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VIEWPOINT

# On account of trans fatty acids and cardiovascular disease risk – There is still need to upgrade the knowledge and educate consumers

A. Niforou [a], E. Magriplis [b], E. Klinaki [a], K. Niforou [a], A. Naska [a,*]

[a] Department of Hygiene, Epidemiology and Medical Statistics, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece
[b] Department of Food Science and Human Nutrition, Agricultural University of Athens, Athens, Greece

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**Abstract** *Aims:* Trans fatty acids (TFAs) are unsaturated lipids either of industrial origin or naturally occurring in ruminant meat and milk. TFAs generated through food processing (industrial) is the main source in our diet and studies provide converging evidence on their negative effect on cardiovascular health. Since April 2021, the European Commission has put into effect a regulation for TFAs providing maximum 2% of total fat in all industrially produced foods. In light of this development, we review the evidence regarding the health attributes of different types of TFAs, their dietary sources and current intakes, and we describe the history of TFA-related legislative actions in an attempt to anticipate the efficiency of new measures.
*Data synthesis:* The PubMed database was searched including original research (observational and intervention studies), systematic reviews and meta-analyses. Scientific reports of competent authorities and organizations have also been screened.
*Conclusions:* Trans-fat elimination provides a fine example of how evidence has led to the application of horizontal regulatory measures regarding legal food ingredients in order to protect consumers' health. In EU Member States, TFAs currently provide on average less than 1% of energy (1%E) and intakes marginally exceed recommendations primarily among young adults. Large dietary surveys however provide evidence for additional, less-well known sources of TFAs in the diet. Raising public awareness of "hidden" trans-fat found naturally in foods such as cheese, as well as of the trans-fat generated through traditional cooking practices is needed, if the goal to eliminate trans-fat from the diet is to be met.


## 1. Introduction

Trans fatty acids (TFAs) are defined as "all the geometrical isomers of monounsaturated (MUFAs) and polyunsaturated fatty acids (PUFAs) having non-conjugated, interrupted by at least one methylene group, carbon–carbon double bonds in the trans configuration" [1]. The TFAs can be either of industrial origin (iTFAs) or naturally occurring known

* Corresponding author. Department of Hygiene, Epidemiology and Medical Statistics, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece, 115 27.
*E-mail address:* anaska@med.uoa.gr (A. Naska).

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as ruminant TFAs (rTFAs) [2]. Specifically, rTFAs are produced by bacterial hydrogenation of unsaturated fatty acids in the first stomach of rumen, such as cattle, sheep and goats [3]. The iTFAs are formulated during technological processes, such as partial hydrogenation of vegetable or marine oils to produce semi-liquid and solid lipids (vegetable/marine fats) or refining through the deodorization of oils high in PUFAs so that the product attains a light color and a neutral flavor and odor [4,5]. TFAs can also be produced when oils are heated at extreme temperatures, such as when frying in already used oils and deep-frying [6,7]. On average, the consumption of rTFAs is very low and reported to contribute to less than 0.5% of total energy intake [8]. Studies have additionally attributed different physiological effects to rTFAs, possibly due to structural differences compared to their industrial counterparts [9].

Industrially produced TFAs, found in vegetable fats such as margarines and other shortenings, may prolong product self-life, improve sensory/texture conditions as well as tolerance against repeated heating and oxidation. Deep-fried foods, bakery products (biscuits, pastries) and other commercial products made with industrially hydrogenated fat have been reported as major dietary sources of TFAs with a varying final content which may account for up to 60% of total fat content. The fat of animal products (meat, milk) constitutes an important source of the naturally occurring TFAs; however, the TFA content in ruminant fat is considerably lower and may not exceed 6% of total fatty acids [2,10]. The predominant TFAs in ruminant sources are vaccenic acid (trans 18:1n−7) and conjugated linoleic acid (CLA or 9-cis, 11-trans-C18:2); while the elaidic acid (trans 18:1n-9) is the primary trans-fat formed through industrial processes [11–13].

