Trends in Cardiovascular Medicine 29 (2019) 306–310

Contents lists available at ScienceDirect

Trends in Cardiovascular Medicine

journal homepage: www.elsevier.com/locate/tcm

Trans fatty acids linked to myocardial infarction and stroke: What is the evidence?☆

Bhavi Shah, DNP[a], Udho Thadani, MD[a,b,*]

[a] Division of Cardiovascular Section, College of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA
[b] Veterans Administration Medical Center, Oklahoma City, OK, USA

ARTICLE INFO

Keywords:
Trans fatty acids
Myocardial infarction
Stroke
Cardiovascular mortality

ABSTRACT

Consumption of industrially produced trans fatty acids (IP-TFAs) increases LDL cholesterol, either decreases or has no effect on HDL cholesterol, and increases markers of inflammation. Observational studies have shown that consumption of TFA produced by partial hydrogenation of vegetable oils (PHOs) is associated with increased mortality and incidence of MI and stroke rates. Regulatory initiatives to restrict PHOs to less than 2 g per day from food sources, along with concurrent initiatives to reduce tobacco exposure, have been associated with reduction in cardiovascular mortality and MI rates. What remains unknown is whether the consumption of amounts <2 g per day of PHOs is also harmful and whether TFAs present in milk and the meats of ruminant animals is beneficial or harmful.

Introduction

Fats are an important source of dietary calories and, according to currently recommended dietary guidelines, in an average American adult diet providing 2000 to 2500 calories daily, 20% and 35% of calories (approximately 60–70 g) should come from fat, respectively, of which, saturated fats should be no greater than 10% (20 g per day) [1]. The remaining fat calories are from mono and poly unsaturated fatty acids [1]. Since the consumption of saturated fats is associated with an increase in total and low density lipoprotein (LDL) cholesterol [2], mono and polyunsaturated fatty acids intake has been exponentially increasing, especially in the western world [3].

Industrially produced trans fatty acids (IP-TFAs) account for approximately 1–2% of the North American diet [2]. IP-TFAs were invented in Europe during the 20th century and were produced in bulk, mainly to decrease cost, increase shelf life, and allow production of solidified forms of vegetable oils [4]. This led to a rapid increase in their use in cooking worldwide. Increased intake of margarine, soya butter, and Vanaspati ghee (in India, Pakistan, and Iran) [5], essentially replaced or, at least, markedly decreased the consumption of butter and lard during the latter part of the last century. However, in humans, these user friendly IP-TFAs not only increased LDL cholesterol (like saturated fats), but also, either decreased or had no effect on high density lipoprotein (HDL) cholesterol and also exerted other detrimental physiological effects. Observational and case control studies showed that consumption of IP-TFAs was associated with an increase in cardiovascular morbidity and mortality [6,7]. For example, Mozaffarian et al., summarized the results of prospective cohort and case-control studies suggesting that a 2% increase in energy intake from partially hydrogenated oils (PHOs) or IP-TFAs was associated with a 23% increase in the incidence of cardiovascular heart disease [6,7]. This has led to increasing efforts to reduce IP-TFA intake. This brief review focuses on the effects of TFAs on cardiovascular health and whether their reduced consumption has had an influence on cardiovascular mortality, myocardial infarction, and stroke.

What are trans fatty acids

Unsaturated fatty acids consist of cis and trans isomers [8]. Cis-fatty acid isomers contain hydrogen atoms on the same side of the carbon double bond [8]. They have a tortuous formation making it relatively less rigidly packed and hence, difficult to adhere [8]. On the other hand, trans-fatty acids contain hydrogen atoms on the opposite side of the carbon double bond making the fat more linear and rigidly packed allowing better adherence and cell penetration (Fig. 1) [8].

TFAs are a type of mono and polyunsaturated fatty acids with at least one carbon double bond in the trans configuration (Fig. 1) [9]. Naturally occurring TFAs are found in small amounts in milk and meat of ruminant animals such as cows and sheep, where they are formed due to anaerobic bacterial fermentation (bio-

☆ Conflicts of interest: None.

