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Editorial Article

Biographical notes on Ancel Keys and Salim Yusuf: Origins and significance of the Seven Countries Study and the INTERHEART Study

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Abstract: Ancel Keys and Salim Yusuf are both pioneers in preventive cardiology. Each overcame significant obstacles to demonstrate, through large international studies, how culture and environment influence cardiovascular disease. This paper will explore the origins and outcomes of their landmark studies: the Seven Countries Study, a prospective cohort model, and the INTERHEART Study, a case-control model. Each study advanced our understanding of the interplay between lifestyle, culture, and heart disease.

Paul Dudley White, cardiologist to President Dwight D. Eisenhower, who suffered a heart attack after 27 holes of golf on September 23, 1955, once said "A heart attack after age eighty is the work of God, before age eighty, a medical failure."[1] According to the American Heart Association,[2] over 50% of the heart attacks in America occur before age 75 (for men, almost 70% are before age 74, whereas for women, the figure is 40%). Our current understanding of how modifiable risk factors can promote or prevent heart disease owes much to two men who lead original and ambitious international field studies with limited resources, motivated by the desire to prevent heart attacks.

The first man, Ancel Keys, came to be known as "Mr. Cholesterol." His major study tracked over 12,000 men in seven countries for 10 years.[3] Published in 1970, it concluded that saturated fat in the diet and blood cholesterol levels were the principle risk factors for heart disease. The American Heart Association endorsed these findings and through effective public campaigns beginning in the 1970s, succeeded in significantly reducing saturated fat and cholesterol in the American diet.

The second man, Salim Yusuf, conceived and organized a study across 52 countries with 29,972 subjects. Instead of observing his subjects over time, like Keys, he and his team enrolled 15,152 at their presentation to the hospital with a first heart attack, and 14,820 as random age and gender-matched subjects categorized by not having any evidence of heart disease. Those with heart attacks were "cases," and those without heart disease were "controls." Yusuf's study, called INTERHEART,[4] published in 2004, showed that the risk for heart attacks was due to nine modifiable risk factors, which, if effectively controlled, would prevent over 90% of first heart attacks around the world.

Ancel Keys

Keys was born in Colorado Springs in 1904. His parents were teenagers with no formal education.[5] In search of a better life, they moved to California and settled in Berkeley. Ancel's early interest in science became evident when, at his eighth birthday party, he tried to chloroform a fly and inhaled enough fumes to lose consciousness himself.

After finishing college in 3 years with honors, Keys worked briefly at Woolworths, then returned to Berkeley and earned an MS in Biology, followed by a PhD from the Scripps Institute of Oceanography. In 1930 he traveled to Copenhagen to work with Nobel laureate August Krogh, studying the ability of eels to survive in both fresh and salt water environments. He then went to Cambridge and earned a second PhD in animal physiology from King's College.

When Keys returned to the United States in 1933, he joined the Fatigue Laboratory at Harvard, renowned for its research in exercise physiology. His first project was a study on the effects of altitude on blood oxygenation,[6] which he believed might have practical benefits for Chilean copper miners. He took a small group down to the Chilean Andes and gradually acclimatized to an altitude of 22,000

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feet, collecting blood samples on himself and others along the way. Reminiscing in 1979 for the University of Minnesota newsletter, he said "We had a little snow shelter—put up a few poles and blankets over them—and crawled in there to get out of the wind and cold. At night the temperature dropped to 50 below. We didn't do much cooking, of course. Through it all I lost a little weight but wasn't sick in any important sense, though of four others who came up from time to time two were very sick. One of them was John Talbott, who later was editor of the Journal of the American Medical Association…. We had an awful time getting him down. He was not blue but black with gas pain and retching. We thought he was going to die."

Keys' work eventually came to the attention of the United States War Department. In 1939 he was asked to develop and test a food ration for parachute troops. By this time, he had established the Laboratory of Physiologic Hygiene at the University of Minnesota. It was from this location, under the bleachers of the football stadium, that he would conduct studies on human nutrition over the next several decades. His first project for the War Department would produce K-rations ("K" for Keys). The little meals, eventually assembled by the Cracker Jack Company, achieved iconic status as America's World War II soldiers' food. Each waterproof box of 3200 daily calories contained meal units for breakfast, lunch, and dinner. A tin could contain meat or cheese, biscuits, a chocolate bar and hard candy, coffee, lemon or soup powder, chewing gum, toilet paper, and cigarettes.