During the 1960s margarine was considered a healthy alternative to animal lipids, and has been increasingly used in the food supply. At that point in time and in the years that followed, margarines and vegetable cooking fat were constituting the major source of TFAs, whose intake increased substantially providing approximately 2%–3% of the overall daily energy intake [14]. The landmark work of Mensink and Katan (1990) [15] together with important research that followed have shaped our current understanding on how TFA intake may enhance disease risk [16].

## 2. Trans fatty acid intake and health outcomes

Observational and experimental epidemiological studies have provided robust evidence on the effect of TFAs on human health in general and the cardiovascular system in particular [15,17–22]. The adverse effects of TFAs on blood cholesterol levels and cardiovascular disease (CVD) risk were first brought to the spotlight in the early 1990s through the publication of an intervention study [15] on the effects of differing types of fat intake; saturated fatty acids (SFAs), oleic acid (cis-9 monounsaturated fatty acid), and its trans isomer. In this trial 34 healthy women (mean age 26 years) and 25 men (mean age 25 years) were randomized to three dietary regimes of similar caloric and nutrient content, differing only in 10% of total energy content. In particular, 10% of total energy was provided by saturated fat, cis-oleic acid and trans-oleic acid respectively, in the three diets under investigation [15]. This well-conducted controlled trial provided evidence on the unfavorable effects of TFA intake on serum lipoprotein profile, not only through raising low density (LDL) cholesterol but also through decreasing high density (HDL) cholesterol levels. A few years later, Willett and colleagues (1993) [17] assessed how the TFA intake of 85.095 females enrolled in a large prospective cohort study, the Nurses' Health Study, was associated with the risk of coronary heart disease (CHD). Based on cases reported during a mean follow-up of 8 years, a higher intake of trans isomers was associated with increased CHD risk (RR for highest vs lowest quintile: 1.47, 95% CI: 0.98–2.20), after adjusting for several well-established CHD risk factors [17]. Since then, numerous observational and intervention studies have provided additional evidence on the direct association between TFA intake and CVD risk [23–30]. In 2006 Mozaffarian and colleagues published a meta-analysis of four large US prospective cohort studies including 139,836 participants and estimated that an isocaloric substitution of 2% of the carbohydrate-derived energy intake with TFAs was associated with a 23% increase in CHD incidence (multivariable adjusted RR = 1.23; 95%CI: 1.11 to 1.37) [31]. More recently, in a meta-analysis of 24 prospective cohort studies published up to July 2018, Zhu et al. [32] confirmed previous findings on the positive association between TFA intake and CVD risk and further estimated that the risk increased by 16% (95% CI: 7%–25%) for every 2% increase in daily energy intake from TFAs [32].

Reliable assessment of TFA intake can be performed through various methods. Most commonly, TFA intake rely on self-reported dietary questionnaires (24 h recalls, food records, or food frequency questionnaires) whose accuracy is additionally dependent on the availability and quality of the underlying food composition data. Biological samples have also been used to assess TFA intake reliably through their levels in biological samples (biomarkers of intake). Specifically, TFA levels in adipose tissue is considered to reflect long-term intake; erythrocytes can be used to assess intake over the previous months; and plasma/serum levels are best used to assess intake over the previous week [33,34]. Based on either dietary questionnaires or biomarkers, studies on TFA intake collectively point to an association between higher TFA intake and an unfavorable lipid profile, as reflected in increased blood total and LDL-cholesterol levels, decreased HDL and the subsequent increased total to HDL-cholesterol ratio. It is worth noting that this relationship has been found to be more consistent than the respective one between SFA intake and blood lipid levels [20]. An increase in plasma activity of the cholesteryl ester transfer protein, responsible for the transfer of cholesteryl esters from HDL to LDL and very low density particles, together with TFA implication in inflammation have been proposed as possible mechanisms of TFA action [35–37].

