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Healthy Skepticism: The Relationship between Funding Source and Conclusion in Nutrition-Related Scientific Articles on Saturated Fat

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Healthy Skepticism: The Relationship between Funding Source and Conclusion in Nutrition-Related Scientific Articles on Saturated Fat

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Abstract:

Recently published scientific articles have led to mixed nutritional advice on dietary saturated fatty acids. Lesser et. al 2007 identified that mixed conclusions in scientific articles on sweetened beverages can be attributed industry funding, as articles funded by the beverage industry are four to eight times more likely to report conclusions in favor of the sponsor's products[1]. This thesis applies Lesser's methods to determine whether industry funding influences the inconsistent conclusions on saturated fatty acids. This thesis analyzed 100 articles on foods high in dietary saturated fatty acids. While studies with food industry funding are more likely to produce favorable conclusions, this trend is not significant ($p= 0.205$). On the other hand, the odds ratio of a favorable versus an unfavorable conclusion in articles where investigators disclosed a food industry related conflict of interest is 2.67 (95% CI, 1.03 to 6.88). The prevalence of both industry funding and conflict of interest have increased over time, yet the percent of articles reporting favorable conclusions has not changed over time. This suggests that while industry funding and conflict of interest might skew nutrition research, the mixed conclusions in articles on saturated fatty acids are largely influenced by other factors. Therefore, all nutrition-related scientific articles on saturated fatty acids should be critically evaluated before informing dietary recommendations.

Introduction:

Food industry sponsored nutrition research has been associated with results that confirm the benefits of the sponsor's products. Lesser et. al 2007 explored this association by analyzing 206 articles on soft drinks, milk and juice.[1] Lesser's key finding was that articles funded by food or beverage companies were four to eight times more likely to have conclusions favorable to the financial interests of the sponsoring company. This thesis will modify the methods used by Lesser in order to investigate whether food industry funding and conflict of interest are associated with more favorable conclusions in nutrition studies on foods high in dietary saturated fatty acids. Saturated fatty acids were chosen as the focus because there has been recent controversy in scientific studies surrounding the health effects of saturated fatty acids.

The Biology of Saturated Fatty Acids

Dietary fats are a type of lipid constructed of triglycerides. Triglycerides consist of three fatty acids attached to a glycerol backbone[2]. Triglycerides can be made up of saturated fatty acids, those that contain only single bonds in its hydrocarbon chain, unsaturated fatty acids, those that contain one or more double bonds, or a combination of the two (Figure 1). Saturated fatty acids are considered to be 'saturated' with hydrogen because the maximum number of hydrogen atoms are attached to the carbon skeleton. A fatty acid with one double bond is monounsaturated, and one with multiple double bonds is polyunsaturated. These dietary fatty acids are a rich energy source, a building blocks for the hormones needed to regulate bodily systems and a carrier for fat-soluble vitamins[2]. Dietary saturated fatty acids are most often distributed as palmitic acid, stearic acid, myristic acid and lauric acid (Figures 2-5)[4]. These saturated fatty acids are found in a variety of foods. The effect of dietary saturated fatty acids on health

outcomes in humans is typically studied by measuring the consumption of food sources (e.g., coconut oil) rather than the consumption of isolated saturated fatty acids (e.g., lauric acid).

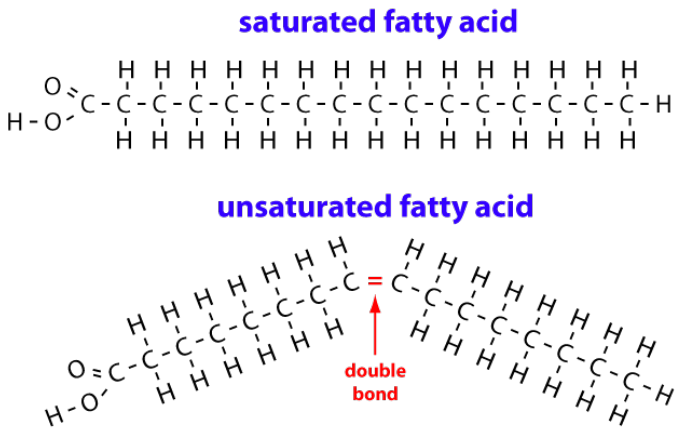

Figure 1. A saturated fatty acid compared to a monounsaturated fatty acid[3]

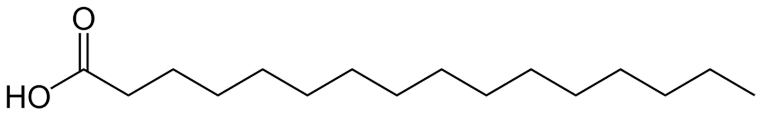

Figure 2. Chemical structure of palmitic acid (16-carbon), a common dietary saturated fatty acid found in palm oil and animal fats[5].

