. Findings showed that the high sugar diet caused no differences in glucose tolerance, serum cholesterol, or serum phospholipid levels.[66]

However, Walker noted that one-third of subjects on the high sugar diet exhibited hyperinsulinemia, and patients with previously established peripheral vascular disease on the high sugar diets also experienced this outcome.[66] This led to the suggestion that the high sugar diet could cause adverse effects in people with a predisposition to develop "sucrose-induced hyperinsulinism," as Yudkin called it. These trials, while intriguing, suffered from a confounding factor: The diets were not isocaloric. Those experiencing the hyperinsulinism were gaining weight. Walker reported that in subsequent trials, Mann et al. tested the results of reducing sugar intake in participants, and weight loss was a confounding factor.[66] As has been seen numerous times in human diet trials, it is difficult to adjust intake of a single nutrient or macronutrient while maintaining isocaloric intake.

Further, the majority of case control and population observational studies that had been completed by the mid-20th century found that those with coronary heart disease weren't consuming significantly more sugar than those without it.[66] Dietary studies swapping sucrose for other types of carbohydrate — namely starch — also found that sugar had no overall relationship to health, although some studies found slightly raised plasma triglycerides. In some case-control studies, the amount of sugar consumed by those affected by heart disease was much less than the amount consumed by the control

groups without heart disease.[66] This was difficult to square with a risk of heart disease proportional to sugar intake.

In addition to Yudkin's lack of statistical calculations — his association between population data on sugar intake and heart disease relied on a scatter plot and no calculated correlation coefficients — his population-wide observational studies suffered from selection bias (a fault frequently attributed to Keys). In a critique by Ancel Keys, he pointed out that countries with high sugar intakes, but low reported heart disease, like Brazil, Colombia, Nicaragua, Uruguay, and Mauritius, were left out of Yudkin's analysis.[38] It didn't help that other scientists had found that sugar intake was statistically correlated with a smoking habit, further muddying the waters in the crude ecologic relationship between sucrose and heart disease.[66]

To much of the nutrition community at the time, links between sugar intake and heart disease risk were simply unconvincing, especially when compared to the amount of data linking saturated fat and heart disease.[66]

TABLE 2

MEAN SUGAR INTAKE (g *per diem*) IN GROUPS WITH AND WITHOUT CORONARY HEART DISEASE

All subjects were males unless otherwise stated.

Authors	*Control groups*			*Ischaemic heart disease groups*		
	no. of subjects	*age (years)*	*sugar intake*	*no. of subjects*	*age (years)*	*sugar intake*
YUDKIN AND RODDY[27]	25	56	77	20	56.4	132
YUDKIN AND MORLAND[28]	20	55.4	78	20	55.4	148
PAPP *et al.*[30]	20	43–65	117	20	42–64	121
PAUL *et al.*[31]	85	40–55	96	66	40–55	116
FINEGAN *et al.*[32]	50	under 60	69	100	under 60	65.9
FINEGAN *et al.*[33] (females)	50	under 60	65.2	50	under 60	59.7
HOWELL AND WILSON[34]	1158	44–58	79	170	44–58	67.0
BURNS-COX *et al.*[35]	160	under 60	96.9	80	under 60	99.1
M.R.C. Studies[24]						
Middlesex Hospital	160	55.1	97.1	80	54.4	100.1
Hammersmith Hospital	21	56.5	100.3	21	56.4	103.5
Scottish Hospitals	94	52.4	146.6	49	53.2	167.1

Atherosclerosis, 1971, 14: 137–152

Figure 7: From "Sugar intake and coronary heart disease," 1971, Atherosclerosis. This image has been reproduced from widely available reproductions accessible online. Permission to reproduce the original has been sought from the publisher, and a response is pending at this time.

A follow-up in 1999

A recent lay press article that dealt with the SCS — scintillatingly titled "The Sugar Conspiracy" — tried to make the case that SCS was later discredited by one of its own lead authors, Dr. Alessandro Menotti.[15]

"Years later," the article said, *"the Seven Countries study's lead Italian researcher, Alessandro Menotti, went back to the data, and found that the food that correlated most closely with deaths from heart disease was not saturated fat, but sugar."*[15]

The correlations and conclusions mentioned above are not reported in the 1999 paper.[16] When asked for comment, Dr. Menotti could not account for this conclusion: "I never said that sugar was more correlated to coronary heart disease than other food groups."[67]

The 1999 follow-up on the dietary data was an attempt to look at the relationship between specific foods and heart disease mortality. In earlier iterations of the study, each food was broken down and analyzed according to its macronutrient components; this new study took a "whole foods" approach.[16]

Unlike the conclusion reported in "*The Sugar Conspiracy*," this analysis did not find that sugar was more associated than saturated fat with heart disease mortality. Saturated fat was not assessed individually, since it is a nutrient component and not a food.[16] However, foods that are often considered proxies for saturated fat, like butter and other animal fats, were assessed.

A significant positive association was found between sugar and death from coronary heart disease (r=+0.60) that was consistent with earlier findings of the SCS.[3,16] Foods that contained high amounts of saturated fat, however, such as butter (r=+0.887), pastries (a mix of sugar, carbohydrates, and fat (+0.752)), and all animal foods (r=+0.798), all had stronger correlations with mortality from heart disease than did sugar.[16]

Accordingly, it is false to contend that SCS ignored or didn't address the possible relationship of sugar to heart disease. Today, there is more evidence that sugar and other refined carbohydrates are not an advisable replacement for saturated fat sources in a healthy diet.[39,68–70] At the time of SCS, no experimentally determined mechanism existed that linked sugar intake to heart disease. More importantly, sugar was not ignored. Researchers assessed sugar intake, but no correlation between sugar and coronary heart disease was found once saturated fat intake was controlled for in the analysis.[3] In other words, sugar intake in the SCS analysis correlated with coronary heart disease only to the extent it correlated with intake of saturated fat.