As millions of people across the world suffered the consequences of disrupted food supplies, Keys began a research project called the Minnesota Starvation Experiment.[7] He wanted to identify the effects of semistarvation on the human body, and then define nutritional techniques for restoring health in the aftermath of starvation. His subjects were chosen from conscientious objectors at the Civilian Public Service work camps. The brochure used to recruit potential participants was entitled "Will you starve that they be better fed?"

The final results of the experiment filled 1385 pages in a two-volume tome entitled, "The Biology of Human Starvation," published in 1950. The book became a classic in the field of human starvation. It was the first study to show how starvation can profoundly alter personality, inducing depression, apathy, and obsessive behavior. It was the first study to document the effects of food deprivation on physiologic parameters such as blood pressure, basal metabolism, serum cholesterol levels, and resting heart rate. The rehabilitation phase of the study showed that up to 4000 calories a day for several months would be needed to build up tissues that had wasted away. Perhaps most importantly, Keys came away from the study with a new understanding of the complex interactions between nutrition and human health. Ironically, his great future contributions would be focused on the effects of diets with too much fat and cholesterol, as he now turned his attention to the epidemic of heart disease in affluent middle-aged American males.

Keys' work on starvation gave him access to data on health and disease in post-war Europe. A finding that intrigued him was the dramatic drop in heart attacks that occurred in countries where the populations had been deprived of their typical high fat, high calorie diets. This trend quickly reversed as the countries recovered during the post-war period. He was also puzzled by the new epidemic of heart attacks in affluent middle-aged businessmen. He suspected that dietary factors, particularly saturated fat, might play a key role in clogging the coronary arteries. To establish the connection between saturated fat and blood cholesterol levels, he conducted a series of carefully designed experiments where subjects were fed diets with varying amounts of saturated fat, polyunsaturated fat and cholesterol. He was able to derive an equation, called the Keys Equation:

$$\Delta\text{chol}\left(\frac{\text{mg}}{\text{dl}}\right) = \left(2.16\Delta\%\text{sat.fat kcal.} - 1.3\Delta\%\text{pol}y\text{unsat.fat kcal.} + \sqrt{1.5\text{ dietary chol. (mg)}}\right) \div \frac{1000\text{ kcal}}{\text{day}}$$

The equation predicted a 2.7 mg/dl rise in cholesterol for every 1% of calories derived from saturated fat. The equation also showed that polyunsaturated fat lowered serum cholesterol, and dietary cholesterol raised serum cholesterol, but to a lesser extent than saturated fat. This equation remains one of the most important in nutritional science.

Keys then proceeded to design a new kind of trial for teasing out the causes of coronary heart disease. The concept of risk factors did not yet exist. In 1947 he proposed to enlist 283 businessmen and professionals from Minnesota, between the ages of 45 and 55. Keys explained the rational for the study as follows: "The aim of this study was to find individual characteristics in apparently healthy middle-aged men related to the future tendency to develop coronary heart disease, an aim based on the conviction that the physico-chemical characteristics of the individual should have predictive value".

The Minnesota men were followed for 40 years, when only 54 remained alive. The most frequent cause of death was heart disease. Keys' results showed that men with entry cholesterol levels greater than 260 were four times more likely to suffer a heart attack compared to men with cholesterol levels below 200.[8]

In 1951 Keys took his family to Oxford for a 1-year sabbatical. While there, an Italian colleague bragged that heart disease was almost nonexistent in Italy. Keys was skeptical. He took his wife, Margaret, a biochemist who often worked at his side, and set up a portable laboratory in Naples. He soon verified the low incidence of heart disease, and also found that Neapolitans had very low serum cholesterol levels. Keys and his wife then visited several European and African countries to measure cholesterol levels and conduct diet surveys. Gradually a pattern emerged, suggesting that diets rich in saturated fats, by raising serum cholesterol, were a principle cause of coronary heart disease.

In the 1950s, the notion of diet causing heart disease was controversial. Keys presented his ideas for the first time in an international setting at the World Health Organization in 1955. His ideas were met with skepticism. Sir George Pickering, the Oxford physician who was one of the world's experts on hypertension, challenged him: "Yes, and Professor Keys would you be kind enough to cite for us the principle piece of evidence that you think supports this diet-heart theory of yours?"[3] He was unable to defend his position against Pickering's skepticism. He came away from the meeting humiliated, but all the more motivated to prove his theory. He would spend the next 15 years designing, implementing, and analyzing the Seven Countries Study.