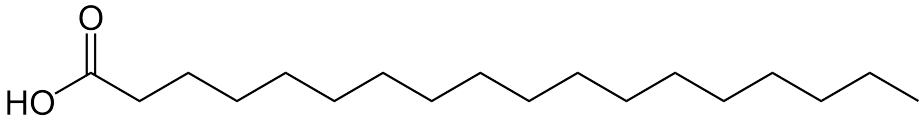

Figure 3. Chemical structure of stearic acid (18-carbon), a common dietary saturated fatty acid found in animal fats and cocoa butter[6].

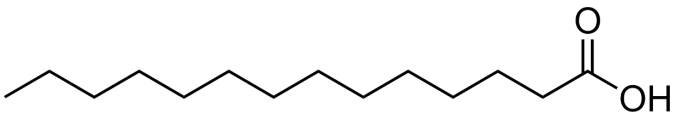

Figure 4. Chemical structure of myristic acid (14-carbon), a common dietary saturated fatty acid found in various oils[7].

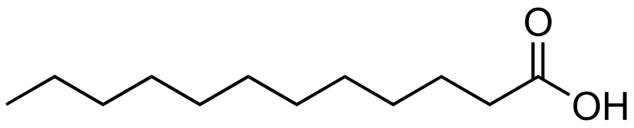

Figure 5. Chemical structure of lauric acid (12-carbon), a common dietary saturated fatty acid found in various oils[8].

The food sources with the highest percent saturated fatty acids - of the total fatty acid composition - include butter fat (66%), coconut oil (92%), palm kernel oil (82%), cocoa butter (61%), lard (42%) and other animal fats[2]. While these foods are high in saturated fatty acids, each is a source of both saturated and unsaturated fatty acids. Therefore, the nutrition-related scientific studies included in this thesis compare the health outcomes associated with consuming foods high in saturated fatty acids versus consuming foods low in saturated fatty acids. Moreover, the nutrition studies often measure health outcomes associated with high consumption of the top sources of saturated fatty acids in the United States. These include dairy products such as milk, butter and cheese, meat, eggs, and food processed with palm or coconut oil.[9]

While saturated fatty acids are difficult to isolate in nutrition studies, their effect on biological and metabolic pathways has been studied in vitro and in animal models. Palmitic acid and myristic acid are directly involved in protein fatty acid acetylation, a post-translational modification of proteins[4]. Palmitic acid has also been shown to influence gene transcription through recruiting transcription factors[4]. Additionally, saturated fatty acids have been shown to be involved in lipogenesis, fat deposition, polyunsaturated fatty acids bioavailability and apoptosis[4].

Dietary Saturated Fatty Acids, Cholesterol and Disease

Dietary saturated fatty acids are thought to increase plasma low density lipoprotein (LDL) cholesterol concentrations, potentially increasing the risk for coronary heart disease. The effect of saturated fatty acids, lauric acid and palmitic acid, and unsaturated fatty acids on serum lipids and lipoproteins were studied in healthy women and men[10]. Saturated fatty acids significantly increased blood LDL cholesterol levels when compared with unsaturated fatty acids. This might be because saturated fatty acids have an effect on cell membrane fluidity. In turn, saturated fatty acids might alter cholesterol synthesis and lipoprotein distribution. LDL cholesterol is thought to be a potential risk factor for coronary heart disease. Epidemiological studies have shown elevated levels of plasma LDL cholesterol and apolipoprotein B (apoB), the main structural protein of LDL, to be associated with atherosclerosis[11]. LDL cholesterol is thought to induce atherosclerosis through the generation of macrophage foam cells, or fat-laden macrophages[11]. These foam cells participate in inflammatory responses and tissue remodeling (Figure 6).