* Corresponding author at: 920 SL Young Blvd, AAT 5400, Cardiovascular Section, Oklahoma City, OK 73104, USA.
E-mail address: udho-thadani@ouhsc.edu (U. Thadani).

https://doi.org/10.1016/j.tcm.2018.09.011
1050-1738/

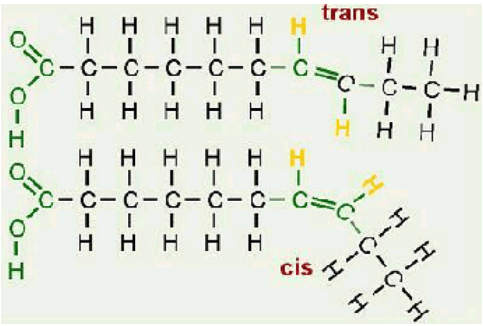

Fig 1. Cis-oliec acid and trans-oliec acid [9].

hydrogenation) and transferred via breast milk and meat products [10]. Small amounts are also naturally present in some vegetable oils and nuts. Due to their presence in lower concentrations, natural TFAs have contributed relatively less to the overall consumption globally [2]. Industrially, TFAs are produced by partial hydrogenation of the unsaturated fatty acids in the presence of a catalyst such as Nickel, or by heating oils at high temperatures [11].

Historical perspectives

TFAs arose from the intent of increasing the usability of unsaturated fatty acid oils [12]. Although the idea of hydrogenation of oils was coined at the turn of the 20th century [12–14], the industrial use of the process started in the early 1900s and continued without any obstacles until mid to late 20th century [15,16].

Over the years there have been many theories about the truth behind these assumed "consumer-friendly" fats. The knowledge of unhealthy effects of then widely used IP-TFA surfaced during the 1950s [17]. However, it was not until the 1990s that it was suspected that consumption of IP-TFAs was associated with increased cardiovascular mortality and morbidity in observational studies [17]. With this new "trans-fat" awakening in the mid-1990s, Denmark became the first country to enforce laws on reduction/control of industrial IP-TFA rich foods intending to improve population health [18–20].

Effects of trans fatty acids on lipids, inflammation and vascular function (Table 1)

As partially hydrogenated fatty acids, TFA have multiple effects on human physiology [21]. The IP-TFA effect on serum lipoprotein levels was considered to be of prime importance for a long time. Early research on this topic has, for the most part, concluded that consumption of IP-TFAs increase serum LDL-cholesterol almost as much as saturated fatty acids [21] with a striking contrast in their effects on HDL-cholesterol. IP-TFA do not increase and may actually decrease HDL-cholesterol concentrations and additionally, increase triglyceride levels [21–25]. This strengthens the positive relationship between IP- TFA intake and CVD risk. TFA use is associated with a high HDL apoA-I catabolic rate and a lower LDL apoB-I catabolic rate [22,23].

TFA association with cardiovascular health is much more than predicted by its effect on serum lipids. Inflammation plays a critical role in CVD especially in the atherosclerotic process [26]. High sensitivity C-reactive protein (hsCRP) and pro-inflammatory cytokines, IL-6, IL-1β, and TNF-γ, are mediators of the inflammatory process [7]. Diets high in IP-TFAs increase inflammation in healthy adults [27]. Epidemiological and clinical studies indicate that TFAs are directly associated with an increase serum concentrations of hsCRP, IL-6, and TNF-γ levels [7,27,28].

Table 1
Effect of TFA on LDL, HDL, hsCRP, IL-6, and TNF [22–29].

LDL	HDL	hsCRP	IL-6	TNF-γ
⇑	=/⇓	⇑	⇑	⇑

TFA – trans fatty acids, LDL – low density lipoprotein, HDL – high density lipoprotein, hsCRP – high sensitivity c-reactive protein, IL-6 – interleukin 6, TNF-γ - tumor necrosis factor-γ.