In the vast majority of studies, TFA intake primarily refers to the intake of iTFAs, since rTFAs are only present in small amounts in the diet. Thus, the question remains on whether TFAs obtained from ruminant sources are equally harmful. The evidence from observational studies and controlled intervention trials on the association between rTFAs with CVD risk is generally less clear [17,18,27,38–40]. In a meta-regression of thirteen randomized clinical trials on rTFAs intake and markers of CVD risk, Gayet-Boyer et al. [41] found no effect on the lipid ratios (total to HDL-cholesterol and LDL to HDL-cholesterol) for a rTFAs intake up to 4.2% of daily energy intake. In addition to this finding, in a meta-analysis of 33 prospective cohort and 17 case–control studies (including 6 studies nested in prospective designs) in which TFA intake was assessed either through dietary questionnaires or levels of biomarkers, de Souza et al. [42] found no significant association between rTFAs and coronary events. The RRs (95%CI) for CHD mortality and total CHD (as defined by the authors) were 1.01 (0.71–1.43) and 0.93 (0.73–1.18), respectively. In contrast, iTFAs were found to increase CHD mortality (RR: 1.18, 95% CI: 1.04–1.33) and total CHD risk (RR: 1.42, 95%CI: 1.05–1.92). Authors however commented that the wider range and the higher mean intake of iTFAs reported in the studies (mean intakes of about 1.8% of energy and range between 0.3 and 3.7% of daily energy intake) as compared to those of rTFAs (mean intakes of about 0.7% of daily energy and range from 0.6 to 0.8%) may provide stronger statistical power to evaluate associations [42]. Overall, considering that rTFAs are generally consumed at small amounts, their intake does not appear to be of major public health concern [43].

In a recent analysis of data collected between 2013–15 through the country representative Hellenic National Nutrition & Health Survey (HNNHS) including 3537 adults residing in Greece, participants diagnosed with dyslipidemia were more likely (40% higher odds) to report a combination of higher TFA and SFA intakes than those who were not diagnosed with the condition [44]. Authors commented that in light of this finding, TFA intakes should probably be viewed in combination with other nutrients. At present, most EU countries report intakes below target levels; however, the effect of moderately higher TFA intakes combined with imprudent consumption of other nutrients, such as SFA, has not yet been studied.

Next to increased CHD risk, TFA intake has also been associated with other chronic conditions. It has been associated with impaired insulin resistance, especially among individuals with underlying predisposition such as adiposity and low physical activity [45,46]. Nonetheless, studies on the effect of TFA on the incidence of type 2 diabetes generally provide inconsistent results [42,47]. Emerging evidence also describes associations between TFA intake, assessed through biomarkers, with the risk of breast [48–50], prostate [51] and colorectal cancer [52].

## 3. Secular trends in trans fatty acid intakes and related recommendations

Partially hydrogenated oils entered the US food supply around 1920. Since then and particularly due to the increasing demand for solid lipids to face the economic consequences of World War II, industrial hydrogenation of edible oils quickly developed. In 1960s, margarines and vegetable shortenings used in cooking, rapidly gained ground as healthier to butter and other animal fat alternatives, which were then reported to increase blood cholesterol levels and CVD risk. During that period, the production of margarines and vegetable cooking fat steadily increased constituting the major source of iTFA [14]. In the early 1990s and in the light of evidence on the unfavorable effects of TFAs on CVD risk, large multinational food companies decided upon the elimination of iTFAs from their food supply and removed them from all margarines in retail [53].

A US citizen petition submitted in 1993 sparked the fight against iTFAs which lead WHO/FAO in 2003 to state that at population level TFA intake should be as low as possible and not exceeding 1% of total energy intake (1%E) [54]. Global regulatory measures in the EU and abroad have also been put into place to reduce TFAs intake through: (i) mandatory food labelling; (ii) concentration limits in the final product; and (iii) a ban on technologies that generate TFAs [55]. In response, population intakes started to decrease and downward trends were more pronounced in the US than Europe [34].