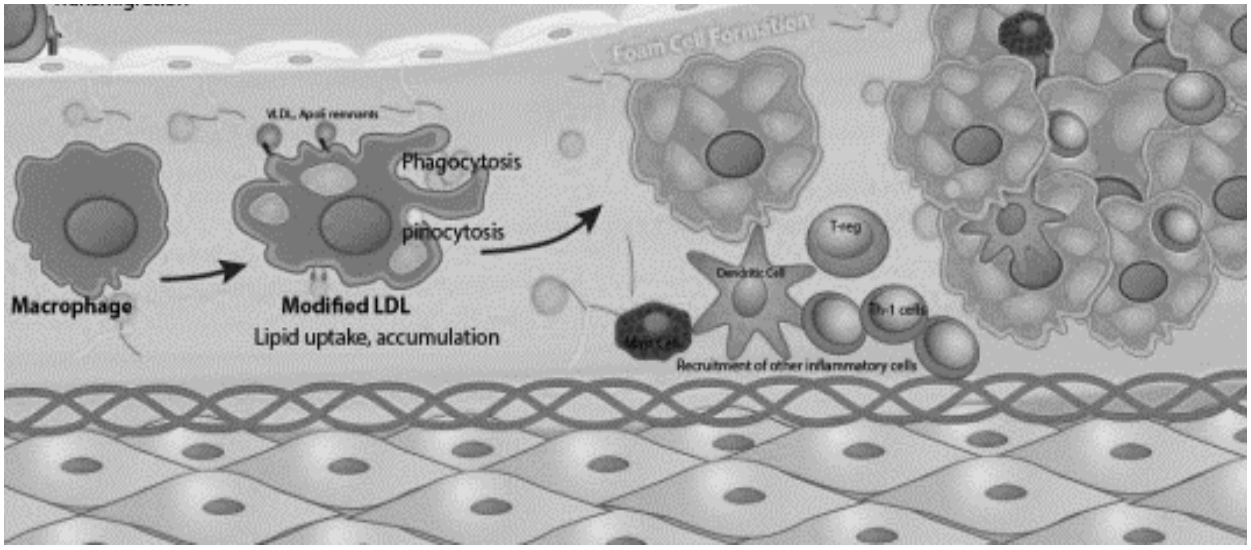

Figure 6. Potential mechanism for LDL and apoB involvement in atherosclerosis[11]

Recent studies suggest the potential lack of an association, or even an inverse association between LDL cholesterol and mortality. In 2016, an analysis of 19 observational studies found high LDL cholesterol to be inversely associated with mortality[12]. The results of this study contradict the previous hypotheses that LDL cholesterol is atherogenic. Therefore, because saturated fatty acids are thought to increase LDL cholesterol, this study calls question to whether dietary saturated fatty acids increase the risk of heart disease. This thesis investigates whether food industry funding influences theses conflicting conclusions in literature surrounding saturated fatty acids, LDL cholesterol, and health outcomes.

History of Dietary Saturated Fatty Acid Research

A negative reputation was built around saturated fat following several studies performed in the 1950s. These findings came about after the pioneering of ultracentrifugation to separate lipoproteins[13]. Lipoproteins could be separated based on flotation rates in salt solutions, leading to the terminology low density lipoprotein (LDL) and high density lipoprotein (HDL). In 1950, the first literature was published suggesting the atherogenic potential of LDL, as there was higher prevalence of coronary artery disease in people who had higher levels of LDL[13]. Dietary fat was attributed as a key factor in this relationship. At the same time, physiologist Ancel Keys began conducting comparative population-based dietary investigations focused on dietary fats and saturated fatty acids[14]. In an observational study including data from seven countries, Keys found a significant association between dietary saturated fat intake and heart disease mortality[15]. These findings lead to the diet-heart hypothesis, or the idea that diets high in saturated fat and cholesterol are a major cause of coronary heart disease[16].

Since the early research in the 1950s, the low-fat diet-heart hypothesis gained publicity and even influenced dietary recommendations in the United States. A report published by the American Heart Association (AHA) in 1957 claimed that diet may play an important role in the pathogenesis of atherosclerosis. Specifically, the AHA suggested that dietary fat and the ratio between saturated and unsaturated fat may be key determinants in this cardiovascular disease[17]. A decade later, the AHA's committee on nutrition published dietary recommendations including: decrease saturated fats, increase polyunsaturated fats, reduce animal fat and reduce cholesterol. In 1977, the U.S. Senate's Select Committee on Nutrition and Human Needs furthered the publicity of the diet-heart hypothesis[18]. The committee chair, George McGovern, stated that too much fat, sugar and salt is directly linked to heart disease, cancer, obesity and stroke. Eventually these recommendations were included in the first U.S. Dietary recommendations report in 1980.

More recently, similar to with LDL cholesterol, observational studies have shown an inverse relationship between dietary saturated fatty acids and negative health outcomes. In 1997, the Framingham Heart Study data showed higher saturated fat intake to be associated with reduced stroke incidence in middle aged men[19]. In 2004, a review found greater saturated fat intake to be associated with a lesser progression of coronary atherosclerosis in postmenopausal women with relatively low total fat intake[20]. Further, this review attributed progression of coronary atherosclerosis to a higher intake of carbohydrates; not saturated fats.

In 2010, Siri- Tarino et. al reopened the diet-disease hypothesis debate after taking a second look at the evidence on the association between saturated fat and cardiovascular disease[21]. Siri-Tarino published a meta-analysis of prospective epidemiological studies concluding that there is no significant evidence that saturated fat is associated with cardiovascular disease. The meta-analysis included data from 16 studies with congenital heart

disease as an endpoint and 8 studies with stroke as an endpoint. It was noted that the lack of association may be attributed to the reliance on the accuracy of dietary assessments, which varies between studies. For example, it was noted that short term (4-7 day) food records are most accurate, but generally 24-hour food recalls are most feasible in a large cohort. Siri-Tarino questions whether the data collected in these nutrition studies accurately reflect long term dietary patterns and health outcomes. This meta-analysis lead many others to question the evidence for current dietary saturated fat recommendations.

Despite the recent nutritional controversy around saturated fat, the AHA has maintained their campaign for the reduction of dietary saturated fatty acid consumption[22]. AHA recognizes the controversy surrounding saturated fat but argues that many who question recommendations rely on evidence from studies that the organization believes has methodological limitations [22]. Namely, the AHA claims that many studies do not take replacement nutrients into consideration as when dietary saturated fat is decreased, another dietary component is increased. For example, many studies compare a diet high in saturated fatty acids to a diet high in carbohydrates. This makes it difficult to determine whether the differing health outcomes among study groups is caused because of a decrease in saturated fat or an increase in carbohydrates.