Inflammation is also one of the principal causative factors of vascular endothelial dysfunction [29]. Under healthy conditions, nitric oxide (NO) produced in the endothelium promotes vasodilation while preventing platelet aggregation and adhesion. Impairment in generation of NO increases the risk of atherosclerosis [29]. TFAs are associated with reduction in NO production and activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NK-κB) that induce transcription of inflammatory cytokines [30]. This subsequently leads to endothelial dysfunction, thus increasing the possible risk of atherosclerosis. Despite much research on the effects of TFA on cardiovascular health, precise molecular pathways by which certain physiological changes occur still remain unknown.

Beneficial and harmful effects of industrially produced and naturally occurring trans fatty acids on cardiovascular health

At present there are no known beneficial effects of IP-TFAs, but the effects of naturally occurring TFAs including trans-palmitoleic acid/oil on cardiovascular health remain incompletely understood [31]. A meta-analysis of 4 prospective cohort studies showed an insignificant relationship between intake of naturally occurring TFA and cardiovascular disease [9,32].

To date there are no randomized trials addressing the detrimental effects of IP-TFAs on cardiovascular health. However, multiple observational and epidemiological studies have suggested a positive correlation between IP-TFAs and cardiovascular disease [20,33–41]. One of the most cited studies in the west is the Nurses' Health Study that was initiated in 1976 where researchers examined the association of dietary fat intake with the risk of coronary heart disease (CHD) [33]. This was a 20-year study including over 75,000 healthy women free of cardiovascular disease and diabetes [33]. Multiple follow-ups were completed for the study with the first 8-year follow-up showing 431 incident cases of new CHD (non-fatal MI or death from CHD) and a direct correlation between intake of IP-TFA and risk of CHD (Table 2) [33].

Subsequent follow-ups at 14 and 20 years confirmed above findings [34,35], with a higher incidence of non-fatal MI or death from CHD in women under the age of 65 years of age [35]. Nurses' Health Study identified doubling of CHD with IP-TFA intake [34,35]. This longitudinal cohort study had a nested case-control study, which showed 166 cases of CHD (non-fatal MI or death from CHD) further strengthening TFA association with CHD [36]. The 14 year follow-up of the study identified 2507 incident cases of type 2 diabetes suggesting an increase in the risk of developing diabetes mellitus (DM) with increased TFA exposure, by changing insulin sensitivity [37,38]. A meta-analysis of observational studies done in 2015 found no association between TFA and type 2 diabetes mellitus [39]. However, this analysis was confounded by heterogeneity [39].

A case control study done in Boston between 1982 and 1983 studied the association between TFA intake and risk of MI. This was a study of non-fatal MI in six hospitals in the Boston area including 239 cases and 282 controls [39]. Researchers used a

Table 2
Effect of TFA on MI, stroke, DM, and mortality [34–41,43–45].

Epidemiologic-observational studies	MI	Stroke	DM	Mortality
Nurses' Health Study				
8-Year follow-up	⇑			⇑
14-Year follow-up	⇑		⇑	⇑
20-Year follow-up	⇑			⇑
Boston Health Study	⇑			
Australian Case-Control Study	⇑			
Prospective Case-Control Study nested in Women's Health Initiative Observational Study		⇑		
Prospective Cohort Study – REGARDS		⇑		

TFA – trans fatty acids, MI – myocardial infarction, DM – diabetes mellitus.

Table 3
Effects of TFA restrictions on MI, stroke, DM, and mortality [21,42].

Observational-interventional studies	MI	Stroke	DM	Mortality
Denmark Case-Control Study				⇓
New York – Retrospective Observational Pre-Post Study	⇓	⇓ (SNS)		

TFA – trans fatty acids, MI – myocardial infarction, DM – diabetes mellitus, SNS – statistically not significant.

food frequency questionnaire to calculate TFA consumption and found a significant association between TFA intake and risk of MI [40].

In 1996, Australia eliminated TFA as an ingredient from margarine [41]. Australian case-control study examined TFA levels in adipose tissue and first MI. The study showed 209 cases of first MI between the years of 1995 and 1997 [41]. TFA levels prior to 1996 were found to be significantly higher in cases vs controls than TFA levels between cases and controls after 1996 [41].