In 2003, Denmark was the first country in the world and the first EU Member State to introduce a TFA elimination policy through setting a limit of TFA levels up to 2% of total fat [56]. This initiative encouraged several EU Member States (Austria, Hungary, Latvia, Slovenia, Romania and Lithuania) to apply similar legislative actions. Also in 2003, US set mandatory trans-fat labelling, according to which the amount of TFAs has to be displayed in all products containing more than 0.5g of TFAs per serving [57]. This legislation led to changes in the use of industrially produced fats and oils, as well as the reformulation of many food stuffs. Following the introduction of mandatory labelling in 2005, Canada put into effect the Healthy Food for Healthy Schools Act and Trans Fat Regulation calling schools to avoid selling foods containing TFA, such as baked goods and deep fried food. In 2015, the US Food and Drug Administration banned partially hydrogenated oils in all food products as they were no longer "generally recognized as safe" and further acknowledged that the intake of iTFAs should be as low as possible to minimize health risks [58]. By 2018, the food companies were forced to reduce or eliminate the use of partially hydrogenated oils, changing thus the production process by which TFAs are formed. The examples of 'New York City Ban' which included restriction of iTFAs to less than 0.5 g per serving in all New York City restaurants and the project of BanTransFats.com in California encouraging restaurants to use trans-fat free oils, are indicative of the prominent role of local authorities in health promoting actions [55].

In 2018, WHO officially called for the elimination of TFAs from the global food supply chain, and set a maximum of 2% TFA in the total fat content by 2023 [59,60]. In April 2019, the EU adopted the Regulation 649/2019 [61] which set a maximum limit of 2% of total fat consisting of TFAs (other than those naturally occurring) in all industrially produced foods intended either for the consumer or for retail trade. The regulation entered into force on April 1st 2021. In light of the EU Regulation, some measures were adopted by European countries (e.g., the Netherlands, Belgium, Germany, Greece, Poland and the UK), whereas others (Finland, UK, Bulgaria, Malta and Slovakia) fostered dietary recommendations [55]. Regarding food labeling in Europe, TFAs are not included in the mandatory food information in the ingredient lists and can be included on a voluntary basis in the nutrition declaration. Instead of TFAs, 'fully' or 'partially' hydrogenated oils, together with an indication of the oil type, are required to be listed in the ingredient list. However, since the amount of TFAs present in these oils varies, consumers cannot easily interpret the information they receive [55]. Before implementing regulatory measures, the EC assessed the effectiveness of setting mandatory TFA labelling and concluded that the measure has significant limitations and therefore questionable efficiency [62]. Firstly, low consumer awareness on the effects of TFA intakes narrows the impact of labelling and consumers' limited understanding of information provided through labelling could increase the complexity of decision making and ultimately the selection of a healthier food choice. Secondly, mandatory labelling may promote inequalities among consumers as well as food producers. Small-scale enterprises, which are the majority of food business operators in the EU, are expected to encounter challenges and higher costs as compared to large food companies when implementing the measure. It is worth noting, however, that the 2015 EC report has laid the first stone for undertaking impact assessments of the implementation of new public health measures.

The data on global trans-fat intake and its dietary sources have been reviewed by Wanders and colleagues [2]. According to national dietary surveys and studies of smaller scale in 29 countries published up to May 2017, the average TFA intake ranged from 0.3% to 4.2% of total energy intake and in five countries in North and South America, Lebanon and Iran average intakes were higher than the recommended maximum of 1%E [2]. In the context of the Global Burden of Diseases study, national intakes of different types of fatty acids estimated through a Bayesian hierarchical model were pooled to estimate absolute and proportional attributable CHD mortality rates [63]. From 1990 to 2010, mean TFA intakes increased globally by 0.1%E leading to an estimated proportional CHD mortality increase by 4%. This was primarily driven by increased intakes of TFA in low- and middle-income countries, where increased exposure derived from industrially produced foods and the use of partially hydrogenated oils in products provided by restaurants and street vendors [63]. In contrast, the TFA attributable CHD mortality decreased in high-income countries, reflecting the application of trans-fat elimination strategies [34,38,63]. In line with earlier studies [34,64], this review also described a decrease in total TFA intake over the past 20 years, mainly due to the elimination of iTFAs. Authors additionally distinguished among the TFA dietary sources with intakes of trans-fat of animal origin being higher than those from industrial sources in 16 out of 21 countries [2].