Unlike the AHA, many others have changed their stance on saturated fatty acids. In 2010, Harvard Heart Letter published an article called *New Thinking on Saturated Fat* that argues that a healthy diet can include moderate saturated fat consumption [23]. The article notes that the case against saturated fat is based on high saturated fat diets increasing the cholesterol circulating in the bloodstream inside LDL particles. Harvard Health notes that the connection between saturated fat intake and supposedly harmful LDL cholesterol is difficult to measure when saturated fat accounts for less than 10% of calories in the diet. Additionally, the article argues

that saturated fat does not exist in a vacuum. Therefore, the mechanism by which saturated fat it affects the body is determined by amount of cholesterol and polyunsaturated fat in the diet along with exercise, genetics and environmental factors. Ultimately, this lead Harvard Health to argue that there is much more to uncover about saturated fat before we can draw major conclusions[23].

Others take it a step further and argue that an ideal diet should be high in saturated fatty acids. *The Perfect Health Diet,* written by Dr. Paul Jaminet and Dr. Shou-Ching Jaminet named saturated fatty acids the 'safe fats'[24]. The book cites several studies to support their argument that SFAs are not only nontoxic, but that they are beneficial. Ultimately, the science-based PHD diet, recommends eating foods with high quantities of saturated fat for improved lipid profiles and muscle mass.

Conflict of Interest in Scientific Research

It is possible that this recent mixed evidence on saturated fat could be attributed to the funding source of studies and conflict of interest. Conflict of interest refers to when professional judgement concerning a primary interest, such as the validity of research, is influenced by a secondary interest, such as financial gain[25].

The awareness of conflict of interests in medicine came about in the 1980s, following new collaborations with universities and industry[26]. These relationships came to fruition as a result of pressures of the federal budget, the growing pharmaceutical industry and incentives for universities to develop discoveries commercially. This threatened the integrity of scientific investigations and the public's trust in medicine. Therefore, several measures were taken to restore this trust. For instance, in 1984, the New England Journal of Medicine announced that it

would begin asking authors to disclose relationships with companies that could affect published findings[26].

Financial conflict of interest is also prevalent in the food and drug industries. Studies sponsored by the pharmaceutical industry have been found to be four times more likely than studies sponsored by other sources to produce outcomes favoring the sponsor[27]. Additionally, it has been found that research funded by the pharmaceutical industry is less likely to be published than studies funded by other sources. More recently, conflict of interest has gained attention in nutrition research. Conflict of interest in nutrition research differs from the pharmaceutical industry because drug companies have to submit the results of their studies to regulatory agencies before the drug will be approved. Human foods nor nutrition labels are approved by the FDA before being marketed [28]. Rather, the FDA requires that 1) nutritional information must appear on most foods and 2) all claims must be truthful. These requirements are not nearly as stringent as those with drugs and biologics.

Adding to the problem, food companies are incentivized to fund research that will increase consumer demand for their products. Of 204 research publications sponsored by Coca-Cola and Mars Center for Cocoa Health Science, the most common topic investigated was physical activity (40.7%) as opposed to the health impact of sugar (10.8%).[29] Research sponsored by Coca-Cola and Mars appears to skew the evidence to support solutions (e.g., exercise) that do not involve reducing consumption of sugar. It is in the interest of these companies that consumers to make positive lifestyle changes that do not involve reduction of soda or candy consumption. For this reason, large food companies fund research that makes claims beneficial to their product.

Marion Nestle, nutrition professor at New York University and author of *Unsavory Truth: How Food Companies Skew the Science of What We Eat,* blogged about several examples of studies paid for by food businesses with a financial interest in the outcome of the study[30]. For example, Mars, Inc. funded a study concluding that habitual intake of flavanols support healthy cognitive function. Similarly, Juice Products Association funded a study concluding that fruit juice delivers essential nutrients and phytonutrients. Additionally, Nestle writes about her own financial relationships with food and beverage companies as a nutrition professor. Nestle thinks carefully about conflicted situations, but writes that she is not wealthy enough to pay travel expenses for regular conferences [31]. She writes that she goes to meetings sponsored by food companies, reads journal sponsored by food companies, receives frequent gifts, and accepts reimbursements from food companies for travel. Nestle exemplifies that conflict of interest is prevalent in nutrition research and might skew scientific evidence to support the sponsors.

An added challenge is that researchers are not always aware of their own biases. Dr. Young, co-editor-in-chief of the Journal of Psychiatry and Neuroscience and professor at McGill University writes, "We are not always aware of our own biases. The idea that scientists are objective seekers of truth is a pleasing fiction, but counterproductive in so far as it can lessen vigilance against bias." [32] Therefore, it is very plausible that conflicting of interest in nutrition research can influence the interpretation of the data and affect the takeaways stated in the conclusion.

