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European Society
of Cardiology

The PURE study and the enigmatic aspects of the diet: is it possible that an high saturated fat consumption would not be harmful?

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KEYWORDS

Saturated fats;
Cardiovascular risk;
All-causes-mortality

According to the results of a recent observational epidemiologic study, the PURE study, an elevated consumption of saturated fats in the diet would not be detrimental for the cardiovascular risk, and would not increase all-causes-mortality. A part for the criticism the study received, for being conducted in eastern countries and mainly in rural settings, its results are substantially in agreement with the most recent epidemiological literature, which gradually redefined the pro-atherogenic role of the saturated fats. It is possible that this type of fats, in this instance, would have a limited and restricted effect, and rather represent the overall effect of the food-stuff in which they abound, in the prevalent dietetic habits of the population studied. The results of the PURE study can be integrated with little difficulties, with the recent revision of the role of the alimentary fats in determining cardiovascular risk and all-causes-mortality. The revision doesn't support (assuming adequate calories and weight control) a limitation of the total dietary fats, saturated fats in particular. An excessive reduction of saturated fats, particularly in Europe, could lead to an unnecessary and unsolicited limitation of certain foods (most commonly cheese), whose final impact on overall health is favourable.

Some recent publications, relating to the effect of fat and carbohydrates on cardiovascular risk and mortality from all causes, have given rise, both in the media and in the scientific literature, to a rather intense debate. Especially triggered by the data obtained in the PURE study (Prospective Urban Rural Epidemiology), a large observational study designed to gather information on the relationship among lifestyles, nutrition, and cardiovascular risk even in countries with a low or intermediate per capita income, enlisting subjects resident in both rural and urban areas, coordinated by the Canadian group of Salim Yusuf at McMaster University.⁴ Between January 2003 and March 2013, PURE enrolled approximately 140 000 individuals of both sexes, aged between 35 and 70, residing in over 600 communities, mostly located in the Far East and in rural areas. In fact, rural China is among the countries most

represented in the cohort, with a contribution of around 40% of the total subjects enrolled.

The result that emerged from the PURE study that attracted more attention from the media and professionals is the correlation between the intake of fat and food carbohydrates, cardiovascular risk, and mortality from all causes.¹ These results can be summarized as follows: mortality (both total and due to cardiovascular events) decreases with increasing caloric intake from total fat, and is not substantially influenced by the intake of saturated fat, even when this is very high; on the other hand, as the intake of mono- and polyunsaturated substances increases, mortality tends to fall instead. If the calories from carbohydrates exceed about 60% of the caloric intake, on the other hand, the total mortality begins to rise, moving in parallel to that for cardiovascular events.

How to interpret these data, apparently in total disagreement with the recommendations of the majority of the global guidelines on the subject? The simplest

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observation to explain is probably the increase in mortality associated with a high proportion of carbohydrates in the diet: this feature is in all probability, is simply an indicator of an incomplete and little changed alimentary habit. Those who consume 70% or more of the calories from carbohydrates, especially in the rural east where the study was largely conducted, are probably fed predominantly with boiled rice, characterized among other things by a high glycaemic index: the lack of nutrients and protective principles available in a more varied diet, and the limited nutritional value of the carbohydrates consumed (and not their excess), are the probable cause for the increase in mortality observed in this subgroup of the population.

The absence of an excess of unfavourable events among people who consume more than 30% of calories from fat (the minimum mortality rate for all causes is observed among those who consume about 45% of calories from total fat, which is the maximum value detected) is not a real novelty. Already in the WHI study, conducted with the support of the US government in the early 90s of the last century, the reduction of about a quarter of the total fat caloric share had no impact on the incidence of cardiovascular events;² data similar to those of PURE are then observed in the PREDIMED study, conducted in Spain, where the minimum mortality is observed in the quintile with the highest intake of total fat,³ and in a Japanese cohort.⁴ But if the inappropriateness of considering the effects of dietary fat as a whole (adding saturated, mono-unsaturated, and polyunsaturated) has therefore emerged for some time, the existence (or rather the absence) of damage associated with high or excessive consumption of saturated fat returns to be, after decades of shared visions, the subject of debate. In PURE, the figure is apparently very clear: with the increase in consumption of saturates fats the total mortality tends to fall, to at least around 15%, then remaining substantially unchanged for greater consumption. The major cardiovascular events are instead stable for saturated fat consumption between 10% and 18% (the maximum detected) of the total caloric intake. It could easily be argued that more or less extreme data emerged in the rural communities of the East studied in the PURE study, with an often insufficient or inadequate diet, are probably of little relevance to define the optimal food pattern in western, and specifically the Mediterranean populations, such as ours.

