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Newspapers and magazines frequently contain items or articles on health, recent studies and advice related to health issues. When the results of an important new study are about to be released, the online before-print publication will frequently be available to the media and discussed in a news release picked up by newspapers, Google and even the TV media if deemed sufficiently sensational. The release many originate from an academic institution where the principal investigators work, or may come from an industry source. Can the audience for these releases properly interpret the content and the “take-home-message?” I suggest the answer is a definite no and in fact these articles deserve little attention. The principal reason is that they frequently represent spin at its highest level of perfection, especially if the news is about a new drug or a new combination of already approved drugs. The same problem exists when one downloads a study the full text of which is free and found on Google.

Results are generally presented in relative terms. The new drug with an unpronounceable name will be touted as reducing the risk of some disorder by 20% or maybe even 40% or 50%. The reader is lead to believe that if a room full of individuals, say 100, all take this drug, it will prevent as high as half from developing the disorder over, for example 5 years. This is a big deal. The spin has accomplished its goal. The fundamental problem is the reader has been deceived and the truth either buried in the research publication or not even available or understandable by the lay person. A 50% relative risk reduction can in fact be equivalent to needing to treat 200 or 500 or more to prevent one event. Without such numbers, the report cannot be interpreted and can be ignored. However, it is rare indeed that such numbers are in news releases or presented so that lay persons can understand the implications. In fact, it is common to read or hear on TV commentary or advertising that some drug “significantly” reduces some risk or some symptom or some problem, but this is statistical jargon and without the numbers needed to treat, is quite uninformative. Thus the lay audience is in a hopeless position of rarely being able to make an informed decision about interventions and therapies being promoted in the media, even if they manage to get a few full text reports.

Unfortunately the same situation may well exist in the doctor’s office when the patient is given a prescription. In preventive medicine for chronic diseases,

most interventions leave the majority without benefit and the majority can be as high as 99.9% of those treated, a number needed to treat of 1000 to achieve one benefit. A source of many examples is the web site theNNT.com which represents the efforts of a group of physicians to add some clarity to a seriously deceptive practice. They also add additional clarity by providing numbers needed to harm based on adverse side effects although these may be based on serious underestimation of actual side effects if from industry sponsored studies. The name of the game here is that the absolute benefits should exceed the absolute harm. This website lists a large number of common disorders and the accepted or mainstream therapy and presents a view not available anywhere else.

Wishing you and your family continuing good health,

William R. Ware, PhD, Editor

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TAKING STATINS TO PREVENT PROGRESSION OF ATHEROSCLEROSIS IS NOT EVIDENCE-BASED

There appears to be a well-established belief among some in the medical community that one of the important reasons for taking statins is that this drug halts or reverses the progression and even the development of coronary atherosclerosis. This has been used as an argument for treating individuals with low risk of acute cardiovascular events. The evidence given below suggests that this is incorrect and in fact the opposite appears true. Furthermore, the case for statin therapy has been seriously weakened by discovery that guidelines are now using a risk calculator that overestimates by a staggering factor of approximately 5 for non-diabetics.

Individuals at low risk of hard cardiovascular events are not immune from recommendations of statin therapy. The new American College of Cardiology/American Heart Association suggests considering this therapy for those who according to their new calculator have a 10-year risk between 5% and 7.4%. Since this calculator overestimates risk by a factor of about 5, the targeted group in fact has a very low risk. Others who recommend treatment of low risk individuals are referring to those with

somewhat higher risk, but generally below guideline thresholds such as 10% by the ACC/AHA calculator now even promoted by the U.S. Preventive Task Force. If adjusted for overestimation this is a 10-year risk of fatal and non-fatal heart attack and strokes, i.e. cardiovascular (CVD) “hard” events of 2%.¹ One of the justifications in the context of primary prevention is that statins arrest or reverse coronary atherosclerotic deposits, but the measurements cited are made by invasive ultrasonic measurements and the changes are over short periods and small.² In a short report just published, Dykun *et al* have examined this question by measuring the plaque burden by electron beam computerized tomography (EBCT) and acquired baseline coronary artery calcium scores (CACS) as well as after > 5 years.³ This non-invasive imaging approach has been used for several decades to quantify coronary plaque burden and the positive relationship between the CACS and CVD events is well established. There is even an online calculator which allows the input of the CACS based on the large Multi Ethnic Atherosclerosis Study (MESA) which created a database which has been used in about 100 studies thus far.