Food Industry Funding

The food industry continues to provide funding for nutrition research for several reasons. For one, public research funds are limited and nutrition research usually does not qualify for

biomedical funding from these public institutions[33]. Additionally, food companies are also responsible for providing science-based evidence to support health claims on nutrition labels, and sometimes for providing evidence that a product is safe[34]. All the while, academic researchers that receive public funding are incentivized to partner with industry, as receiving funds from diverse sources strengthens the case to receive tenure.

Though the food industry provides substantial funding for nutrition research, evidence suggests that this does not influence the methodological quality of scientific research. A review of 2539 articles in the American Association's Evidence Analysis Library database was performed to determine whether industry funding of nutrition research is associated with lower research methodological quality[35]. Methodological quality was determined by the American Diabetic Association using either a Primary Research Quality Criteria Checklist or Review Research Quality Checklist. After controlling for research design, industry funded reports were no more likely to receive a poor rating than those funded by government source.

In contrast to Lesser's findings, not all research suggests that industry funding influences conclusions. For example, one review investigated 79 obesity-related studies funded by either the National Institute of Health or semi-public programs for Fluid Milk and Dairy[36]. The review did not find consistent evidence that industry funding is associated with conclusions favorable to the dairy products. However, the review found that NIH sponsored studies were the only ones to report unfavorable conclusions, suggesting a publication bias in research sponsored by the food industry. Additionally, the review noted that there is limited NIH funding available for research specifically on dairy consumption and obesity. This suggests that a funding source might not impact scientific research results, but rather the food industry might be more likely to fund nutrition research with health outcome measures that could make their product seem desirable.

Similarly, of 12 reports on industry funding in nutrition, industry sponsored studies were more likely to have favorable conclusions than non-industry sponsored studies, but the results were not significant[37]. Additionally, there were no associations with scientific methodological quality and industry sponsorship. This thesis attempts to understand food industry funding and conflict of interest as it relates to studies on foods high in saturated fat.

Public Perception of Saturated Fat

This thesis is relevant to the current health and nutrition landscape as there is a mixed public perception of saturated fats. For instance, several popular fad diets advocate for high-fat, low carbohydrate diets - including the Atkins diet, Ketogenic diet and the Perfect Health Diet. At the same time, other diets and government nutrition recommendations advocate for limiting certain types of fat. This is problematic as the public is receiving mixed messages about health and nutrition, and there is scientific evidence to support both sides of the contradictory fat claims.

There are several high-fat diets that are thought to be healthy and effective for weight loss. For example, the Atkins diet, developed in the 1960s by a cardiologist, recommends restricting carbohydrates and encourages eating a diet high in protein and fat[38]. Another high-fat diet, the Ketogenic diet, is gaining publicity. Originally intended as a therapeutic diet for children with epilepsy, the Ketogenic diet is being promoted for the general population by health and fitness magazines[39]. These diets cite meta-analyses that claim low-fat diets do not lead to long-term weight loss[40]. Similarly, the Perfect Health Diet, developed by Dr. Paul Jaminet and Shou-Ching Jaminet, claims that saturated fatty acids can be eaten in high quantities. This diet cites studies that show a lack of toxicity and reduced likelihood of stroke[24]. In contrast to these

diets, the AHA recommends a moderate-fat diet replacing saturated fats with polyunsaturated fats[22].

With mixed messages from science, the media, and government organizations, there is no question that knowledge surrounding dietary fat is conflicting. The general public appears to be confused about which types of fats have health benefits. Of 6,426 subjects in 16 countries, 59% think fat should be avoided[41]. Most subjects had heard of different types of fat such as 'saturated fat', but the majority were unsure which types were healthiest. This confusion makes sense as the scientific studies surrounding saturated fatty acids report mixed conclusions. Based on scientific literature, it is unclear whether saturated fatty acids should be avoided, reduced, or consumed as part of a healthy diet.

This thesis investigates whether industry funding and conflict of interest influence the mixed evidence on saturated fat. Given the Lesser's findings, I hypothesized that studies funded by the food industry will be more likely to report favorable conclusions. However, knowing that saturated fatty acids are difficult to isolate in human nutrition studies, I hypothesized that there will be some variation in conclusions independent of the funding source. The goal of this report is to better understand the factors influencing the mixed scientific evidence on saturated fatty acids: be it industry funding, conflict of interest, or another factor.

Methods:

Creation of Data Spreadsheet

Different from Lesser, I did not perform this study with multiple investigators. In order to avoid potential biases, I created spreadsheet to separate selection of articles, classification of conclusion and characterization of sponsor. A visual explanation of this process is included in the appendix (Figures 11-13).

The spreadsheet contained the following tabs: 1) Raw Data, 2) Conclusion Classification, and 3) Funding Source and Conflict of Interest. On the Raw Data tab, information was entered upon selection of articles. These data include: 1) Article Title, 2) Random Number Code, 3) Date, 4) Author, 5) Conclusion Raw Text, 6) Funding Raw Text and 7) Conflict of Interest Raw Text. The 'Random Number Code' and 'Conclusion Raw Text' data was linked to the 'Conclusion Classification' tab. The 'Random Number Code', 'Funding Raw Text' and 'Conflict of Interest Raw Text' data was linked to the 'Funding Source and Conflict of Interest' tab.