Between 1955 and 1958 Keys began to organize teams of clinicians and scientists in several countries. The study would require fieldwork that took researchers deep into the lifestyles of predominantly rural populations. It required the transportation of bulky medical equipment, such as electrocardiograph machines that were much larger and more primitive than those in use today. For each area chosen, the entire male population between the ages of 40 and 59 had to be convinced to participate. Once the data was collected, it was sent to back to "Gate 27," the nickname for Keys laboratory under the bleachers at the University of Minnesota stadium. The techniques that were developed eventually formed the basis for a manual published by the World Health Organization on cardiovascular disease survey methods. From the thousands of electrocardiograms that were collected and sent to Gate 27, the team developed a precise system for coding electrocardiographic abnormalities. It came to be known as the Minnesota Code, and is still one of the most widely used coding systems for population studies and clinical trials.

Alessandro Menotti gave one example of the challenges the field workers faced with their primitive electrocardiograms when he reminisced at the 35th Anniversary Conference of the Seven Countries Study in Fukuoka, Japan, in 1993: "In the mornings between 9:30 and 10:30 the electrocardiograms were terrible because of AC interference. After three days of this, we discovered that in the basement of our building was a kitchen. At that moment each day, the cook started an enormous potato-peeling machine, and the electrical fields created were disturbing the ECG recording. We had to call back the men who had been seen during those hours, because their records weren't readable at all by the Minnesota Code!"[9]

The countries included in the study were Yugoslavia, Italy, Greece, Finland, the Netherlands, the United States, and Japan. Why were these particular countries chosen? Yugoslavia offered coastal and inland populations with vegetable fat versus animal fat diets. Italy represented a prototypical Mediterranean lifestyle, with a diet full of grains, pasta, legumes, fruits and vegetables, olive oil, bread, and wine. Greece provided a setting with very high dietary fat intake, principally in the form of olive oil, but very little saturated fat. Finland had an exceptionally fit population, but high rates of heart disease, and a diet extremely high in saturated fat. The Netherlands represented a European population with an intermediate dietary pattern, with meat, butter, and tuberous vegetables. The United States component consisted of railroad workers, originally chosen to study the effects of different activity levels on heart disease, but then incorporated into the Seven Countries Study because the participants tended to remain in one place over time, making follow-up relatively simple. Finally, Japan was chosen as representing a lifestyle with minimal dietary fat intake.

The chief operations officer for the study was a young doctor named Henry Blackburn. He had joined Keys' laboratory in 1956, just after completing his medical fellowship. During the many months of field work, he noted his impressions in a personal journal.[10] These writings provide an invaluable picture of the trials and tribulations encountered by the teams of clinicians and technicians, as they worked in primitive conditions with limited resources.

The Seven Countries Study formally began September 28, 1958 at the Hotel Jadran in Makarska, on the Adriatic coast. Two regions had been chosen in Croatia: coastal Dalmatia, and Slovania, further inland. Keys was interested in seeing how disease rates would be affected by the primarily vegetable (low saturated) fat diet on the coast compared to the inland animal (high saturated) fat diet.

For 3 weeks the little band of scientists moved down the Adriatic coast, setting up their station in each village between Makarska and Dubrovnik. They encountered the wind known as the Bura, which would sweep down from the mountains to the sea, taking anything in its path that was not firmly anchored. When they hung cholesterol specimens on filter paper to dry, they found that the microscopic smudges left by flies contained enough cholesterol to throw off their results.

Today an electrocardiogram (ECG) can be done in 2 or 3 minutes. But in 1958, the ECG had to be done using brine-soaked bits of cotton, while the technicians awaited the arrival of electrode paste from America. Each of the 12 leads that make up a standard electrocardiogram was traced onto separate strips, which were then cut and stapled onto cardboard. Because of problems with local electricity, a U.S. Army surplus gasoline generator was frequently used to run the electrocardiographs and centrifuge machines.

Once they had finished with all males between the ages of 40 and 59 in one village, the team would break camp, hop a ferry, and head for the next location. Gradually they made their way from Tucepi down to Gradac. When the last of the coastal villages was finished in mid-October, the team moved inland.