Dykun *et al* found that statin medication *enhances* the progression of coronary artery calcification. Compared to baseline mean values of 5.9 and 58.8 for CACS for non-statin vs. statin users, at the end of follow-up the non-statin users had a mean score 21.2 vs 141 for statin users. At follow-up statin use was associated with 39% higher absolute progression of CACS compared to non-users. When the study group was divided into those with LDL cholesterol above or below 115 mg/dL at the start of the study, those with higher LDL had lower rates of progression. They also examined the absolute risk reduction for coronary events over 5 years and found the resultant 1.9% consistent with other studies concerning primary prevention. In this study the comparison was with matched non-users. The paradoxical increase in atherosclerosis and the decrease in risk of events were explained by a stabilizing effect of plaque calcification and the low CACS range in this cohort. The authors fail to mention two earlier randomized controlled trials that found the same enhanced CACS progression on comparison between statin and placebo. One found 26% vs. 18% per year,⁴ the other 9% vs. 5% per year.⁵ In addition another randomized controlled trial found no effect⁶ and a recent meta-analysis also found no effect on progression.⁷

These results are consistent with the position taken in a review that the mainstream hypothesis that LDL cholesterol drives atherosclerosis has been falsified by non-invasive (EBCT) imaging of coronary plaque progression.⁸ Furthermore, extensive studies cited failed to find a positive correlation between either total cholesterol or LDL cholesterol and plaque burden.^{8,9} A recent review described “inexorable CAC progression despite the implementation of intensive contemporaneous medical therapy.”¹⁰ This is also consistent with an earlier randomized controlled trial showing progression despite intensive lipid-lowering.⁴

Major overestimation is also an issue with the recent 2016 recommendations of the US Preventive Services Task Force mentioned above concerning the use of statins in primary prevention of CVD events.¹ They recommend that individuals 40-75 with no history of CVD use a low to moderate dose of statin for prevention of CVD events and

mortality when both of the following criteria are met: (1) one or more CVD risk factors (dyslipidemia, diabetes, hypertension or smoking), and (2) a 10-year risk \geq 10% according to the ACC/AHA calculator. The authors mention the risk of overestimation and all the important papers are cited, but do not suggest an alternative tool, and in fact claim that the ACC/AHA calculator is “the only US-based CVD risk prediction tool that has published external validation studies in other US-based populations.” There is no mention of the large and disturbing overestimation in an external validation using a contemporary US cohort even though the report by Rana *et al*¹¹ was cited. Using 10% as a threshold rather than 7.5% would seem to be a completely inadequate adjustment for a factor of five overestimation. However, the Task Force report did briefly remark on overestimation creating a problem for clinicians and this should enter into their discussions with patients. Finally, the ACC/AHA and Task Force guidelines differ significantly in that for the latter, treating diabetics requires a 10-year risk \geq 10% whereas in the former, statin treatment is automatic. In addition, the Task Force recommendation introduces the gender factor for diabetics which, while large, is routinely ignored in guidelines.

In a commentary¹² in the same JAMA issue containing the Task Force paper, R.F. Redberg and M.H. Katz (editor in chief and deputy editor of *JAMA-Internal Medicine*) discuss the weakness of the evidence, pointing out that statin therapy in the Task Force’s meta-analyses found 5-year **absolute** risk reductions vs. a placebo for all-cause mortality and CDV mortality of only 0.40% and 0.43% respectively. One can also calculate from the Task Force meta-analyses absolute risk reductions from statin treatment of 0.44%, for fatal and non-fatal stroke and 0.81% for fatal and nonfatal MI.¹³ Redberg and Katz point out that an absolute risk reduction of 0.40% requires treating approximately 250 individuals for 5 years to prevent one event (1/0.004). They discuss the importance of shared decision-making and point out that it is important to recognize that 5% to 20% of those taking statins will experience muscle aches, fatigue, cognitive dysfunction, and increased risk of diabetes, i.e. risks exceeding absolute benefits by a wide margin. The Task Force meta-analysis for diabetes as a side effect gave a null result, but recent non-industry supported studies that found highly significant increased diabetes risk with statin treatment were ignored.^{14,15}

When a patient is told that they have high enough cardiovascular risk to justify drug intervention, perhaps for life, one consequence is the associated burden of psychological stress and for some, an almost pathological concern for their cholesterol levels and fear of an MI. It is well known that psychological or psychosocial stress is a major risk factor for cardiovascular disease, and depending on age and gender, can exceed the risk of elevated lipids by a wide margin and be comparable to current smoking.^{16,17} Refusing lipid lowering therapy or failure to tolerate it can also add to the stress. This underscores the serious nature of major overestimation which can produce highly alarming 10-year absolute risks.