At least one day after raw data were entered, the raw text data on the 'Conclusion Classification' tab were used to determine 1) Study Type, 2) Conclusion Classification, and 3) Food Source of Fat. At least two days after raw data were entered and at least one day after conclusions were classified, the raw text data on the 'Funding Source and Conflict of Interest' tab were used to determine 1) Funding Source and 2) Declared Conflict of Interest. The data on the 'Conclusion Classification' and 'Funding Source and Conflict of Interest' tabs were linked to 'Raw Data'. The final file used in Data Analysis included 1) Random Number Code, 2) Date, 3) Study Type, 4) Conclusion Classification, 5) Food Source of Fat, 6) Funding Source and 7) Declared Conflict of Interest.

Selection of Articles

The search algorithm used to find articles was a modification of that used in a previous meta-analysis of saturated fat and its association with mortality[42]. Interventional, observational and scientific literature reviews were included in this analysis. Searches were conducted on the U.S. National Library of Medicine's PubMed. Searches were targeted at foods high in saturated fatty acids (e.g., dairy, butter, meat, palm oil, cocoa, coconut oil) or saturated fatty acids (e.g., lauric acid, stearic acid). Additionally, searches looked for studies with endpoints measuring health outcomes associated with saturated fatty acids (e.g., mortality, coronary heart disease, high cholesterol). The search specified that studies must be limited to human studies in adults.

Studies included in the data analysis had to meet specific inclusion criteria. 1) Studies must relate directly to dietary saturated fat. 2) At least one main endpoint must relate directly to health, disease, or a disease marker. 3) The article must involve or consider research with humans. 4) The conclusion must relate directly to the dietary saturated fat source under study. For example, an article examining the effect of dietary fat on cardiovascular disease would be included only if implications to the health effects of saturated fat consumption are stated explicitly. 5) The article must be classified as an interventional study, an observational study, or a scientific review. These classifications are outline in 'Assessments of Covariates' below.

Classification of Conclusion

As in the review conducted by Lesser, conclusions were classified as either *Favorable*, *Unfavorable* or *Neutral*. Additionally, in this thesis, if a conclusion was unfavorable for saturated fat, but favorable for unsaturated fat products, this was noted in the 'Conclusion Classification' column that linked back to raw data. This was considered as the funding source might benefit

from consumers choosing to replace unsaturated fat with saturated fat. Conclusions were classified as follows:

Favorable: Suggests beneficial health effects or absence of adverse health effects.

Unfavorable: Suggests adverse health effects or absence of beneficial health effects.

Neutral: Does not fit the criteria for favorable or unfavorable.

A conclusion would be classified as neutral if the conclusion suggested an absence of adverse health effects but expressed strong doubts of the methodology of the study.

Characterization of Sponsor

As in the study conducted by Lesser, funding sources were classified as either *Industry*, *No Industry*, *Mixed* or *None Stated*. Additionally, in this thesis, if a funding source was classified as 'Industry', but the sponsor would benefit from consumers replacing saturated fats with unsaturated fats (e.g., Canola Oil Board), a note was made in the 'Funding Source' column. The funding sources were characterized as follows:

Industry: Solely for-profit and nonprofit affiliations with the food industry (e.g., US National Dairy Council).

No industry: Solely governmental agencies with no industry association (e.g., US National Institute of Health), university, independent foundations, philanthropies, and other nonprofit organizations.

Mixed: Funding sources from both of the groups described above.

None Stated: If there was no mention of the source of the funding acquired for the study.

Ultimately, a total of 100 studies met the inclusion criteria (Figure 7). Of these 100 articles, 13 did not list a funding source. Of the 87 articles listing a funding source, 24% were

funded entirely by industry, 66% were funded entirely with no industry support, and 10% were funded by a mix of the two sources.