Slovania was described by Blackburn as a grim land, with poor villages surrounded by fertile plains and abundant livestock. Wealthy farmers were distrustful of government and men of science. They feared having their taxes increased if word got out of their rich diet. Peasants were suspicious and resentful. A constant rain fell. Blackburn had to take the electrocardiograph to Paris for repairs. The testing center was damp from incessant fog and was surrounded by geese and pigs. But by November 3, the work was done and all eligible men had been enrolled except for one, who was away at sea.

The experience in Croatia provided a solid foundation for the rest of the Seven Countries Study. Challenging conditions required ingenious solutions, and the manual of procedures evolved into a roadmap that would become a template for similar studies. The teams returned to Croatia again in 1963 and in 1968, for the 5- and 10-year follow-ups.

From 1958 to the early 1970s, the Seven Countries team built their database, translating cultural differences into a set of equations that could predict heart disease.[11] Five years and 10 years after the initial visits the teams returned for follow-up visits with the participants, identifying those who had experienced a heart attack. The lowest rates were found in Crete, the highest in East Finland. The second highest rates were in the American cohort, the railroad workers. After Crete, the lowest rates were in Japan, followed by Corfu. Comparing East Finland to Crete, there was an almost 100-fold increase in the incidence of heart attacks. On average, 3.2% of the participants experienced heart attacks over the 10-year study period. In Crete, the rate was 0.1%, whereas in East Finland it was 9.5%. The U.S. railroad workers had a rate of 5.7%, whereas Japanese fishermen had a rate slightly under 1%.

The variables that were measured were smoking, overweight status, physical activity, resting pulse rate, lung capacity, blood cholesterol level, blood pressure, and diet. Keys and his team used multivariate logistic analyses to build mathematical models that combined all the measured variables and then determined which ones were related to heart attack rates.

Seven Countries was the first study ever done providing prevalence rates of heart attack and stroke in contrasting cultures. Even at the beginning, during enrollment, striking differences were found in rates of disease. In Japan, only 0.3% had evidence of heart disease at entry, whereas in the United States, 4.6% did. The study also was the first to describe population differences in risk factors. For example, the bell-shaped curves describing serum cholesterol levels in Eastern Finland and in Japan were so far apart there was almost no overlap. In Finland, 77% of the population had cholesterol levels over 200, whereas in Japan only 3% were in this range. Diets between countries varied between 3% and 22% of calories from saturated fat, and between 9% and 40% for total fat calories.

Saturated fat as a percentage of calories was the most powerful lifestyle predictor of heart disease. Blood cholesterol was the most important physiologic variable, explaining 40% of the variation in heart attack rates. Keys' equation had shown that cholesterol level could be predicted by saturated fat intake. The second most significant risk factor for heart attacks was high blood pressure. Blood cholesterol and high blood pressure together accounted for 60% of heart disease risk.

Keys was the first medical scientist to understand the importance of the Mediterranean diet. Together with his wife he wrote "Eat Well and Stay Well,"[12] and "How to Eat Well and Stay Well the Mediterranean Way." He lived for many years in Italy, following his own advice. He died at the age of 100. His obituary appeared in the New York Times on November 23, 2004,[13] and was written by Jane Brody, the well-known medical journalist.

Henry Blackburn, in a tribute to Keys, wrote: "He has had a major influence on the public, its food choices and eating patterns. We physicians and fellow scientists learned from him that if common diseases are the result of mass behaviors there is a social responsibility for us to address these larger issues in practice and in our communities…. He showed us that there is a personal responsibility to model behavior so as to provide an example of healthful living to our families and our patients. This is the large legacy of Minnesota's senior scientist, Ancel Keys."[14]

Salim Yusuf

Dr. Salim Yusuf is a soft-spoken yet intense cardiologist based at McMasters University in Hamilton, Ontario.* In 2004 he published the results of the INTERHEART Study, which concluded that 90% of heart attacks were due to nine modifiable risk factors. Dr. Yusuf grew up in India, and in 1976 received a Rhodes Scholarship to Oxford University. His joy at receiving this honor was cut short by the premature death of his father at age 56 from coronary heart disease. He acknowledges that on an unconscious level this loss played a role in the evolution of the INTERHEART Study. In 1984 he moved from Oxford to the National Institutes of Health, where he worked in the clinical trials branch of the National Heart Lung and Blood Institute. In 1992 he came to McMasters to set up the new Division of Cardiology. He served as its Chief of Cardiology for over a decade, and currently occupies the Heart and Stroke Foundation Chair in Cardiology and is Director of the Population Health Research Institute.