STRENGTHS AND LIMITATIONS OF *THE SEVEN COUNTRIES STUDY*

At the time of its inception, SCS was groundbreaking. Comparing incidence rates of coronary heart disease across populations with vastly different traditional diets provided information on risk that was not previously available.[3] Though definitive causes of heart disease could not be determined, it was clear that coronary heart disease was not simply a matter of fate, but could be influenced by environment, lifestyle, and diet.

Prior to SCS, Keys and other researchers had noted seemingly different incidences of chronic diseases, or diseases of aging, among populations they studied. Observational studies of individual cultures limited researchers' ability to compare diet, lifestyle, and risk factors across cultures due to differences in study design, methodological quality, and measured outcomes. Previously, national mortality and dietary statistics were highly variable, which complicated attempts to compare diet and disease prevalence between nations, such as in Keys' 1953 paper and Yerushalmy and Hilleboe's subsequent response.[6,7,47,55] SCS was able to bridge the gap by deliberately choosing vastly different cohorts and comparing each with strictly standardized measures.

The development of these methods, including the Minnesota Code, which standardized methods for measuring incidence of heart disease and confirming heart disease mortality, represented a major breakthrough in epidemiology.[21] Dietary records were equally impressive and much more thorough than many recall tools used today, and the chemical characterization of nutrient intake for the regions was unique.[3,12]

But like all scientific studies, especially groundbreaking ones, the study had limitations, which were largely acknowledged and dealt with in SCS publications.

SCS was unable in its earlier follow-up years to detect any significant excess risk for coronary heart disease or mortality associated with overweight or obesity.[3] In fact, the 1980 study report for the 10-year coronary rates found that BMI was inversely correlated

with death rate in all cohorts. At the time, most participants were at least moderately active, healthy men in their 40s and 50s, and the overall prevalence of obesity was low compared to today's levels.[3] It is possible that SCS suffered from the same issue here that occurred with smoking — there was not enough variation in individual or population rates to reveal a meaningful correlation. It is consistent with modern research to find an increased risk of death at weights below a BMI of 18, which was common in this study. However, the average BMI in most countries hovered around 25, without extreme variation within or among regions — meaning that most people were around normal weight or slightly overweight.[3] This would prevent SCS from finding many effects of obesity or overweight.

Secondly, due to the lack of physiological evidence or plausible mechanism connecting sucrose and atherosclerosis, refined sugar and carbohydrates were not given prime attention. **Modern epidemiological studies modeling the effects of swapping saturated fat for refined carbohydrates and sugar suggest that there is no change in risk when one is substituted for the other.**[71] In other words, the models suggest that butter should not be swapped for sugar, or vice versa, to avoid excess heart disease risk. Numerous studies observe that sources of polyunsaturated fats and whole grain or unrefined carbohydrate products are superior.[39,40] It is possible that this relationship was not seen in SCS because sugar and saturated fat intake were highly correlated.[3] Even so, saturated fat was independently associated with heart disease rates, while sugar was not.

The SCS team was unable to take all of the measurements they wanted due to practical constraints. For example, they initially were interested in getting glucose tolerance tests and fractionated lipoprotein cholesterol, but were limited by the difficulty of collecting these measures, shipping them to the central laboratory, and the associated expense. Glucose tolerance would have put a major time burden on the participants coming in and may have hurt participation rates. Additionally, lack of funds for incidence studies in the U.S. cohort after the five-year mark meant that researchers could assess outcomes only in coronary heart disease mortality in American men during the later years of the study.[3]

The ecological design of SCS imposed important limitations, probably most importantly difficulty in controlling for confounding. Because the primary outcomes compared cohorts rather than individual participants' values, correlations were drawn using only 16 data points; the cohort means for measurements taken. This limited how much could be inferred from more complex statistics employed in the study, like the multivariable regression, because findings are limited by a modest sample size and degrees of freedom. Additionally, sites were non-random and not meant to be representative samples of each country, but purposefully varied in diet.[18] This allowed Keys et al. to see stark contrasts between diet, lifestyle, and disease outcomes but made them less able to infer that these same variations in risk would carry over to populations outside of the study samples.[3]

Though the 1980 publication gave little attention to foods, including sugar, BMI, or smoking, in relation to total mortality, these are all limitations caused by lack of statistical power or logistical challenges. Even with perfect data collection and analysis, SCS can only report the comparative risks related to diet and heart disease within the specific populations it studied.[3] The diets of all cohorts in 1959-1964, when SCS dietary data collection took place, were dissimilar to diets we think of as the "Standard American Diet" today. Populations were not eating the high calorie, highly processed foods now so common in diets across the globe, so it is sensible to be cautious when extrapolating the findings of this single study.