Recently, Li et al. [65] examined the association between the consumption of foods and beverages and plasma TFA concentrations among 2.595 adults in the US who participated in the NHANES 2009–2010 study. Dietary data were collected using two 24-h dietary recalls per participant and blood samples were provided after a minimum 8-h fasting. Palmitelaidic, elaidic, vaccenic and linolelaidic acids were the four TFAs primarily present in the reported food consumption. After adjustment for potential confounders, consumption of cream substitutes; cakes, cookies, pastries and pies; milk and milk desserts; beef/veal, lamb/goat, and venison/deer; and, butter were found to be significantly associated with increased plasma TFA levels.

According to data collected in several EU Member States, the TFAs intake ranges between 1 and 2% of total energy intake [16], with Mediterranean countries reporting lower values possibly due to the more preferable consumption of olive oil as added lipid [34]. According to a 2014 report of the Joint Research Centre of the European Commission (EC), mean intakes of TFAs were at 1% of energy intake or below in all countries and most population sub-groups. This was based on data from 13 studies published between 2006 and 2013. TFA intakes slightly above 1% of total daily energy intake were observed in 25% of the surveyed individuals between the age of 20 and 30 years, consisting the age group with the highest intake (maximum observed intakes at 1.2%E) [66].

In their recent analysis of data collected through the HNNHS, Magriplis and colleagues (2022) reported that the median TFA intake in the Greek population was 0.53%E (Tertile 1, T1 = 0.27% and T3 = 0.95%, P for trend $<0.001$) and that the intake of approximately 16% of study participants (54% females) exceeded the recommendation of 1% E. They were primarily younger individuals (44% were up to 40 years of age) and of high education (45%). Furthermore, six out of ten males reporting high TFA intake were ex- or current smokers. The major foods contributing to trans-fat intake included both natural and industrially produced TFAs, with cheese being the main contributor, followed by the group of "processed/refined grains", in which puffed pastry and fried batter are included, fried fish, sweets and baked goods. Interestingly, fried fish was found to be an important source of TFAs in all age groups and a primary TFA contributor among individuals older than 50 years of age [44]. In an earlier study in Greece, Marakis and colleagues chemically determined the fatty acid profile of foods known to be sources of TFA. Pies and pastries made with puff and shortcrust pastry had the highest content and about 16% of all samples analysed had an iTFA content that exceeded 2% of total fat. The more recent evidence from the HNNHS survey point out the additional importance of food preparation methods, another aspect that calls for our attention in the process of eliminating TFA from the diet [67].

## 4. Consumer awareness on TFA intake

Trans-fat elimination has gathered momentum as a global health priority. According to WHO, "*among various measures to tackle dietary risks, elimination of industrially produced TFAs is a relatively straightforward, low-cost, one-time policy measure that is within reach and has significant long-term health benefits*." Next to the call for global removal of iTFAs by 2023, the WHO has also launched the REPLACE action framework which provides a guide for governments to implement an efficient and sustained strategy to restrict TFA in their national food supply [68].

The TFA story provides a fine example of how evidence-based risk assessment has led to the application of horizontal regulatory measures regarding legal but harmful food ingredients (as is the case of iTFAs) and has been widely acknowledged as a paradigm for future similar fights to protect consumers' health. Still, the question remains relevant. Has the target fully been reached?