Around the time that he moved to Canada, Dr. Yusuf began to collaborate with his former colleague Dr. Prem Pais, now the Dean of St John's Medical School in Bangalore. Although he did not realize it at the time, the relatively small study they conducted together would become a pilot for the INTERHEART Study. Dr. Yusuf wanted to explore the causes of premature heart disease in India. With little money available, he could not conduct a trial like Seven Countries, known as a prospective cohort study. Large prospective cohort studies became the dominant model for studying the epidemiology of heart disease as a result of the Framingham Heart Study.

* Dr. Wright interviewed Dr. Yusuf, who kindly provided many personal biographical insights as well as updated information on the INTERHEART study.

Dr. Yusuf, however, did not have the funds for this kind of study. He needed a method that would provide meaningful results with several hundred participants, not several thousand, enrolled over 2 to 3 years, and not followed for 2 to 3 decades. He decided to use a method called a case-control study. The concept is simple: subjects are enrolled when they present to the hospital with a first heart attack. Then someone of the same age and gender is identified who is free of heart disease. The former is the "case" and the later is the "control." Baseline data is collected on the cases and controls. Unlike a cohort study, where only a small percentage of the total participants have a cardiac event, half the participants in a case-control study by definition have the disease, making it easy to see significant differences between the cases and the controls. In Seven Countries, by contrast, the rate of heart attacks over 10 years was 3.2%, meaning only 408 of 12,763 subjects had a definite coronary event, whereas 96.8% had no event. The small number of events can make it difficult to identify weaker risk factors.

A major challenge for a case-control study, according to Dr. Yusuf, is the selection of the control. Extreme care must be taken to assure that the controls have no heart disease. Often the controls were chosen from patients hospitalized at the same time as the case. Controls could not have emphysema, for example, because emphysema is usually caused by cigarette smoking, which increases the likelihood of heart disease. Even someone admitted for a hernia repair would be disqualified, because hernias are more common in smokers, who cough more. An acceptable control would be someone admitted for acute trauma, or for an elective procedure such as ear surgery. Another challenge for Dr. Yusuf was a psychological one, known as recall bias. People who have just had a heart attack tend to distort their memories about diet and exercise, and their perceptions of stress levels before the event. Field workers have developed techniques for minimizing recall bias.

The small Indian case-control study was a success. It was finished in 3 years. The results were published in the British medical journal the *Lancet* on August 10, 1996.[15] With only 400 subjects, the study clearly demonstrated that the strongest predictor of a first heart attack in Bangalore was cigarette smoking. High blood pressure, blood sugar level, and abdominal obesity were also associated with higher risk. Cholesterol levels were not a risk factor. Vegetarianism and higher socioeconomic status were protective.

During the 1990s, cardiovascular disease was becoming a global epidemic. Dr. Yusuf believed that the case-control model he used in Bangalore might well be standardized for use across many countries. A global prospective cohort study, like Seven Countries or Framingham, would be impossible to do, as it would require hundreds of thousands of subjects followed for 5–10 years. Therefore, the case-control method seemed to be a reasonable alternative. He believed the study would identify different risk factors at work in different countries. He also believed, along with many experts, that risk factors would only be able to explain about half the risk, with unknown genetic factors accounting for the rest.

INTERHEART began with a $25,000 grant from Merck Pharmaceuticals. With this seed money, Dr. Yusuf convened a meeting of former collaborators from around the world, and described the INTERHEART concept: the largest study ever done to map out the global causes of cardiovascular disease. From this humble beginning, the concept slowly built momentum. Little by little he added countries and medical centers. Recruitment remained low until he gave an impassioned plea at a large international conference nearly a year after the Merck-funded meeting. Dr. Yusuf used his considerable persuasive skills and international reputation to galvanize the crowd of medical scientists representing dozens of countries. From then on, INTERHEART became a movement of committed researchers, willing to work almost for free. Final funding permitted payment of around $50 per subject enrolled, but many researchers participated for only $15 per patient. People signed on because they believed in Dr. Yusuf's vision. Was there a chance to really understand the causes of heart disease at work in different parts of the world? Could the global burden of heart disease be reduced by finding these causes? In the end, 252 centers in 52 countries participated. Funding ultimately came from 41 separate sources, and totaled $2.5 million, a paltry sum for such a large and demographically complex study. But the true cost of the study will never be known, because all the participants donated so much of their time for free. Dr. Yusuf estimates that he visited about half of the 52 countries, but only went to a participating center if it was for another study, and then stayed an extra day or two to work on INTERHEART. Through years of conducting international clinical trials, Yusuf had built up a network of clinical researchers who were friends and collaborators, and who now supported and promoted his cause. In some cases, they would only ask for a few dollars to rent freezer space for blood samples, and do all the rest for free, or seek a local funding source. Yusuf described the funding process as "quilt work built up from the trenches."