The calcium score mentioned above is greatly underappreciated in the context of screening for CVD risk. In one recent large study the, Multi Ethnic Study of Atherosclerosis (MESA) which included a wide range of age and gender, 50% of the

participants had a CACS of zero which translates to essentially very low risk of adverse CVD events. That is, no coronary plaque to rupture, no heart attacks. Note however, that the coronary CT scan misses uncalcified lesions which can rupture, so the zero score is not an absolute guarantee.

MORE EVIDENCE CONCERNING DANGERS OF FRUCTOSE CONSUMPTION

Over the past decade, there has been growing concern about increasing fructose consumption that has gone hand in-hand with table sugar consumption, the latter reaching mind-boggling amounts in recent years. In fact, average per capita sugar consumption in the US is about 100 pounds per year (45 kg). Sucrose is made up of glucose and fructose and a recent study reinforces the dangers of too much dietary fructose.

Sucrose, aka table sugar, is a molecule made up of one molecule of glucose and one molecule of fructose. High fructose corn syrup on the other hand is merely a blend of fructose and glucose in nearly the same proportions, eliminating the sucrose break-up step in its metabolism. High fructose corn syrup is a very common sweetener used in many prepared foods and beverages. Concern regarding fructose stems from its unique metabolic and neuroendocrine properties. It is metabolized mostly in the liver, serves as the basis for fat synthesis, increases liver triglyceride levels, generates reactive oxygen species and chemically reacts with molecules by adding a molecule of fructose. It does not suppress the hunger hormone ghrelin and thus rewards continued ingestion.

Consumption of 100 pounds of sugar per year, although estimates vary concerning this, is roughly equivalent to 500 calories a day or 20% of the caloric intake for a typical 2500 calorie per day diet. This large intake is partly made possible because some of the sugar intake is hidden as added sugar. In addition, these numbers are averages meaning that many consume higher amounts.

A recent study using prepared meals investigated the impact of replacing fructose in the diet with the same number of calories of starchy food including what is considered junk food to examine the effect on markers of the metabolic syndrome in children.¹⁸ The study was led by Dr. Robert Lustig who is in the department of pediatrics, University of California--San Francisco medical school. Calories as a percentage of total calories were reduced from 28% to 10% from sugar and from 12% to 4% from fructose. Calorie intake was adjusted to maintain weight and the controlled diet study ran over 9 days. At the end of the study researchers found improvements in diastolic blood pressure, LDL cholesterol, triglycerides, fasting blood glucose and insulin and liver function. What was remarkable was that these significant changes occurred over only 9 days and in fact represented a reversal of the metabolic syndrome, even though the replacement calories came from less than ideal food. Thus the notion that "a calorie is a calorie" is an oversimplification since how the food representing the calories is metabolized is critical.

These studies involved eliminating excessive sugar consumption at constant calorie intake. The results make it clear that the detrimental health effects of sugar are independent of its caloric value or effects on weight. Additional studies will be needed to clarify the observed effects in adults and as well, their durability.

This study also adds strength to the new American dietary guidelines which set a limit on calories from sugar to 10% of total calories. A gram of sugar is equivalent to about 4 calories and a teaspoon 16 calories.

It has been estimated that sugary soft drink consumption alone kills about 200,000 individuals per year,¹⁹ and it is well known that that a countries' sugar consumption is closely related to the incidence of type 2 diabetes.

Two books are recommended for more insight. The first is just published entitled *The Case Against Sugar* by the famous medical journalist Gary Taubes. Then there is Dr. Lustig's *Fat Chance. Beating the odds against sugar, processed food, obesity and disease*.

PREGNANCY AND RISKS TO MOTHER AND CHILD OF HAVING DIABETES

With the dramatic increase in the prevalence of type 2 diabetes, it has become urgent that all women of childbearing age become aware of the associated risks to the mother and the baby of a number of serious developmental and gestational problems. Guidelines are pushing for diabetic women having preconception counselling and take very seriously the need for near ideal glucose management prior to becoming pregnant. If the pregnancy was not planned, the need is still there for aggressive management of the disease, but only with metformin or insulin. The simplest solution for the diabetic woman contemplating pregnancy is to use the Newcastle diet to return glucose metabolism to normal but if the diabetes is of long duration (>8 years) this will probably not work.

Diabetes during pregnancy is a serious problem which has been getting more and much deserved attention recently. Many countries are facing a dramatic increase in obesity and type 2 diabetes, and the latter is frequently undiagnosed. Diabetes is now increasingly prevalent in younger individuals including children. Thus the number of individuals reaching childbearing age with preexisting diabetes will continue to increase as will the prevalence of diabetes in general in all pregnancies. This phenomenon raises a number of issues which will be briefly discussed.