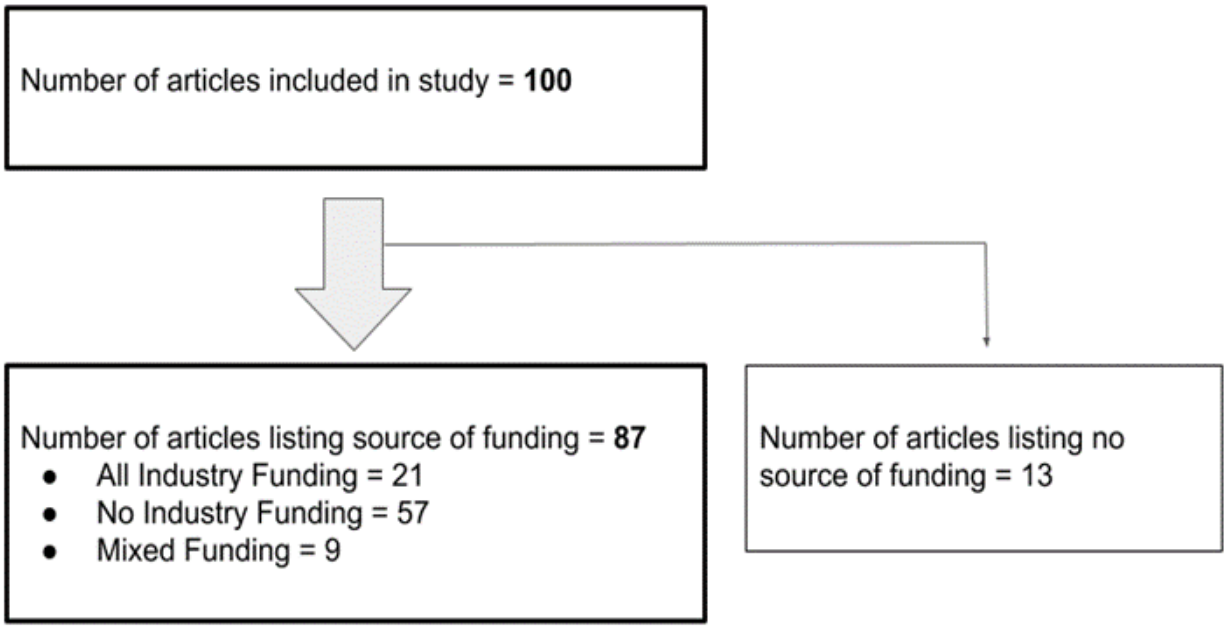

Figure 7. Flow diagram for inclusion of articles in the study

Characterization of Conflict of Interest

Extending upon the review conducted by Lesser, this analysis also noted whether studies had a declared conflict of interest. This was classified as *Yes* if a conflict of interest was declared. A note was made if the conflict of interest related to a party that would benefit from consumers replacing saturated fats with unsaturated fats. This was classified as *No*, if there was a statement claiming no conflict of interest. This was classified as *None Stated* if there was no conflict of interest statement included in the study.

Assessment of Covariates

Two covariates were examined: publication year and article type. Publication year was available on PubMed. Article type was classified according to the same definitions as in Lesser's

study. Studies were classified as *Interventional* if a human consumed food with the intention of measuring a biological response [1]. Studies were classified as *Observational* if health outcome data were collected on participants without intervention from the investigators[1]. Studies were classified as *Scientific Review* if no original data were reported, but rather published research was analyzed in a systematic fashion[1].

Statistical Treatment

The relationship between conclusion and funding source was focused on discrete categories of funding: either all industry benefit or no industry. Studies with industry antagonism (e.g., Canola Oil Board) that would benefit from consumers perceiving unsaturated fatty acids as a superior choice to saturated fatty acids were excluded from the analysis. Additionally, studies with mixed funding were excluded because they represent a group with different proportions of industry funding which could potentially obscure the relationship. Finally, studies with no listed funding source were excluded from the study. The association between article conclusion and funding source was evaluated using a Chi-Square test for nominal data.

Building off Lesser's work, the relationship between conclusion and conflict of interest was evaluated also focusing on the most discrete categories: all-industry benefit conflict of interest and no conflict of interest. Studies with industry benefit funding were encompassed in the studies with industry benefit conflict of interest. The studies where a note was made about potential industry antagonism (e.g., Canola Oil Board) were excluded. Additionally, studies with no conflict of interest statement were excluded. The association between article conclusion and conflict of interest was evaluated using a Chi-Square test for nominal data.

Additionally, the Odds Ratios (ORs) were computed of conclusions for all industry and no industry funding. Two sets of ORs were computed. In the first, articles with favorable and neutral conclusions were collapsed into one group, and in the other no neutral articles were included. One article funded by all industry antagonism was originally categorized as unfavorable; however, the sponsor was perceived to benefit from a negative conclusion about products with saturated fat. Therefore, the article was reclassified as it was favorable to the funder's interests.

The ORs were computed of conclusions for conflict of interest and no conflict of interest. The same as with funding source, two sets of ORs were computed. Five articles with all industry antagonistic conflict of interest originally categorized as unfavorable, were reclassified as the conclusions were favorable to the funder's interests. ORs were determined to be statistically significant if the 95% Confidence Interval was entirely greater than 1.

A $p < 0.05$ (two tailed) was used as a criterion for statistical significance. Computations were performed using RStudio 1.1.463 with the `coin` Package.

Results

This analysis found that articles with food industry funding were more likely to produce favorable conclusions; however, this trend was not significant (Table 1; $X^2(2)=3.168$, p=0.205). Similarly, favorable article conclusions were not significantly associated with industry benefit conflict of interest (Table 2; $X^2(2)= 2.645$, p= 0.266).