CONCLUSIONS

SCS provided invaluable information about the connections between diet and coronary heart disease, in addition to developing important tools for standardizing nutrition and diet research. Monographs published with five and 10-year follow-up data showed that coronary heart disease and mortality were significantly associated with diets higher in saturated fat.[2,3] Follow-up data from 15 years of tracking all-cause and coronary heart disease mortality found that diets high in saturated fats were associated with increased risk for dying of heart disease, consistent with earlier findings.[4] Allegations that SCS was deliberately designed in order to find specific, preconceived outcomes are decisively without merit.

Like all scientific studies, SCS had limitations, largely due to its ecological design, and should be interpreted in the context of other evidence. Other concurrent, carefully conducted studies, including the Framingham Heart Study, reached similar conclusions for the associations between blood cholesterol levels and coronary heart disease risk.[24] These other studies then inspired a series of randomized controlled dietary trials testing the effects of fat substitution on heart disease risk that had findings consistent with those of the large-scale epidemiological nutrition studies.[72] The aggregation of this evidence, together with other scientific findings and many other influences, contributed to the original 1980 dietary guidelines and still influences the guidelines today.[73] All sets of dietary guidelines have advocated for limited intake of saturated fats as well as sugars.[73,74] Of note, Ancel Keys was only briefly interested in total fat intake as an important variable; his own data quickly dissuaded him from that focus, and shifted his attention to saturated fat.

Misleading, or negligent criticism of seminal research in nutrition science undermines the credibility of all science and the process by which understanding advances. Detractors invite false equivalence by allowing studies of smaller impact and dubious quality to be compared against large-scale, scrupulously conducted research. Current examples of the insidious dangers of such a process include climate change denial, and false allegations

about the effects of childhood immunization. As a result of the latter, the United States and other developed nations have seen an increase in vaccine preventable diseases and subsequently an increase in deaths from these diseases.[75] The public health impact of false or misleading narratives about nutrition research is potentially much larger even than that of vaccines.

Heart disease is the number one killer in America and worldwide.[76,77] The thesis of the many articles and books disparaging SCS and the life work of Ancel Keys is that serum cholesterol and saturated fat foods are not related to heart disease. Heart disease has decreased significantly since the 1950s, however, and despite the increase in obesity during that same time period. These declines are thought to be due to public health interventions addressing lifestyle practices, including a significant shift from dietary sources of saturated fats to sources of unsaturated fats, as well as medical advances.[76] In North Karelia, Finland, where the SCS findings and the work of Ancel Keys were used directly and with fidelity as the basis for intervention at the community level, heart disease rates plummeted over 80% in the decades that followed, and average life expectancy increased by a full ten years.[78–80] There, too, along with other changes, calories from dietary sources of saturated fat, especially dairy fat, were replaced largely with dietary sources of unsaturated fats.

Recently, the decline in coronary heart disease incidence in the United States has slowed.[76] Rates of heart disease in North Karelia, Finland, have risen slightly for the first time in half a century, in apparent tandem, whether coincidentally or causally, with popular messaging about the advantages of eating more "meat, butter, and cheese."[81]

In the preface for the 2002 monograph *Prevention of coronary heart disease: Diet, lifestyle and risk factors in the Seven Countries Study*, Ancel Keys summarizes:

"The results of the Seven Countries Study… should be viewed in this broader context of the role of the diet, lifestyle and risk factors in relation to all causes of deaths and to longevity. This should be the ultimate goal of epidemiologic research."[18]

Like all studies, SCS should be analyzed and utilized in context, with strengths and weaknesses acknowledged. By deliberately or carelessly misrepresenting historical events, distorting scientific findings, and misstating researcher intent, modern critics of the SCS routinely impede, rather than advance, understanding in nutritional epidemiology.

EDITORIAL EPILOGUE:
The Legacy of Ancel Keys and the SCS

By David Katz, MD, MPH

This White Paper, relying preferentially and to the extent possible on primary sources and first-hand accounts, decisively falsifies the popular disparagements directed at Ancel Keys and the *Seven Countries Study*. The *Seven Countries Study* included exactly seven, and neither six nor 22, countries. Keys and colleagues **did not** cherry-pick the participating countries; they **did not** exclude France; they **did not** present or graph their data selectively; they **did** include dietary intake surveys in Greece during Lent intentionally, for reasons clearly articulated at the time, and with proof that this did not introduce any distortions; and they **did** analyze sugar in all the same ways they analyzed saturated fat, and reported just what they found.

The popularization of flagrant falsehoods about all of the above is possible for several reasons: the primary source materials are now decades old, and few have or bother to seek recourse to them; the Internet lacks reliable editorial filtering or fact-checking mechanisms, so idle opinion passes routinely for expertise; repetition in cyberspace and social media is nearly effortless, and oft-repeated falsehoods can "drown out" evidence and truth with sheer volume; messages are invariably distorted in sequential transmission, as in the party game, "telephone;" and, conveniently for his detractors, Keys is unavailable to defend himself posthumously against even the most readily refuted falsehoods.[82,83]

This much the paper establishes. It stops there, however, because that was the charge to which it was responsive: a reality check about history, and a response to revisionist alternatives. But what about the legacy of Keys and the SCS and its reverberations into modern public health?