Dr. Yusuf's grant proposal for the study was based on the hypothesis that different risk factors would be important in different parts of the world. He believed that there would be differences between developing and developed countries, or between Eastern and Western or Northern and Southern countries. His second hypothesis was that only about 50% of the risk would come from known and modifiable risk factors. He hoped to discover a number of novel risk factors, especially in non-Europeans/non-Americans. The final results, quoting Yusuf directly, "blew our minds." He never expected that the risk factors would be virtually the same everywhere, nor that over 90% of the risk would be modifiable, meaning preventable.

INTERHEART involved the collection of data from 52 countries, including people from China, South and Southeast Asia, Africa, Europe, North and South America, the Mideast, and Australia. To keep costs down, data collection was limited to a simple, eight-page questionnaire, blood samples, and anthropomorphic measurements. The amount of data collected was so great that papers will continue to be published for at least another decade.

To examine the population effect of a risk factor, the study, in addition to calculating odds ratios, also looked at "population attributable risk" or PAR. PAR represents the impact of a risk factor on the entire population's risk. If the risk factor were not present at all in the population, by how much would one lower the total population's risk for a first heart attack?

Overall, the average age for presentation with a first heart attack was only 58 for men, and 65 for women. North Americans were close to this average, with men presenting at age 59 and women at 64. The youngest victims were in the Middle East, with men presenting at 51 and women at 57. The oldest were in China and Western Europe, where men were 63 and women were 67 and 68, respectively. Why these age differences? Are there genetic reasons, or can all the variability be explained by known risk factors? INTERHEART demonstrates that these age differences are entirely due to the prevalence of the nine modifiable risk factors.

An individual with all nine risk factors has 129 times the risk for a first heart attack compared to someone with none of the risk factors. If all nine risk factors were removed from a population, there would be a 90% reduction in the number of first heart attacks (based on the PAR calculations).

INTERHEART showed that the most important risk factor is the ApoB/ApoA1 ratio. ApoB is the structural protein in the spherical particles circulating in our blood that can carry cholesterol into the wall of an artery. Measuring the quantity of ApoB protein in the blood is more predictive of risk than measuring LDL cholesterol.[16] Conversely, ApoA1 is the structural protein in HDL (high density lipoprotein). ApoA1 is a better measure of protection than HDL cholesterol. The ratio of ApoB/ApoA1 is about twice as accurate in risk prediction as the ratio of LDL cholesterol to HDL cholesterol. In INTERHEART, those with the worst ApoB/ApoA1 ratio had 3.87 times the risk of those with the best ratio. If everyone in a given population had the best ratio, population risk would be reduced by 54%.

The second strongest risk factor identified was diabetes. Those with diabetes had three times the risk of those without diabetes. Because the number of people with diabetes is much less than the number of people with abnormal ApoB/ApoA1 ratios, eliminating diabetes would only lower population risk by 12.3%.

Cigarette smoking was the next strongest risk factor. A current smoker had 2.95 times the risk of someone who never smoked, whereas a former smoker had 2.27 times the risk. If no one smoked in the entire studied population, heart attack rates would have been reduced by 36.4%. Yusuf was able to calculate risk based on the number of cigarettes smoked a day. The relationship between number of cigarettes and risk is linear. Each cigarette confers a little more risk. Someone who smoked seven to eight cigarettes a day doubled his risk, whereas someone who smoked 21 or more cigarettes a day experienced a six-fold increase in risk.