Pregnancy presents a special problem to women with type 2 diabetes, as does the normally transitory gestational diabetes which as the terminology indicates, develops during pregnancy and is an abnormal type of diabetes.²⁰ We will be concerned only with

type 1 and type 2 diabetes. Maternal diabetes is related to fetal development problems, i.e. morbidity, including limb defects, kidney defects, transposition of the great blood vessels, heart defects, and abnormalities in the gastrointestinal system, and this is an incomplete list. Babies from diabetic mothers tend to be abnormally large and have a lower gestation age. Maternal diabetes increases the risk of miscarriage and fetal mortality. The somewhat low prevalence of these and other related problems does not decrease their significance.

Special guidelines appear regularly for diabetic pregnant women and as well, guidelines for screening for diabetes before the decision is made to initiate a pregnancy.^{21,22} These guidelines now include the recommendation that diabetic women undergo preconception counseling which has been demonstrated to reduce maternal and fetal problems and bad outcomes if the advice provided is followed.²³ In addition, these acknowledge the fact that a significant number of pregnancies are unplanned or come as a surprise, and it is not uncommon for the initial diagnosis of diabetes or prediabetes to occur at the first doctor visit motivated by suspected pregnancy. In the ideal world this does not happen and instead diabetes screening would be a prerequisite for making the decision to become pregnant. Diabetic women are strongly advised to try not to allow unplanned pregnancy to happen. Guidelines also strongly recommend that this whole situation be made clear to diabetic girls before they reach childbearing age and that parents should demand diabetes screening starting at an early age.

Clinical trials related to the association between hyperglycemia (abnormally elevated blood sugar) and bad maternal and fetal outcomes including postnatal and the recommended interventions are rare, and those that have been reported suffer from a very small number of subjects and even smaller number of events. Editorialists have commented on the detail in some guidelines when the evidence is almost nonexistent, a view that corresponds to the expected conclusion of anyone who has searched the literature for relevant clinical trials or examined the citations in recent reviews and guidelines. Nevertheless, the bulk of the evidence points to the validity of the concern, and studies of risk with null results are rare. There are no industry based driving forces for studies and it is probably very difficult to recruit subjects. The major issues appear to be as follows:

- What is the evidence that hyperglycemia is a risk to mother or child and is there a threshold?
- What are the goals and targets associated with preconception counseling and are they evidence based?
- How significant is prediabetes during pregnancy?
- If blood sugar must be managed and controlled during pregnancy, are the medications safe for the fetus.
- Other than diabetes medications, what medications should be avoided in the context of adverse outcomes?
- What are the guideline targets for measures of glycemic control in this context?

First, is hyperglycemia really related to adverse pregnancy outcomes? A study published in 2008 looked at the effect of elevated blood sugar up to the threshold for diabetes in a large number of completed pregnancies.²⁴ The primary endpoints were elevated birth weight, primary cesarean delivery, neonatal hypoglycemia, and fetal hyperinsulinemia. Secondary endpoints were premature delivery, birth injury, need for neonatal ICU care, hyperbilirubinemia, and maternal strongly elevated blood pressure (preeclampsia). The primary endpoints all strongly correlated with maternal glycaemia except for neonatal hypoglycemia where the association was weaker. Elevated blood glucose, especially the 2-hour post meal level, also correlated with all the secondary endpoints. Three other studies looked at HbA1c levels or glycemic control in diabetic type 1 pregnancies where the endpoints included congenital malformation and fetal mortality, spontaneous and therapeutic abortion, still-birth, and major congenital abnormalities.²⁵⁻²⁷ The results in general supported the hypothesis that hyperglycemia even below the threshold for diabetes diagnosis increased the risk of adverse pregnancy outcomes. A major weakness of these three studies was the small number of subjects and events.

That preconception care (counselling) positively and significantly reduced congenital malformations was confirmed in two reviews published in 2011 and 2010 with very little overlap in studies cited.^{23,28} Comparison was with no preconception care. Benefits correlated with the lower HbA1c levels achieved in the counseled groups, one of the main objectives. Preconception care normally would include not only encouraging achievement of glycemic control targets, but advice to not smoke, start folic acid, lose weight and adjust the diet to a healthy standard.