Keys has been routinely implicated in the low-fat dietary digression that brought us such low-fat junk foods as Snackwell cookies; that increased our intake of refined grains, added sugar, and total calories; and that failed to advance leading public health objectives

related to diet.[84,85] This charge, too, is clearly false. Primary sources, and first-hand accounts by investigators both indicate that Keys observed an association between (total) dietary fat intake and heart disease in his early data. According to colleagues, however, Keys routinely did with such observations what good scientists should do: turned them into testable hypotheses, not immutable convictions.[49] He proceeded to test this hypothesis himself, and concluded long before the dawn of the "low fat" diet era that total dietary fat quantity was unimportant, while the sources and quality of fat were important. Over the course of his career, he advocated for restricting saturated (and, albeit with lesser attention, trans fat), fat by shifting from animal-food-centric to plant-food-centric diets; and lent his strongest support to the natively high-unsaturated-fat Mediterranean diet. Keys published a Mediterranean diet cookbook in 1959.[86]

Misadventures in low-fat eating, to say nothing of low-fat junk foods, cannot legitimately be attributed to any position espoused by Keys over the course of his career. That there was a foray into misguided applications of a low-fat dietary approach with ramifications still relevant today is undeniable. Reasons for it are complex, contentious, and beyond the scope of this paper- and perhaps fodder for another. But it is clear that responsibility cannot legitimately be assigned either to Keys, or the *Seven Countries Study*.

There are published claims that Keys was unduly confident about specific associations, such as that between saturated fat and heart disease, given the ecological nature of the SCS. However, the written record and other first-hand accounts indicate that (a) Keys almost without fail carefully avoided any temptation to overstate the significance of his findings in published work; and (b) he based his impressions/conclusions on the overall mass of evidence, not just the SCS. Importantly, his views evolved over the course of his career in accord with the evolving evidence base.

Among the currently popular narratives is that sugar is the culprit saturated fat was long thought to be; that the contributions of sugar to cardiovascular disease were willfully concealed by vested interests; and that Keys and the SCS were complicit in this. The

reality here is that efforts to veil the harms of sugar obviously failed, since the *Dietary Guidelines for Americans* have emphasized limiting sugar intake since the first in 1980.[73,87] Keys, and the SCS, gave sugar its day in court, and reported just what they found. Studies conducted by Keys and his SCS colleagues did reveal an association between sugar intake and cardiovascular disease, albeit a weaker one than for dietary sources of saturated fat. Nothing in this body of work ever encouraged or justified the substitution of added sugar for saturated fat, and Keys was never an advocate for any such thing. There is more than one way to eat badly, and if the American public has been committed to exploring them sequentially, blame for it cannot be laid at the door- or now the grave- of Ancel Keys.

Viewing serum lipids as a key mediator of the effects of diet on the cardiovascular system, Keys was initially interested in total cholesterol, and then both LDL and HDL, but settled on the observation that LDL was of singular importance. His view on this matter seems to have anticipated by some decades the very conclusion now favored by a consensus of experts, and the shifting weight of relevant evidence.[88,89]

The principal conclusion of the SCS germane to public health practice was that heart disease was preventable with lifestyle and not an inevitable consequence of aging (a new concept at the time), and that dietary intake of saturated fat from its prevailing food sources (meat, processed meat, and dairy products then; with fast food and various processed foods appended now) should be reduced and replaced by whole foods, mostly plants, and the unsaturated oils derived from olives in particular, but also nuts, seeds, avocados, fish, and seafood- to lower cardiovascular disease risk. That conclusion has since been reached by diverse experts in diverse settings on the basis of diverse research all independent of the SCS.[40,71,74,90–104]

That conclusion was converted into practice in North Karelia, Finland, with fidelity to the findings of the SCS rather than the distortions that produced low-fat junk food in the United States. The result was a reduction in incident coronary disease of more than 80%, and an average addition to life expectancy of more than ten years.[80] While these results

were not solely attributable to a shift from animal foods to plant foods, with an attendant drop in saturated fat intake, that was a prominent component of the campaign.[78]

Keys may have been somewhat dismissive of trans fat, but mostly because it occupied a very tiny niche in the American diet at the time of his initial work. He may have been somewhat dismissive of the importance of obesity to cardiovascular outcomes, but mostly because weight varied rather little among the workers enrolled in the SCS. He may have been somewhat inattentive to the adversities of smoking, again for lack of variation in the exposure among his study participants. Overall, though, based on both data he generated, and data generated by others, Keys evolved positions remarkably consistent with those reached independently on the basis of the most current evidence on: overall dietary pattern; total dietary fat; saturated fat; unsaturated fat; sugar; LDL; and dietary cholesterol, which Keys recognized as relatively unimportant to serum cholesterol levels.

None of the first-hand accounts of Keys included the claim that he never made mistakes, or the recommendation that he be canonized. All concurred, however, that he was a diligent, meticulous, groundbreaking scientist who followed the data where they led. On the basis of data, and perhaps good intuition as well, Keys anticipated the evidence and consensus-based positions of public health nutrition in 2017 with extraordinary accuracy and consistency. When public health nutrition in the modern era has gone awry, it has never done so in accord with the findings and positions of Ancel Keys. It has done so because such findings have been distorted; such positions misrepresented; and the important lessons of this period of nutrition history, and the singular contributions of Ancel Keys, forgotten and replaced with false narratives.