In reality, the theme is more complex. The two recent meta-analyses that systematically addressed the relationship between saturated fat intake and cardiovascular and total mortality did not detect any increase in the risk of events going from low-consumption groups of these fats to those with high consumption.^{5,6} In de Souza's meta-analysis, high dietary intake levels do not even correlate with cerebrovascular events (fatal and non-fatal strokes) or even with new cases of diabetes.⁶ The results of the PURE study, therefore, would be in substantial agreement with the results of the most recent epidemiological research on the subject, which does not suffer from the geographical limitations of the PURE study itself. If we then try to analyse in detail the correlation between saturated fats and cardiovascular and total mortality in the various countries of the world, we can observe some curious

differences: in many (even if not all) US studies, the contribution of saturated fats is associated with a significant increase, although relatively small (in the order of 5-10%) of cardiovascular events or total mortality,⁷ while in European studies this does not seem to be happening. In the EPIC study mentioned above, there is even an opposite pattern: subjects with the highest saturated intake experience a significantly lower total mortality (-16%), in multivariate analysis, compared to subjects with a minimum intake of these fatty acids.⁸ In the aforementioned PREDIMED study, the trend in coronary events with increasing saturated intake is not significant.³ In the Kuopio study, conducted in a cohort in secondary prevention, coronary mortality appears to decrease as the intake of saturated fat with diet increases.⁹

A possible explanation of this divergence, of interpretation not really simple, may have to do with the prevailing food source of the saturated fats: represented above all by the products of the milk supply chain in Europe, and to a greater extent by the meat and its derivatives in the States US. In Europe, the contribution of saturated fats would therefore be an indirect indicator of the contribution of milk and cheese, while in the USA, it would signal above all the contribution of meat: and the different correlations between saturated fats and health found in these two areas of the world, consequently, would simply reflect the different final effect on the health of the products of the meat chain (unfavourable) and the milk supply chain (favourable or neutral) on the cardiovascular clinical events or on mortality for all causes. In the MESA study, conducted in the USA, in fact, the saturated fats from meat are associated with an increased risk of cardiovascular events, while those from milk and derivatives to a reduction of the same.¹⁰

There are now numerous data on the neutral or favourable effects of products in the milk supply chain on cardiovascular risk: a recent meta-analysis¹¹ showed, for example, how a consumption of 40-50 g/day of cheeses was associated with a reduction of 10-15% of the incidence of coronary and cerebrovascular events; the incidence of these events was highest among those who claimed not to consume cheese at all. Even in the most recent published work based on the data from the PURE study, the consumption of about 30 g/day of cheeses (curiously especially of full-fat cheeses) is associated with a reduction in the risk of cardiovascular events and total mortality over time.¹²

On the other hand, it cannot be considered that the direct metabolic effects of saturated fatty acids, tested in cellular models or in acute human intervention studies, are largely unfavourable. The lipid profile, as we remembered, worsens after their consumption, with a significant and constant increase in both LDL cholesterol and HDL cholesterol.¹³ But the scarce importance of these direct effects of saturations on the lipid profile, at least as far as cardiovascular risk is concerned, clearly emerges from the observation that the saturates fats with greater effect on the lipid profile itself (palmitic and myristic) do not seem to have, in the aforementioned EPIC study (but not even in a study conducted in the USA), a different effect on the risk of infarction compared to stearic, a saturated fatty acid that has no discernible effects on LDL cholesterol.⁸

Even the levels of inflammation markers, however, are increased by the dietary intake of the saturated fats, while the anti-inflammatory adipokines move in the opposite direction.¹⁴ The significance of these data can however perhaps be traced back to the overall dietary context: hypothesizing that this effect becomes relevant only when these fatty acids are included in an excessively caloric (and therefore pro-inflammatory) diet like the US diet.

It should also be remembered that although many data, summarized and discussed in this article, tend to reduce the role of saturated fats in determining cardiovascular risk, the evidence that partial substitution of the saturated ones with mono- or poly unsaturated fatty acids is completely convincing, and associated with a reduction in the same risk.^{7,15} However, it is reasonable to imagine, in the light of the evidences examined, which do not attribute unfavourable direct effects to saturated fats, that the result of the substitution could instead be attributed to a direct protective action carried out by these unsaturated fats on the risk, due to their specific metabolic effects, or of components of the foods that are rich in them (such as the polyphenols contained in extra virgin olive oil, which is the main source of mono-unsaturated fats in the Mediterranean area). The substitution of saturated with refined carbohydrates, on the contrary, does not significantly change the overall risk.

In conclusion, the results of the PURE study are framed without too many difficulties in the recent review of the role of dietary fats in determining cardiovascular and mortality risk for all causes. In a nutshell, this review does not support (in the context of an adequate control of total calories and therefore of weight) the limitation of total fats, and of saturated ones in particular. An excessive restriction of the saturated fats, especially in Europe, can in fact result in a useless or inappropriate restriction of food (such as the often mentioned cheeses) whose final impact on health tends to be favourable.

Conflict of interest: none declared.

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