The significance of prediabetes is illustrated by one study that examined the first issue since the subjects were prediabetic and the study made clear that this level of hyperglycemia was sufficient to increase the risk of adverse maternal and fetal outcomes. Reversal of prediabetes by diet and exercise has been accomplished. The issue of medication safety has not received the attention it deserves, but the guidelines backed by some evidence recommend only metformin or insulin for blood glucose control achieving and maintaining a target HbA1c.

There are other medications that guidelines suggest avoiding. Two classes of antihypertensive drugs are contraindicated, ACE inhibitors and angiotensin receptor blockers. In addition, chronic diuretic use is discouraged and statins should also be avoided.²¹

If a woman is diabetic and perhaps obese, she would be advised according to guidelines to manage the diabetes to where the ideal HbA1c is < 6% and the satisfactory target range is 6% to 6.5%, and lose some weight before attempting to become pregnant. While the evidence is not very strong the risk of not doing this is significant and should be worrisome. Weight loss is always difficult and the control of diabetes is with drugs since the vast majority of individuals are unsuccessful with diet and exercise and achieving targets.

For the diabetic woman trying to achieve satisfactory glycemic control preconception, one possibility is with low carbohydrate or ketogenic diets. The table below indicates what can be accomplished with individuals having diabetes. All the studies lasted 24 weeks.

Study	CHO (g)	HbA1c (%)	FBG (mmol/L)	Calories	ΔW (lbs)
Krebs ²⁹	20*	7.4→6.3	9.7→8.0	Ad lib	20
Westman ³⁰	20	8.8→7.3	9.8→8.8	Ad lib	23
Hussain ³¹	20*	7.8→6.3	9.3→6.3	Ad lib	26
Yamada ³²	130	7.6→7.0	7.7→6.8	1630	5.7
Tay ³³	50	N SIG	7.9→6.8	1430	26

*Initial--Atkins diet. FBG fasting blood glucose. CHO, Approximate dietary carbohydrate content.

ΔW , weight change from baseline

The Atkins diet involves an induction phase that is ketogenic with initially severe carbohydrate restriction, followed, with increasing carbohydrate intake by 5 g increments provided weight loss continues. Typical final carbohydrate consumption was 50-100 g/d. Thus these diets are only initially ketogenic. In three of the studies, diabetes regressed to prediabetes by at least one measure. Variations between studies may reflect the management of medication during the trials and the degree of adherence to the dietary protocol. If the subjects in the above trials had only been initially prediabetic, it is probable that normal glucose metabolism would have been restored, possible in fewer than 24 weeks.

Once pregnancy is present, there is the unresolved issue of the danger of such diets to the fetus and a different approach to glucose control using metformin and insulin along with diet and exercise is appropriate. The ADA guidelines are silent regarding diet in this case and the National Institute for Clinical Excellence (NICE in UK) 2015 guidelines (see internet) merely mention it but provide no specific advice concerning nutrition and exercise for pregnant diabetics. Presumably this is left up to the physician managing the pregnancy since it is of course an issue that must be addressed for all pregnant patients.

The Newcastle diet mentioned should easily accomplish prediabetes reversal in 8 weeks since it can do this for actual diabetes in the same time interval. For diabetics, this diet restores pancreatic beta cell insulin excretion to normal. The diet quickly reduces liver fat to normal and as well circulating and pancreatic triglycerol which is toxic to beta cells. However, total regression may still take up to 8 weeks even in prediabetics, although this seems unlikely. If an abnormal glucose tolerance test, but still prediabetic was present initially and returns to normal after 4 weeks, this may be an indication to stop the diet and simply maintain weight loss. Impaired glucose tolerance as revealed by the oral glucose tolerance test implies both an impaired initial insulin

response (phase 1 response) and significant beta cell dysfunction and damage. Fasting glucose will undoubtedly be normal by then.