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REFERENCES

1. Keys, A., Aravanis, C., Blackburn, H. W., van Buchem, S. P., Buzina, R., Djordjevic, B. S., Dontas, A. S., Fidanza, F., Karvonen, M. J., Kimura, N., Lekos, D., Monti, M., Puddu, V. Taylor HL. Epidemiological studies related to coronary heart disease: Characteristics of men aged 40-59 in seven countries. *Acta Med Scand*. 1966;460:1-392.
2. Keys A. Coronary heart disease in seven countries. *Circulation*. 1970;41(S1):118-139.
3. Keys, A, Aravanis, C., Blackburn, H., Buzina, R., Djordjevic, B. S., Dontas, A. S., Fidanza, F., Karvonen, M. J., Kimura, N., Menotti, A., Mohacek, I., Nedeljkovic, S., Pussu, V., Punsar, S., Taylor, H. L., Van Buchem FSP. *Seven Countries: A Multivariate Analysis of Death and Coronary Heart Disease*. Cambridge, MA: Harvard University Press; 1980.
4. Keys A, Menotti A, Karvonen MJ, et al. The diet and 15-year death rate in the seven countries study. *Am J Epidemiol*. 1986;124(6):903-915.
5. Framingham Heart Study. Research Milestones. https://www.framinghamheartstudy.org/about-fhs/research-milestones.php. Published 2017.
6. Yerushalmy J, Hilleboe H. Fat in the Diet and Mortality from Heart Disease: A Methodologic Note. *N Y State J Med*. 1957:2343-2354.
7. Keys A. Epidemiologic aspects of coronary artery disease. *J Chronic Dis*. 1957;6(5):552-559. http://www.ncbi.nlm.nih.gov/pubmed/13475453.
8. Blackburn H. personal communication. 2017.
9. Blackburn H, Kromhout D, A M. The Seven Countries Study: A scientific adventure in cardiovascular disease epidemiology. 1994:15-37-159.
10. De Leiris J, Boucher F, Ducimetiere P, Holdsworth M. The French Paradox : Fact or Fiction ? Expert Answers to Three Key Questions. *Dialogues Cardiovasc Med*. 2008;13(3).
11. Teicholz N. *The Big Fat Surprise: Why Butter, Meat, and Cheese Belong in a Healthy Diet*. New York: Simon & Schuster; 2014.
12. den Hartog C, Buzina K, Fidanza F, Keys A, Roine P. *Dietary Studies and Epidemiology of Heart Diseases*. The Hague; 1968. http://edepot.wur.nl/380320.
13. Allbaugh LG. *Crete: A Case Study of an Underdeveloped Area*. Princeton University Press; 1953.
14. Nestle M. Mediterranean diets: historical and research overview. *Am J Clin Nutr*. 1995;61(suppl):1313S-1320S.
15. Leslie I. The sugar conspiracy. *Guard*. 2016. https://www.theguardian.com/society/2016/apr/07/the-sugar-conspiracy-robert-lustig-john-yudkin.
16. Menotti a, Kromhout D, Blackburn H, Fidanza F, Buzina R, Nissinen a. Food intake patterns and 25-year mortality from coronary heart disease: cross-cultural correlations in the Seven Countries Study. The Seven Countries Study Research Group. *Eur J Epidemiol*. 1999;15(6):507-515.

doi:10.1023/A:1007529206050.
17. Keys A, Menotti A, Aravanis C, et al. The Seven Countries Study: 2,289 Deaths in 15 Years. 1984;154:141-154.
18. Kromhout D, Menotti A, Blackburn H. *Prevention of Coronary Heart Disease: Diet, Lifestyle and Risk Factors in the Seven Countries Study*. New York: Kluwer Academic Publishers; 2002. doi:10.1007/978-1-4615-1117-5.
19. Lozano R, Murray C, Lopez A. Miscoding and misclassification of ischaemic heart disease mortality. *World Health*. 2001;12(12):1-19.
20. Rose G, Blackburn H. *Cardiovascular Survey Methods. World Health Organization Technical Report Series No. 56*. Geneva: World Health Organization; 1968.
21. Blackburn H. Electrocardiographic classifiction for population comparisons: The Minnesota code. *J Electrocardiol*. 1969;2(1):5-9. doi:https://doi.org/10.1016/S0022-0736(69)80044-0.
22. Blackburn H, Keys A, Simonson E, Rautaharju P, Puntsar S. The Electrocardiogram in Population Studies A Classification System. *Circulation*. 1960;XXI:1160-1175. doi:https://doi.org/10.1161/01.CIR.21.6.1160.
23. Kromhout D, Keys A, Aravanis C, et al. Food consumption patterns in the 1960s in seven countries. *Am J Clin Nutr*. 1989;49(5):889-894. http://ajcn.nutrition.org/content/49/5/889.abstract.
24. Mahmooda SS, Levy D, Vasan RS, Wang TJ. The Framingham Heart Study and the epidemiology of cardiovascular diseases: A historical perspective. *Lancet*. 2014;383(9921):1933-1945. doi:10.1016/S0140-6736(13)61752-3.The.
25. Tsao CW, Vasan RS. Cohort Profile: The Framingham Heart Study (FHS): Overview of milestones in cardiovascular epidemiology. *Int J Epidemiol*. 2015;44(6):1800-1813. doi:10.1093/ije/dyv337.
26. Keys A, Taylor H, Blackburn H, Brozek J, Anderson J, Simonson E. Coronary Heart Disease among Minnesota Business and Professional Men Followed Fifteen Years. *Circulation*. 1963;28(3):381-395. doi:10.1161/01.CIR.28.3.381.
27. Borhani NO, Hechter HH, Breslow L. Report of a Ten-Year Follow-Up Study of the San Francisco Longshoremen: Mortality From Coronary Heart Disease and From All Causes. *J Chronic Dis*. 1963;16:1251-1266. http://www.ncbi.nlm.nih.gov/pubmed/14104335.
28. Beaton GH, Milner J, Corey P, McGuire V, Al. E. Sources of variance in 24-hour dietary recall data: Implications for nutrition study design and interpretation. *Am J Clin Nutr*. 1979;32(12):3546-3559.
29. Jacobs DR, Anderson JT, Blackburn H. Diet and serum cholesterol: Do zero correlations negate the relationship? *Am J Epidemiol*. 1979;110(1):77-87. doi:10.1093/oxfordjournals.aje.a112791.
30. Liu K, Stamler J, Dyer A, McKeever J, McKeever P. Statistical methods to assess and minimize the role of intra-individual variability in obscuring the relationship between dietary lipids and serum cholesterol. *J Chronic Dis*. 1977;31(6-7):399-418. doi:https://doi.org/10.1016/0021-9681(78)90004-8.
31. Kaplan H, Thompson RC, Trumble BC, et al. Coronary atherosclerosis in indigenous South American Tsimane: A cross-sectional cohort study. *The Lancet*. 2017.