In the year 2004, Denmark was the first country to regulate content of IP-TFA in food products [20]. A study assessing the effectiveness of this policy found a significant decrease (by 14.2 deaths per 100,000 people per year) in cardiovascular disease (CVD) in the three years after the policy was implemented compared to synthetic controls (Table 3) [20].

Between the years of 2007 and 2011, New York State instituted TFA restrictions in eateries of 11 counties [42]. A retrospective observational pre-post study of residents in counties with TFA restrictions was done in comparison to the residents of counties without restrictions from 2002 to 2013 [42]. A significant decline in MI and stroke combined was seen in counties with TFA restrictions compared with the non-restricted counties (Table 3) [42]. The study used a food frequency questionnaire to calculate TFA consumption and found a significant association between TFA intake and risk of MI and a marginal, statistically insignificant reduction in stroke rate (Table 3) [42]. It must be recognized that with a ban on smoking in public places in certain New York counties, there was a decline in smoking rates during this interventional trial period and healthy life style measures were also in practice, which by themselves could have influenced the results [42].

A prospective case-control study nested in the Women's Health Initiative Observational Study examined the association between serum fatty acid concentrations and the incidence of ischemic stroke in post-menopausal women aged 50–79 year between 1993 and 2003 [43]. The study concluded that serum trans, saturated, and monounsaturated fatty acids are positively associated with ischemic strokes [43].

A prospective cohort study investigated the association between TFA intake and incidence of stroke between African American and Caucasian men and women ($n = 17{,}107$) [44]. The study showed that every 2 g increase in TFA intake per day resulted in a 14% increase in risk of stroke in the male population but not in women indicating that sex modifies the association between TFA and stroke [44].

FDA mandate regarding industrially produced trans fatty acids on food labels

Many studies showing the interrelationship between TFA, CHD, and improved outcomes following the initiation of TFA restrictions in countries like Denmark provoked national attention and led to the United States Food and Drug Administration (US-FDA) mandate of restrictions on TFA in 2003. This mandate required TFA content to be declared on nutrition labels of conventional foods and dietary supplements effective January 2006 [6,45]. The disclosure of TFAs on all pre-packaged foods resulted in reformulation of food products to reduce the amount of trans fats since the ruling was instituted. In addition to the ruling in 2003**,** the FDA made a final determination regarding partially hydrogenated oils (PHOs) in 2015 when it was declared, based on the available scientific evidence, that PHOs were no longer generally recognized as safe (GRAS) for any use in human food [46]. Subsequently, the FDA ordered a complete ban on PHOs/IP-TFAs by the end of June 2018 with a one year extension for foods manufactured prior to the date of June 18, 2018 [47].

According to the FDA labeling regulation, servings containing less than 0.5 g of trans fats could be expressed as "0 g" [48]. Considering this regulation, even zero content should be of concern because it can be relatively easy to consume more than the suggested <2 g per day of IP-TFAs, either by eating multiple servings of the same product or by consuming multiple products suggesting "0 g" of trans fats, when, in reality, the content could be as high as 0.4999 g per serving.

World Health Organization (WHO) initiative on industrially produced trans fatty acids

Unfortunately, in many Eastern and Western European countries, and especially in many Asian countries the use of PHO and TFA containing foods remains high [49]. To address this issue, the World Health Organization (WHO) has recently introduced an initiative to globally ban IP-TFA from all industrially produced foods by 2023 [50].

Conclusion

Observational data and interventional open label trials show that consumption of IP-TFA increases cardiovascular morbidity and mortality. However, it must be recognized that these interventional trials were not randomized double blind trials and were carried out simultaneously with smoking cessation initiatives and life style modifications, which, collectively, could have influenced the outcomes. Further research in the form of randomized clinical trials is warranted on the effects of specific isomers of TFA and ruminant TFA. After reviewing multiple observational and a few clinical studies, we conclude that IP-TFAs seem to have deleterious effects on cardiovascular health and given the lack of any positive health effects, their consumption needs to be markedly curtailed and preferably, abandoned.