It appears that nowhere in any recent guidelines is the Newcastle diet even mentioned as an option. A quick cure for type 2 diabetes is not on the mainstream radar. For women with type 2 diabetes of less than 8 years duration, an 8 week highly restricted calorie diet (600-800 calories/day) is almost certain to eliminate the diabetes (medication for diabetes was stopped at the beginning of the study) and dramatically lower weight, and if the end-of-diet weight is maintained, then the results appears to be durable.^{34,35} The diabetes is cured. The normal function of the pancreas is restored and the pathophysiology responsible for the disease is normalized. The diet involves no hardship since it appears that one can eat their ordinary diet, merely adjusted to the caloric limit. In spite of the fact that this diet was featured in the Banting Memorial Lecture in 2012 which was also published in a major journal³⁶ and Dr. Roy Taylor's group continues to publish papers regarding this diet and its implications regarding the pathophysiology of type 2 diabetes (IHN, Oct 14, Jul 15, Dec 15), no one appears to be paying any attention and one gets the impression that the diabetes community is happy with the status quo and their fine-tuned pharmaceutical approach even though the progression of the disease is still relentless. The notion that a simple 8-week diet can cure the disease thousands of medical and drug development scientists have devoted their careers bringing it to its present therapeutic state is easy to reject as a pipe dream. Ignore it and it will go away. Yet there appear to be no papers attempting to discredit the research of Taylor and colleagues and critics have had 6 years to think about it. However, the evidence is in fact much stronger than what backs up the current guidelines in area we have been discussing. Nevertheless, this diet is just what is needed to solve the two problems that are standing in the way of a pregnancy, type 2 diabetes and obesity, although the success of the diet does not depend on weight dropping to normal. Of course, type 1 diabetes is currently incurable and a woman presenting at a counselling clinic with this type will need to follow the conventional advice, aim for optimum blood glucose control and hope for the best.

The targets recommended by the American Diabetes Association (ADA) for preconception and during pregnancy are:

- Fasting blood (plasma) glucose \leq 95 mg/dL (5.3 mmol/L) **and either**
- One-hour postmeal glucose of \leq 140 mg/dL (7.8 mmol/L) **or**
- Two-hour postmeal glucose \leq 120 mg/dL (6.7 mmol/L).
- HbA1c $<$ 6-6.5 % early in gestation (A1c drops naturally during gestation).

These targets would be easily met with the Newcastle diet but there are safety concerns if the individual is already pregnant which rule it out until the question is studied, which is unlikely. For preconception dietary-induced regression to the targets, the 8 weeks needed is highly significant and should be very appealing, especially as it is accompanied by significant weight loss.

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MINI RESEARCH REVIEW

THE FRENCH PARADOX BECOMES THE FRENCH MYSTERY

The French Paradox based on phenomenally low rates of heart disease coupled with what was traditionally considered an unhealthy diet has died with the elevation of the harmful French dietary components to the status of healthy. Included are saturated fats and dietary cholesterol. Nevertheless, why the French, along with the Portuguese and Italians, have remarkably low rates remains unclear, as does the unique place France occupies when the prevalence of some other health issues is compared to comparable countries in the European Union.

The French Paradox reviewed in IHN in 2007 is based on the notion that the French eat a diet rich in butter, fatty sauces, foie gras from artificially fattened geese, fatty cheeses, foods high in cholesterol, and have traditionally shunned low-fat products, i.e. theirs is a diet conventional wisdom held and to some extent still holds as not heart-healthy and yet the incidence of heart disease is very low in France compared to most other countries in the EU and the world. Another way of describing the paradox is that it describes a lower than expected coronary heart disease (CHD) mortality in a country where the classic CHD risks are no less prevalent than in other industrialized countries and in addition where the diet has been historically high in saturated fat.¹ A related issue is illustrated by the title of Mireille Guiliano's entertaining book, *French Women Don't Get Fat*.² The phrase French Paradox started appearing in the medical literature a long time ago with what some might consider the landmark paper published in 1992.³

Very recently a serious problem arose for the French Paradox. Fat including saturated fat and cholesterol were removed from the list of demons and awarded the status of healthy. One is reminded of the article in the *New York Times Magazine*, July 7, 2002 by Gary Taube's "What If It Has All Been A Big Fat Lie?" which was already casting doubt among the general public on the fat-heart disease hypothesis which had been surviving contrary studies and meta-analyses for decades.^{4,5} ***If one does not consider the heavy fat intake in many French diets a risk factor for heart disease, then there is no paradox.*** Nevertheless, the fact remains that France has one of the lowest rates of cardiovascular mortality of any country in the world, largely unexplained in a definitive manner. Recent World Health Organization data available on the internet has France the second lowest with a rate per 100,000 of about 30 deaths. South Korea is lowest, and Japan next above France, but many unique aspects of the Asian culture confound any comparison. Other European countries with very low CVD mortality rates are Portugal, Switzerland and Italy (range 30-48 including France). Out of 172 countries with data, these four countries rank second, sixth, fifteenth and seventeenth. The developed country highest in the list is Russia at 320 so the developed country range is about a factor of 10. The US comes in at 78 and Canada at 56, both more than twice that of France.