32. A. MJ, Masesa Z, Strømme SB, Al E. Daily energy expenditure and cardiovascular risk in rural and urban Bantu Tanzanians. *Br J Sports Med*. 2010;44:121-126.
33. Orlich MJ, Fraser GE. Vegetarian diets in the Adventist Health Study 2 : a review of initial. *Am J Clin Nutr*. 2014;100:2-7. doi:10.3945/ajcn.113.071233.Am.
34. Blackburn H. 20th-Century " Medical Marco Polos " in the Origins of Preventive Cardiology and Cardiovascular Disease Epidemiology. *Am J Cardiol*. 2012;109(5):756-767. doi:10.1016/j.amjcard.2011.10.038.
35. Kromhout D. Personal Communication. 2017.
36. Blackburn H. Personal Communications. 2017.
37. Katz D, Wild D, Elmore J, Lucan S. *Jekel's Epidemiology, Biostatistics, Preventive Medicine, and Public Health*. 4th ed. Saunders; 2013.
38. Keys A. Sucrose in the diet and coronary heart disease. *Atherosclerosis*. 1971;14(2):193-202. doi:10.1016/0021-9150(71)90049-9.
39. Hu F, Willett W. Optimal diets for prevention of coronary heart disease. *J Am Med Assoc*. 2002;288(20):2569-2578. http://dx.doi.org/10.1001/jama.288.20.2569.
40. Katz DL, Meller S. Can We Say What Diet Is Best for Health? *Annu Rev Public Health*. 2014;35(1):83-103. doi:10.1146/annurev-publhealth-032013-182351.
41. Keys A, Anderson JT, Grande F. Prediction of serum-cholesterol responses of man to changes in fats in the diet. *Lancet*. 1957;273(7003):959-966.
42. Grande F, Anderson JT, Keys A. The influence of chain length of the saturated fatty acids on their effect on serum cholesterol concentration in man. *J Nutr*. 1961;74:420-428.
43. Borén J, Williams KJ. The central role of arterial retention of cholesterol-rich apolipoprotein-B-containing lipoproteins in the pathogenesis of atherosclerosis. *Curr Opin Lipidol*. 2016;27(5):473-483. doi:10.1097/MOL.0000000000000330.
44. @ziobrando. The bullshit [asymmetry]. 2013. https://twitter.com/ziobrando/status/289635060758507521.
45. Seven Countries Study. Wikipedia.
46. Keys A. the Diet/Heart Controversy. *Lancet*. 1979;314(8147):844-845. doi:10.1016/S0140-6736(79)90331-3.
47. Keys A. Atherosclerosis: a problem in newer public health. *J Mt Sinai Hosp N Y*. 1953;20(2):118-139.
48. Estruch R, Ros E, Salas-Salvadó J, et al. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet. *N Engl J Med*. 2013;368:1279-1290. doi:10.1056/NEJMoa1200303.
49. Kromhout D, Katan MB, Blackburn H, Menotti A, Jacobs DR, Willett WC. Personal Communication. 2017.
50. Jacobs DR. Personal Communication. 2017.
51. Kesternich I, Siflinger B, Smith JP, Winter JK. The Effects of World War II on Economic and Health Outcomes across Europe. *Rev Econ Stat*. 2014;96(1):103-118. doi:10.1162/REST_a_00353.