References

[1] U.S. Department of Health and Human Services and U.S. Department of Agriculture. 2015–2020 Dietary guidelines for Americans [cited 2018 June 27]. Available at https://health.gov/dietaryguidelines/2015/guidelines/.

[2] Doell D, Folmer D, Lee H, Honigfort M, Carberry S. Updated estimate of trans fat intake by the US population. Food AdditContam A 2012;29(6):861–74. doi:10.1080/19440049.2012.664570.

[3] Harika RK, Eilander A, Alssema M, Osendarp SJ, Zock PL. Intake of fatty acids in general population worldwide does not meet dietary recommendations to prevent coronary heart disease: a systematic review of data from 40 countries. Ann Nutr Metab 2013;63:229–38.

[4] Martin CA, Milinsk MC, Visentainer JV, Matsushita M, De-Souza NE. Trans-fatty acid-forming processes in foods: a review. Ann Brazalian Acad Sci 2007;79:343–50.

[5] Iqbal MP. Trans fatty acids – a risk factor for cardiovascular disease. Pak J Med Sci 2014;30:194–7. doi:10.12669/pjms.301.4525.

[6] Mozaffarian D, Katan AscherioA, Stampfer M, Willett W. Trans fatty acids and cardiovascular disease. N Engl J Med 2006;354:1610–13.

[7] Teng KT, Voon PT, Cheng HM, Nesaretnam K. Effects of partially hydrogenated, semi-saturated, and high oleate vegetable oils on inflammatory markers and lipids. Lipids 2010;45:385–92. doi:10.1007/s11745-010-3416-1.

[8] The kinds of fats and why it matters to you [cited 2018 June 27]. Available from http://www.indiana.edu/~oso/Fat/trans.html.

[9] What is the difference between a cis and a trans form in fatty acid? [document on the internet]. [cited 2018 June 27]. Available from https://www.quora.com/What-is-the-difference-between-a-cis-and-a-trans-form-in-fatty-acid.

[10] Brouwer IA, Wanders AJ, Katan MB. Trans fatty acids and cardiovascular health: research completed? Eur J Clin Nutr 2013;67:541–2.

[11] Gunstone FD. Movements towards tailor-made fats. Prog Lipid Res 1998;37:277–305. https://doi.org/10.1016/S0163-7827(98)00012-5.

[12] Hallock B. Rise and fall of trans fat: a history of partially hydrogenated oil Los Angeles Times [newspaper on the internet][cited 2018 June 20]. Available from http://www.latimes.com/food/dailydish/la-dd-rise-and-fall-of-trans-fat-20131107-story.html.

[13] Patterson HB. Hydrogenation of fats and oils: theory and practice. American Oil Chemists' Society; 1994.

[14] Willet WC, Ascherio A. Trans fatty acids: are the effects only marginal? Am J Public Health 1994;84:722–4.

[15] Ascherio A, Stampfer MJ, Willett WC. Trans fatty acids and coronary heart disease. Departments of Nutrition and Epidemiology, Harvard School of Public Health; 1999.

[16] Booyens J, Louwrens CC, Katzeff IE. The role of unnatural dietary trans and cis unsaturated fatty acids in the epidemiology of coronary artery disease. Med Hypotheses 1988;25:175–82. doi:10.1016/0306-9877(88)90055-2.

[17] Lichtenstein AH. Dietary trans fatty acid. J Cardiopulmonary Rehabil 2000;20:143–6.

[18] Filip S, Vidrih R. Trans fatty acids and human health. The cardiovascular system. Gaze DC, editor. IntechOpen; 2012. Retrieved from https://www.intechopen.com/books/the-cardiovascular-system-physiology-diagnostics-and-clinical-implications/trans-fatty-acids-and-human-health. doi:10.5772/36064.

[19] Bysted A, Mikkelsen AA, Leth T. Substitution of trans fatty acids in foods on the Danish market. Eur J Lipid Sci Technol 2009;111:574–83.