Thus there is no paradox but rather an unexplained very low prevalence of CVD mortality in a small number of countries. However, paradox theories continue to abound and papers continue to appear as the reductionist approach to this health problem is flourishing, judging by that is indexed on PubMed, the US National Library of Medicine's amazing search engine. The explanations which can be considered in addressing the question of the low CVD rates in France are:

- The alcohol consumption.
- The red wine consumption.
- The lifestyle issue. More walking and exercise, longer, regular and more relaxed and social meals, and the wine culture, a strong aspect of the mealtime lifestyle.
- The greater emphasis on food taste rather than quantity, i.e. typically smaller portions, less over-eating and food from local markets.
- The resveratrol and other compounds in red wine including other polyphenols.
- The Mediterranean diet with its higher proportion of fruits and vegetables and fish.
- The low dietary prevalence of commercial and prepared foods, junk food, and fake food and more home cooking. Home cooked meals are much closer to what one might term gourmet than will be found in the US or Canada.
- Most or all of the above.

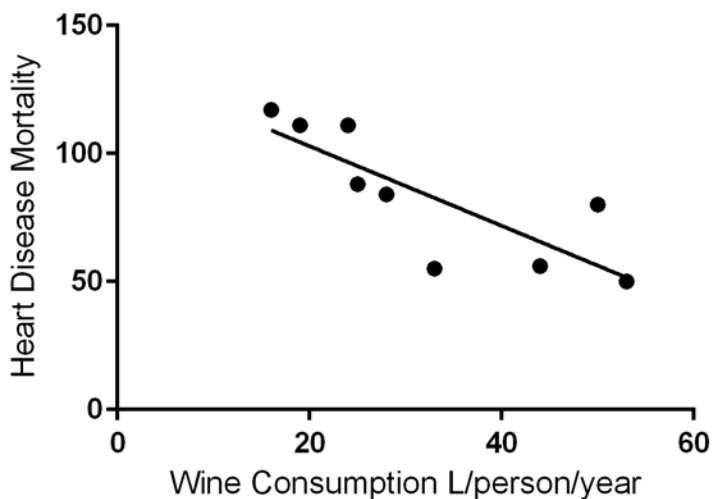
France, Portugal and Italy do indeed have high wine and alcohol consumption and have diets that approximate the Mediterranean style for an unknown but probably significant fraction of the population. However, using the online statistics of the European Society of Cardiology, there is no such tight grouping of countries when the health issues examined are the prevalence of smoking, daily vegetable consumption, moderate weekly physical activity, prevalence of obesity or overweight. The four countries are scattered among thirty countries for each risk factor.

The recent French Paradox literature has looked at single factors focused on heart disease and has used biomarkers, not long-term follow-up with event endpoints. For example, while a very good case can be made for resveratrol found in red wine as a heart friendly polyphenol, this does little to strengthen the importance of red wine as a major contributor to the low rate of disease because, there is considerable variation in levels which are low and red wine contains numerous micro nutrients. Furthermore, correlations using data stratified by country cannot take into account the ratio of red to white wine consumption since data are incomplete.

As with most dietary and lifestyle-proposed solutions to a puzzle, "most of the above" can also be closer to the truth and even "none of the above." should be considered. Thus the major question, given that there is clearly no paradox, what is going on that produces the very low rate in France of heart disease? A major difficulty is that cardiovascular mortality requires either atherosclerosis or an electrical problem where

control is lost on the heart beat rhythm. Atherosclerosis is of course a major factor and it takes years to develop. If either alcohol or wine slow or inhibit this process and if components in red wine such as resveratrol are important, then one must consider the variation in both the changes in wine consumption over the past 20 years or more and the slow switch in favor of red wine. Even the micro components of wine have change over this period as tastes and the influence of the influential wine critics have had their impact on wine making which has produced more full bodied and flavorful wines. Thus meaningful studies are difficult if not impossible.

The following case can be made that wine consumption is important. If one examines the data for wine consumption in liters per capita per year and heart disease mortality expressed as per 100,000 individuals, then if 2008 data for consumption and 2010 data for mortality rate are used, the results presented graphically is shown below for France, Italy, Portugal, Spain, Denmark, Belgium, Germany, the UK and Sweden, the largest and most advanced EU countries. The heart disease numbers are per 100,000 population, age standardized, from the OECD for 2010. The EU as a whole had on average 158 deaths per 100,000 that year.



France is the point at the right hand end of the plot whereas Sweden is at the other end. Note that France has 1/2 the HD mortality of Sweden and 1/5 that of the EU taken together. Among countries that are in the EU, Slovakia had the highest rate at 433 events per 100,000. The correlation coefficient for the above plot is quite good at 0.63. The same plot using alcohol consumption shows no correlation. The Netherlands was omitted since it is an outlier among major European countries in having for unknown reasons a very low HD rate and a very low wine consumption. Sources of data were the Wine Institute and OECD (per capita HD mortality) online databases.