52. Lowe K. *Savage Continent: Europe in the Aftermath of World War II*. New York: St. Martin's Press; 2012.
53. Collingham L. *The Taste of War: World War II and the Battle for Food*. New York: The Penguin Press; 2012.
54. Blackburn H. Famous Polemics on Diet-Heart Theory. http://www.epi.umn.edu/cvdepi/essay/famous-polemics-on-diet-heart-theory/%0D%0D.
55. Hilleboe H. Some Epidemiologic Aspects of Coronary Artery Disease. *J Chronic Dis*. 1957;6(3):210-228. doi:https://doi.org/10.1016/0021-9681(57)90003-6.
56. Bradford-Hill A. The Enviroment and Disease: Association or Causation? *Proc R Soc Med*. 1965;58:295-300. doi:DOI: 10.1016/j.tourman.2009.12.005.
57. Stanhope B-J, Burdette WJ, Cochran WG, et al. Report of the Advisory Committee to the Surgeon General of the Public Health Service. *… , Educ Welfare, Public Heal Serv …*. 1964:1-386. http://profiles.nlm.nih.gov/NN/B/B/M/Q/_/nnbbmq.ocr.
58. Blackburn H, Labarthe D. Stories from the evolution of guidelines for causal inference in epidemiologic associations: 1953-1965. *Am J Epidemiol*. 2012;176(12):1071-1077. doi:10.1093/aje/kws374.
59. Davis M. How World War II shaped modern France. *Euronews*. May 2015. http://www.euronews.com/2015/05/05/how-world-war-ii-shaped-modern-france.
60. Keys A. Wine, garlic, and CHD in Seven Countries. *Lancet*. 1980;315(8160):145-146. doi:https://doi.org/10.1016/S0140-6736(80)90620-0.
61. Tunstall-Pedoe H, Kuulasmaa K, Markku M, Tolonen H, Ruokokoski E, Amouyel P. Contribution of trends in survival and coronary-event rates to changes in coronary heart disease mortality- 10-year results from 37 WHO MONICA Project populations. *Lancet*. 1999;353(9164):1547-1557. doi:https://doi.org/10.1016/S0140-6736(99)04021-0.
62. Ducimetiere P, Richard JL, Cambien F, Rakotovao R, Claude JR. Coronary heart disease in middle-aged Frenchmen: Comparisons between Paris Prospective Study, Seven Countries Study, and Pooling Project. 1980;315(8182):1346-1350. doi:https://doi.org/10.1016/S0140-6736(80)91796-1.
63. Tunstall-pedoe H. Autres pays, Autres moeurs. Theories on why the French have less heart disease than the British Reinvestigate and change the treatment. *Br Med J*. 1988;297(6683):1559-1560.
64. Sarri KO, Linardakis MK, Bervanaki FN, Tzanakis NE, Kafatos AG. Greek Orthodox fasting rituals: a hidden characteristic of the Mediterranean diet of Crete. *Br J Nutr*. 2004;92(2):277. doi:10.1079/BJN20041197.
65. Lustig R. *Fat Chance: Beating the Odds Against Sugar, Processed Food, Obesity, and Disease*. New York: Penguin; 2013.
66. Walker ARP. Sugar intake and coronary heart disease. *Atherosclerosis*. 1971;14:137-152. internet: http://edepot.wur.nl/380320 .
67. Menotti A. Personal communication. 2017.
68. Mensink RP, Zock PL, Kester ADM, Katan MB. Effects of dietary fatty acids and

carbohydrates on serum total to HDL cholesterol and serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. 2003;77:1146-1155.
69. Siri-tarino PW, Sun Q, Hu FB, Krauss RM. Saturated fat , carbohydrate , and cardiovascular disease. *Am J Clinincal Nutr*. 2010;(5):502-509. doi:10.3945/ajcn.2008.26285.INTRODUCTION.
70. Willett WC. Dietary fats and coronary heart disease. *J Intern Med*. 2012;272(1):13-24. doi:10.1111/j.1365-2796.2012.02553.x.
71. Li Y, Hruby A, Bernstein AM, et al. Saturated Fat as Compared With Unsaturated Fats and Sources of Carbohydrates in Relation to Risk of Coronary Heart Disease: A Prospective Cohort Study. *J Am Coll Cardiol*. 2016;66(14):1538-1548. doi:10.1016/j.jacc.2015.07.055.Saturated.
72. Sacks FM, Lichtenstein AH, Wu JHY, et al. Dietary fats and cardiovascular disease: A presidential advisory from the American Heart Association. *Circulation*. 2017;135. doi:10.1161/CIR.0000000000000510.
73. U.S. Department of Health and Human Services, U.S. Department of Agriculture. Nutrition and Your Health: Dietary Guidelines for Americans, 1980. 1980. https://health.gov/dietaryguidelines/1980.asp.
74. Dietary Guidelines Advisory Committee. *Scientific Report of the 2015 Dietary Guidelines Advisory Committee*.; 2015.
75. Phadke VK, Bednarczyk RA, Salmon DA, Omer SB, Health G. Association between vaccine refusal and vaccine-preventable diseases in the United States: A review of measles and pertussis. *J Am Med Assoc*. 2016;315(11):1149-1158. doi:10.1001/jama.2016.1353.Association.
76. Sidney S, Quesenberry CP, Jaffe MG, et al. Recent Trends in Cardiovascular Mortality in the United States and Public Health Goals. *JAMA Cardiol*. 2016;1(5):594. doi:10.1001/jamacardio.2016.1326.
77. Barquera S, Pedroza-Tobias A, Hernández-Barrera L, Bibbins-Domingo K, Lozano R, Moran A. Global overview of the epidemiology of atherosclerotic cardiovascular disease. *Arch Med Res*. 2015;46(5):328-338. doi:10.1016/j.arcmed.2015.06.006.
78. Puska P. Successful prevention of non-communicable diseases: 25 year experiences with North Karelia Project in Finland. *Public Heal Med*. 2002;4(1):5-7. doi:10.1136/bmjopen-2014-006070.
79. Pietinen P, Nissinen A, Vartiainen E, et al. Dietary changes in the North Karelia Project (1972-1982). *Prev Med (Baltim)*. 1988;17(2):183-193. doi:10.1016/0091-7435(88)90062-X.
80. Jousilahti P, Laatikainen T, Salomaa V, Pietila A, Vartiainen E, Puska P. 40-Year CHD mortality trends and the role of risk factors in mortality decline: The North Karelia Project experience. *Glob Heart*. 2016;11(2):207-212. https://www.ncbi.nlm.nih.gov/pubmed/27242088.
81. Vartiainen E. Personal Communication. 2017.
82. Nichols T. The Death of Expertise. *Fed*. January 2014. http://thefederalist.com/2014/01/17/the-death-of-expertise/.
83. Katz D. Opinion Stew. *Huffingt Post*. April 2013. http://www.huffingtonpost.com/david-katz-md/nutrition-advice_b_3061646.html.