[20] Restrepo BJ, Rieger M. Denmark's policy on artificial trans fat and cardiovascular disease. Am J Prev Med 2016;50:69–76. https://doi.org/10.1016/j.amepre.2015.06.018.

[21] Lichtenstein AH. Dietary trans fatty acids and cardiovascular disease risk: past and present. Curr Atherosclerosis Rep 2014;16:1–7.

[22] Aronis KN, Khan SM, Mantzoros CS. Effects of trans fatty acids on glucose homeostasis: a meta-analysis of randomized, placebo-controlled clinical trials. Am J Clin Nutr 2012;96:1093–9. doi:10.3945/ajcn.112.040576.

[23] Lichtenstein AH, Jauhiainen M, McGladdery S, Ausman LM, Jalbert SM, Vilella-Bach M, et al. Impact of hydrogenated fat on high density lipoprotein subfractions and metabolism. J Lipid Res 2001;42:597–604.

[24] Lichtenstein AH, Ausman LA, Jalbert SM, Schaefer EJ. Comparison of different forms of hydrogenated fats on serum lipid levels in moderately hypercholesterolemic female and male subjects. N Engl JMed 1999;340:1933–40.

[25] Aronis KN, Joseph RJ, Blackburn GL, Mantzoros C. Trans-fatty acids, insulin resistance/diabetes, and cardiovascular disease risk: should policy decisions be based on observational cohort studies, or should we be waiting for results from randomized placebo-controlled trials? Metabolism 2011;60:901–5. doi:10.1016/j.metabol.2011.04.003.

[26] Willerson JT, Ridker PM. Inflammation as a cardiovascular risk factor. Circulation 2004;109:2–10. doi:10.1161/01.CIR.0000129535.04194.38.

[27] Han SN, Leka LS, Lichtenstein AH, Ausman LM, Schaefer EJ, Meydania SN. Effect of hydrogenated and saturated, relative to polyunsaturated, fat on immune and inflammatory responses of adults with moderate hypercholesterolemia. J Lipid Res 2002;43:445–52.

[28] Mozaffarian D, Pischon T, Hankinson SE, Rifai N, Joshipura K, Willett WC. et al. Dietary intake of trans fatty acids and systemic inflammation in women. Am J Clin Nutr 2004;79:606–12.

[29] Iwata NG, Pham M, Rizzo NO, Cheng AM, Maloney E. et al. Trans fatty acids induce vascular inflammation and reduce vascular nitric oxide production in endothelial cells. PLoS One 2011;6(12):e29600. https://doi.org/10.1371/journal.pone.0029600.

[30] Tak PP, Firestein GS. NF-κB: a key role in inflammatory diseases. J Clin Invest 2001;107:7–11.

[31] Kleber ME, Delgado GE, Lorkowski S, Marz W, Schacky C. Trans-fatty acids and mortality in patients referred for coronary angiography: the Ludwigshafen Risk and Cardiovascular Health Study. Eur Heart J 2016;37:1072–8. doi:10.1093/eurheartj/ehv446.

[32] Bendsen NT, Christensen R, Bartels EM, Astrup A. Consumption of industrial and ruminant trans fatty acids and risk of coronary heart disease: a systematic review and meta-analysis of cohort studies. Eur J Clin Nutr 2011;65:773–83. doi:10.1038/EJCN.2011.34.

[33] Willet WC, Stampfer MJ, Manson JE, Colditz GA, Speizer FE, Rosner BA, et al. Intake of trans fatty acids and risk of coronary heart disease among women. Lancet 1993;341:581–5.

[34] Hu FB, Stampfer MJ, Manson JE, Rimm E, Colditz GA, Rosner BA, et al. Dietary fat intake and the risk of coronary heart disease in women. N Engl J Med 1997;337:1491–9.

[35] Oh K, Hu FB, Manson JE, Stampfer MJ, Willet WC. Dietary fat intake and risk of coronary heart disease in women: 20 years of follow-up of the nurses' health study. Am J Epidemiol 2005;161:672–9. https://doi.org/10.1093/aje/kwi085.