It is likely that lifestyle and diet differences in different countries between wine drinkers, beer and spirit drinkers, and non-drinkers could confound the above correlation. The following suggests that the confounding might be uniform across the EU countries used in the above correlation.

- Denmark: consumers of wine were better educated and wealthier compared to beer and spirits drinkers.⁶
- Across Europe: Persons with wine preference tended to have a higher quality diet and healthy food intake in some countries.⁷
- In Spain wine drinkers had higher intake of fiber, olive oil, and lower consumption of sugared soda drinks and fast foods.⁸

In addition, a recent study looked at wine purchases at a large French national supermarket chain and found that those who bought a lot of wine also filled their carts with more “heart healthy” food.⁹ Ignoring the belief that saturated fat was considered bad in their definition of healthy food does not have much impact on this apparent confounding. Furthermore, beer purchasers had worse dietary choices in their carts than did wine purchasers, and those who fancied Bordeaux wines appeared to make the best choices in food. A weakness of this study was of course that it was based only on those who patronized supermarkets, but in 2015 it appears that about 80% of wine is purchased there. In fact, there are many differences between wine drinkers, beer and non-wine drinkers that can confound any study trying to tease out the most important factors. However, the potential confounders appear to be present in both the Northern and Southern EU countries being considered in the above correlation.

Correlation does not prove causality. Furthermore, the countries being considered above are slowly but constantly changing as a new generation moves up through adulthood. Nevertheless, among EU countries France has maintained one of the lowest heart disease rates for a long time. Recall that the first scientific presentation of the French Paradox was in 1992 but the paradox had been recognized much earlier. There have been many changes in wine making over the last two decades with concomitant changes in micronutrient content. Wine consumption in many of the EU countries has declined in the past decade but there are large differences between countries with France being among the steadiest. The point is, to establish the cause of the puzzle is not a simple task and some of the likely causes are hard to quantify, especially those that involve lifestyle, income, employment conditions, education etc. which in turn impact everything from psychological stress to metabolism.

A recent international study of pooled studies concerning the reduction of the risk of fatal and non-fatal vascular events according to alcohol consumption showed wine to have a dramatic effect.¹⁰ This study confirmed a broad range of wine consumption that reduced the risk of vascular events but that the relationship was J-shaped showing a drop to an optimum range followed by a slow approach to no risk reduction. The maximum protective effect occurred at between 2 and 3 glasses per day. With regard to the question of the relative importance of wine vs. alcohol alone, so far studies appear to have failed to resolve this issue.

With the paradox gone, France still has a number of unique and unexplained health-related statistics besides heart disease. In comparison with the countries of the EU, France has the lowest death rate for people less than 65, and the longest life

expectancy measured in years. It also has the lowest rate of hypertension. In general, the range of fatal heart disease rates is large, frequently a factor of 10, between France and comparison countries. Thus it is highly unlikely that there is a single factor responsible for this unique position of France in the EU.

In the 2007 IHN review, considerable emphasis was placed on lifestyle issues, and this still seems appropriate. The Mediterranean diet is well known for being very heart healthy although not all French eat in that style, and it of course includes a fair amount of wine, mostly red, but the culture of slow social dining and small portions confounds attempts to sort out what is really going on. Nevertheless, at this point in time, it appears that accounting for this variation in prevalence in a variety of health issues in for example the European Union and why the French appear to have unusual health is an undertaking still in its infancy. For example, it appears that there has never been a study like the Multi Ethnic Study of Atherosclerosis done in Europe and there is no information of the prevalence of coronary calcium among the assorted populations that make up the EU. Scientific studies comparing many lifestyle factors are absent and quantifying them difficult, and they tend to continuously change. Thus the paradox is gone, but a puzzle remains and will no doubt challenge researchers for some time to come.

Meanwhile, the take-home message appears to be, imitate the traditional French diet and lifestyle. However, it may be hard to imitate 2-hour lunches with modest wine consumption and good company and conversations, a 4-week minimum holiday, a short work week, clever manipulation to achieve 4-day long weekends (it is called making a bridge, i.e. over Friday), and the French also have available a much longer seasonal variation in fresh fruits and vegetables. Europe has a higher prevalence of organic food and virtually no GMO food as compared to for example Canada and the US. Avoiding junk and industrialized food is probably the easiest change to make, perhaps followed by more home-cooked meals in keeping with the European and Mediterranean custom.

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