The next risk factor surprised many experts. Stress as a cardiac risk factor is difficult to measure and therefore to prove. Based on a large literature suggesting its importance, Yusuf decided to include a psychosocial stress assessment tool in the questionnaire. He graded responses to questions about stress in the home or workplace, general stress, financial stress, stressful life events, feelings of depression, and the degree to which one felt in control of one's life. Those with the most stress had 2.5 times the risk of those with the least, and if stress were not present in a population (certainly an unrealistic assumption!), the incidence of heart attacks would drop by 28.8%.[17]

Hypertension increased risk by 2.48%, and its removal lowered heart attack incidence in a population by 23.4%. The final risk factor was abdominal obesity. Yusuf determined that the ratio of waist circumference to hip circumference was a much better predictor of risk than the traditionally used body mass index (BMI). BMI is used to classify people as normal weight, overweight or obese, but does not distinguish between muscle and fat, or between different frame sizes. BMI category was a very poor predictor of risk. Waist/hip ratio was a very good predictor. Those with the highest ratio had 2.24 times the risk of those with the lowest ratio, and removing this risk factor reduced heart attack rates by 33.7%. Not only were smaller waists protective, but bigger hips also conferred protection. Dr. Yusuf was unable to provide a scientific explanation for the so-called "hip factor."

Besides the above-described six modifiable risk factors, there were three protective factors: eating vegetables and fruits daily, exercising, and having alcohol in moderation. Each reduced risk by 20% to 30%, and in combination reduced heart attack rates by a bit over 50%.

The conclusion of the study, as published in the *Lancet*, on September 3, 2004, states: "Our study has shown that nine easily modifiable risk factors are associated with more than 90% of the risk of an acute myocardial infarction in this large global case-control study. These results are consistent across all geographical regions and ethnic groups of the world, men and women, and young and old. Although priorities can differ between geographical regions because of variations in prevalence of risk factors and disease and economic circumstances, our results suggest that approaches to prevention of coronary artery disease can be based on similar principles throughout the world. Therefore modification of currently known risk factors has the potential to prevent most premature cases of myocardial infarction worldwide."[2]

The results of INTERHEART confirm Paul Dudley White's earlier quoted words describing a heart attack before age 80 as a medical failure. According to Dr. Yusuf, a close look at all the known genetic factors for heart disease shows their influence on total risk to be modest. The well-known difference in risk levels for men and women can also be explained based on the prevalence of the nine modifiable risk factors. The risks between different ethnic groups are entirely related to these same risk factors. Further analyses of the data have improved the population attributable risk to the 95% range, by refining the diabetes score, the diet risk score, and the quantification of sedentary versus active lifestyles. This means that all but 5% of heart attacks are potentially preventable.

Dr. Yusuf continues to work passionately on the goal of preventing cardiovascular disease. His team published in the *Lancet* on July 10, 2010 another global study called INTERSTROKE, a case-control study in 22 countries with 6000 subjects, half presenting with a first stroke and half serving as the controls.[18] This time, 10 modifiable risk factors were found to account for 90% of the risk for stroke. He is also working on ways to translate his findings into public policy initiatives around the world that would reduce the prevalence of these modifiable risk factors. He has drilled down into his substantial database to look at how owning a car and a television affect risk (each confers about a 47% increase in risk). He has analyzed leisure time physical activity and found that those in the highest category have 45% lower risk. His dietary risk score has been further refined to identify three dietary patterns around the world: *Oriental*, which is high in tofu, soy, and other sauces, *Prudent*, with higher intake of fruits and vegetables, and *Western*, with higher intakes of fried foods, salty snacks, eggs, and meat. The prudent diet is associated with a 30% lower population risk, whereas the Western diet raises population risk by 35%. The Oriental pattern is neutral, probably because the higher intake of fruits and vegetables is offset by other factors, such as high salt intake.

Conclusion

Ancel Keys' and Salim Yusuf's landmark studies across many cultures and ethnic groups confirmed the universality of the major cardiovascular risk factors. Both scientists overcame significant obstacles to accomplish objectives they believed in passionately. Their results advanced our understanding of the complex interactions between lifestyle and heart disease. Keys carried out the first international study of cardiac risk factors. He extended basic research in lipid nutrition to large scale field studies that corroborated the relationships between lipid intake, cholesterol levels and heart disease. Yusuf used the case-control field study method on a global scale and demonstrated the same risk factors at work around the world in many different ethnic groups. His use of population attributable risk showed that interventions to lower risk could prevent 90% or more of heart attacks. As we try to intervene to reduce the worldwide epidemic of cardiovascular disease, the work of these two scientific pioneers gives hope that prevention is a realistic and achievable goal.

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