[36] Sun Q, Ma J, Campos H, Hankinson SE, Manson JE, Stampfer MJ, et al. A prospective study of trans fatty acids in erythrocytes and risk of coronary heart disease. Circulation 2007;115:1858–65.

[37] Risérus U. Trans fatty acids, insulin sensitivity and type 2 diabetes. Scand J Food Nutr 2006;50:161–5. doi:10.1080/17482970601133114.

[38] Salmeron J, Hu FB, Manson JE, Stampfer MJ, Colditz GA, Rimm EB. Dietary fat intake and risk of type 2 diabetes in women. Am J Clin Nutr 2001;73:1019–26. https://doi.org/10.1093/ajcn/73.6.1019.

[39] DeSouza RJ, Mente A, Maroleanu A, Cozma AI, Ha V, Kishibe T, et al. Intake of saturated and trans unsaturated fatty acids and risk of all cause mortality, cardiovascular disease, and type 2 diabetes: systematic review and meta-analysis of observational studies. Br Med J 2015;351. https://doi.org/10.1136/bmj.h3978.

[40] Ascherio A, Hennekens CH, Buring JE, Master C, Stampfer MJ, Willet WC. Trans-fatty acids intake and risk of myocardial infarction. Circulation 1994;89:94–101.

[41] Clifton PM, Keogh JB, Noakes M. Trans fatty acids in adipose tissue and the food supply are associated with myocardial infaction. J Nutr 2004;134:874–9.

[42] Brandt EJ, Myerson R, Perraillon MC, Polonsky TS. Hospital admissions for myocardial infarction and stroke before and after the trans-fatty acid restrictions in New York. JAMA Cardiol 2017;2:627–34. doi:10.1001/jamacardio.2017.0491.

[43] Yaemsiri S, Sen S, Tinker LF, Robinson WR, Evans RW, Rosamond W, et al. Serum fatty acids and incidence of ischemic stroke among postmenopausal women. Stroke 2013;44:2710–17. https://doi.org/10.1161/STROKEAHA.111.000834.

[44] Kiage JN, Merrill PD, Judd SE, He KH, Lipworth L, Cushman M. et al. Intake of trans fat and incidence of stroke in the reasons for geographic and racial differences in stroke cohort. Am J Clin Nutr 2014;99:1071–6. doi:10.3945/ajcn.113.075713.

[45] U. S. Food and Drug Administration. Guidance for industry: trans fatty acids in nutrition labeling, nutrient content claims, health claims; small entity compliance guide [Document on the internet][cited 2018 June 17]. Available from https://www.fda.gov/food/guidanceregulation/guidancedocumentsregulatoryinformation/ucm053479.htm.

[46] Sabrina T. F.D.A. sets 2018 deadline to rid foods of trans fats, New York Times, 2015 June16: A12

[47] Grossman MR. FDA issues order to ban artificial trans fat by 2018. Eur Food Feed Law Rev 2015;10:317–19.

[48] U. S. Food and Drug Administration. Final determination regarding partially hydrogenated oils (removing trans-fat) [document on the internet][cited on 2018 June 20]. Available from: https://www.fda.gov/food/ingredientspackaginglabeling/foodadditivesingredients/ucm449162.htm.

[49] Wang Q, Afshin A, Yakoob MY, Singh GM, Rehm CD, Khatibzadeh S, et al. Impact of nonoptimal intakes of saturated, polyunsaturated, and trans fat on global burdens of coronary heart disease. J Am Heart Assoc: Cardiovasc Cerebrovasc Dis 2016;5:e002891. doi:10.1161/JAHA.115.002891.

[50] Salem T. WHO calls for elimination of trans fats globally by 2023 U.S. News & World Report. [newspaper on the internet][cited 2018 June 18]. Available from https://www.usnews.com/news/health-care-news/articles/2018-05-14/who-calls-for-elimination-of-trans-fats-globally-by-2023.