The urgent need to implement trans-fat reducing measures to protect public health should rely on changes in the food supply chain as these are addressed by the 2019 EU Regulation, but should also foster consumers' education. Are consumers aware of TFA sources in their diet? And even when they are, do they have the knowledge to modify their food choices and dietary behaviors, accordingly? There are several factors that may shape consumers' understanding of nutrition-related issues, including their socio-demographic characteristics, as well as their familiarity with and education about nutrition information and scientific terminology [69]. Although current legislation is designed to protect consumers, there is much debate about the concept of the "average consumer" whom the regulatory measures aim to address. An "average consumer" has been defined as a reasonably informed and circumspect individual who takes into consideration health, social and cultural norms when deciding on his dietary preferences. It is however not clear to what extent messages conveyed through nutrition claims can be understood and satisfy the needs of the "average consumer". In light of the overwhelming mass of information through the web, press and the social media to which the general public now has constant access, the idea of addressing the "average consumer" probably needs to be re-evaluated or even replaced by addressing the "intended consumers", or "information-sensitive consumers" who may additionally motivate the non-informed individuals to make long-term healthy dietary choices [69,70]. Niederdeppe and Frosch [71], showed that although news coverage about TFAs combined with information from labels, appeared to affect consumers' behavior in the short term, they had not been sufficient to encourage sustainable changes in TFA purchases (measured as trans-fat products obtained from grocery store chains).

Consumers' knowledge on TFA intake and the associated health risks is also limited [72]. A study conducted in a representative sample of the general population in Greece revealed major knowledge gaps regarding TFA intake and disease risk. Although the majority of participants acknowledged different types of fatty acids (76% recognized MUFAs and 80% SFAs), only 29% acknowledged TFAs. Furthermore, about four out of ten respondents (43.8%) ignored the differential contribution of types of fatty acids to health or disease risk. Overall, "trans-fat" was a less known term, and consumers were not familiar with either their dietary sources or their health consequences. The study also reported the insufficient perception that industrially processed foods are the only source of trans-fat in the diet, possibly ignoring those naturally occurring or, even more importantly, those that are formed during common cooking methods, such as frying or deep-frying [73].

In a comprehensive health promoting program, nutrition education implemented in multiple settings holds a central role. In schools, knowledge and skills empowering children to make healthy choices should be combined with school meals/canteens that put into practice the principles discussed in class. In clinical settings, dietary counselling can support individuals to establish healthy dietary practices and be informed about diet-related chronic conditions. Nutrition education should also be promoted through the influential role of mass and social media. Traditional approaches through TV and radio programs can be supplemented with nutrition information disseminated though websites, blogs and mobile applications (e.g. behavioral challenges) [74]. An efficient nutrition intervention should have sufficient duration, well-determined objectives and sustained support from policy makers [75]. In parallel, the application of new technologies to reduce TFA formation (e.g., inter-esterification and oleogelation techniques) which would ensure health promoting TFA replacers is imperative [76]. Additionally, food-based recommendations considering the differential impact of fatty acids on health is strongly recommended to assist consumers implementing theory into practice [77]. Finally, the study of associations between TFA intake and the gut microbiota may enhance our understanding on possible mechanisms [78].

In conclusion, recent large-scale dietary surveys in Europe report that TFA intake is generally within the recommended levels and is expected to be further reduced since the 2019 Regulation has been put into force. But how complete and accurate is the picture that these studies provide? Do they take into account cooking practices that are common around Europe and during which TFAs are generated? How aware is the general public of these additional sources? Raising public awareness of "hidden" trans-fat found naturally in foods such as cheese, as well as of the trans-fats generated through food preparation processes is urgently needed if the goal to reduce significantly trans-fat intake is to be met.

Current TFA elimination policies focus on iTFA, but an additional monitoring of the TFA content in processed but non-prepackaged foods such as bakery products and fried fish, and of TFA replacers in processed products is also necessary. Although public awareness on TFA intake has advanced since the 1960s, there is still room to upgrade consumers' knowledge so as to apprehend the rationale behind legislative measures and health recommendations, leaving thus the room for making sustainable, health-promoting dietary choices.

## Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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