84. Nelson L. Watch the rapid evolution of the American diet over 40 years, in one GIF. May 2016. https://www.vox.com/2016/5/18/11704458/american-diet-changes.
85. Moss M. The Extraordinary Science of Addictive Junk Food. *N Y Times Mag*. 2017:1-25. http://www.nytimes.com/2013/02/24/magazine/the-extraordinary-science-of-junk-food.html.
86. Keys A, Keys M. *Eat Well and Stay Well*. Garcen City: Doubleday & Company, Inc; 1959.
87. Katz DL. Sugarcoating Diet Science : Seeking Simple Truth , Past the Frosting. 2017:1-3. https://www.linkedin.com/pulse/sugarcoating-diet-science-seeking-simple-truth-past-david?trk=mp-reader-card.
88. Silverman M, Ference B, Im K, et al. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: A systematic review and meta-analysis. *J Am Med Assoc*. 2016;312(12):1289-1297. doi:10.1001/jama.2016.13985.
89. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk. *J Am Coll Cardiol*. 2016;68(1):92-125. doi:10.1016/j.jacc.2016.03.519.
90. McGinnis J, Foege W. Actual causes of death in the United States. *J Am Med Assoc*. 1993;270(18):2207-2212. doi:10.1001/jama.1993.03510180077038.
91. Khera A V., Emdin CA, Drake I, et al. Genetic risk, adherence to a healthy lifestyle, and coronary disease. *N Engl J Med*. 2016;375(24):2349-2358. doi:10.1056/NEJMoa1605086.Genetic.
92. Ley SH, Hamdy O, Mohan V, Hu FB. Prevention and Management of Type 2 Diabetes: Dietary Components and Nutritional Strategies. *Lancet*. 2014;383(9933):1999-2007. doi:10.1016/S0140-6736(14)60613-9.Prevention.
93. Wang D, Li Y, Chiuve S, et al. Association of Specific Dietary Fats with Total and Cause-Specific Mortality. *J Am Med Assoc*. 2016;176(8):1134-1145. https://www.ncbi.nlm.nih.gov/pubmed/27379574.
94. Trichopoulou A, Bamia C, Trichopoulos D. Anatomy of health effects of Mediterranean diet: Greek EPIC prospective cohort study. *Br Med J*. 2009;338(b2337). doi:10.1136/bmj.b2337.
95. Song M, Fung T, Hu F, et al. Association of animal and plant protein intake with all-cause and cause-specific mortality. *J Am Med Assoc*. 2016;176(10):1453-1463. doi:10.1001/jamainternmed.2016.4182.
96. Springmann M, Godfray HCJ, Rayner M, Scarborough P. Analysis and valuation of the health and climate change cobenefits of dietary change. *Proc Natl Acad Sci*. 2016;113(15):1-6. doi:10.1073/pnas.1523119113.
97. Ford E, Bergmann M, Kröger J, Schienkiewitz A, Weikert C, Boeing H. Healthy living is the best revenge: findings from the European Prospective Investigation Into Cancer and Nutrition-Potsdam study. *Arch Intern Med*. 2009;169(15):1355-1362. doi:10.1001/archinternmed.2009.237.
98. Etemadi A, Sinha R, Ward MH, et al. Mortality from different causes associated with meat , heme iron , nitrates , and nitrites in the NIH-AARP Diet and Health

Study : population based cohort study. *Br Med J*. 2017;357(j1957):1-11. doi:10.1136/bmj.j1957.
99. Freeman AM, Morris PB, Barnard N, et al. Trending cardiovascular nutrition controversies. *J Am Coll Cardiol*. 2017;69(9):1172-1187. doi:10.1016/j.jacc.2016.10.086.
100. Micha R, Peñalvo JL, Cudhea F, Imamura F, Rehm CD, Mozaffarian D. Association between dietary factors and mortality from heart disease, stroke, and type 2 diabetes in the United States. *J Am Med Assoc*. 2017;317(9):912-924. doi:10.1001/jama.2017.0947.
101. Sotos-Prieto M, Bhupathiraju SN, Mattei J, et al. Association of changes in diet quality with total and cause-specific mortality. *N Engl J Med*. 2017;377:143-153. doi:10.1056/NEJMoa1613502.
102. Bernstein AM, Sun Q, Hu FB, Stampfer M, Manson JE, Willett WC. Major Dietary Protein Sources and the Risk of Coronary Heart Disease in Women. *Circulation*. 2010;122(9):876-883. doi:10.1161/CIRCULATIONAHA.109.915165.Major.
103. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346(6):393-403. doi:10.1056/NEJMoa012512.
104. Lorgeril M De, Salen P, Martin J-L, Monjaud I, Delaye J, Mamelle N. Mediterranean Diet , Traditional Risk Factors , and the Rate of Cardiovascular Complications After Final Report of the Lyon Diet Heart Study. *Circulation*. 1999;99(6):779-785. doi:https://doi.org/10.1161/01.CIR.99.6.779.

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