Table 1. Relationship between funding source and article conclusion (n=77)

		Funding Source	
		Industry	**No Industry**
Conclusion p = 0.205	**Favorable**	11	19
	Neutral	2	12
	Unfavorable	7	26

Table 2. Relationship between conflict of interest and article conclusion (n = 86)

		Conflict of Interest	
		Yes	**No**
Conclusion p = 0.266	**Favorable**	17	18
	Neutral	8	8
	Unfavorable	11	24

The OR for a favorable or neutral versus unfavorable conclusion, comparing all industry to no industry support, was 1.68 (95% CI, 0.59 to 4.78). Eliminating neutral articles, the OR for the same comparison was 2.35 (95% CI, 0.78 to 7.08). While neither of the ORs are statistically

significant, these data suggest a higher likelihood of industry funded studies publishing conclusions favorable to the company (Table 3).

Table 3. ORs for favorable conclusions of articles with all industry compared to no industry support

Conclusion	OR (95% CI)
Favorable/Neutral vs. Unfavorable (n=78)	1.68 (0.59 to 4.78)
Favorable vs. Unfavorable (n=64)	2.35 (0.78 to 7.08)

The OR for a favorable or neutral conclusion versus an unfavorable conclusion, comparing industry conflict of interest to no conflict of interest, was 2.52 (95% CI, 1.04 to 6.11). Eliminating neutral articles, the OR for the same comparison was 2.67 (95% CI, 1.03 to 6.88). These ORs are statistically significant and suggest a higher likelihood of authors with conflict of interest publishing conclusions favorable to their competing interest (Table 4). The reason these ORs are significant while the relationship (Table 2) is not has to do with the 5 studies with industry antagonism. These studies were excluded in the Chi-Square test. These studies were included in the OR calculations above, and the article conclusions were reclassified based on the favorability related to the sponsor's products.

Table 4. ORs for favorable conclusions of articles with industry conflict of interest compared to no conflict of interest

Conclusion	OR (95% CI)
Favorable/Neutral vs. Unfavorable (n=91)	2.52 (1.04 to 6.11)
Favorable vs. Unfavorable (n=75)	2.67 (1.03 to 6.88)

There were 100 articles included in the analysis. Of these studies, the majority were not funded by the industry (57%) and half stated that investigators had no conflict of interest (Table 5). Most articles stated a funding source (87%) and included a conflict of interest disclosure statement (91%). The analysis included a relatively even mix of interventional, observational and scientific reviews. A large number of studies included were published within the last decade (Figure 8).

Of the studies included, the percent of articles included reporting favorable conclusions fluctuates overtime, with a slight peak in 2004-2007 (Figure 9). The percent of articles with industry funding and conflict of interest has generally increased over time (Figure 10,11)

Table 5. General Descriptive Data of Articles Included in Study (n=100)

Type of Article		n
Funding Source	All Industry	21
	No Industry	57
	Mixed	9
	None Stated	13
Stated Conflict of Interest	Yes	41
	No	50
	Not stated	9
Article Type	Interventional	32
	Observational	35
	Scientific Review	33

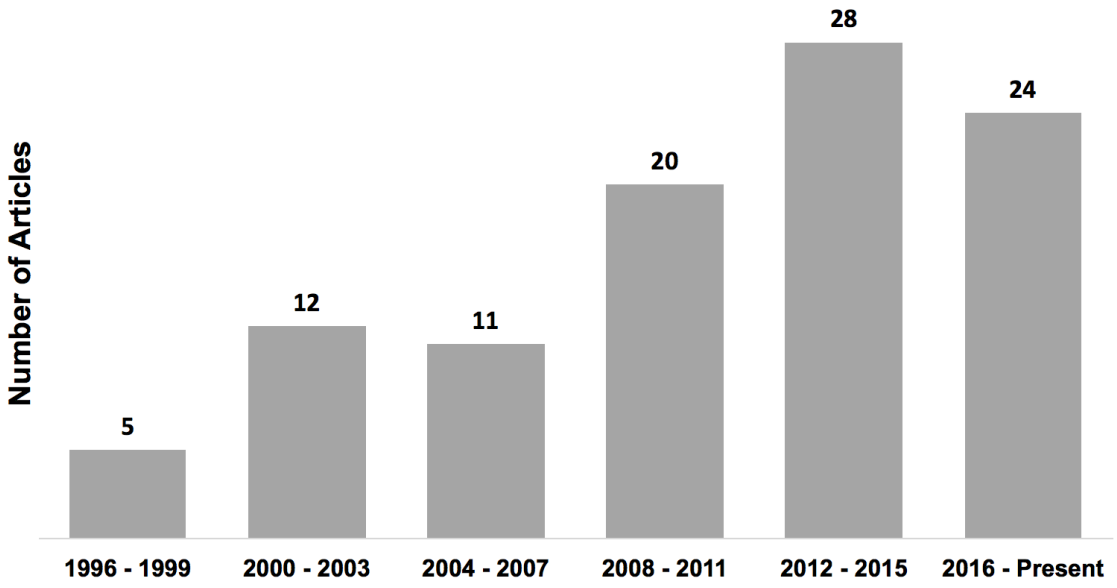

Figure 8. Number of articles included by publication year

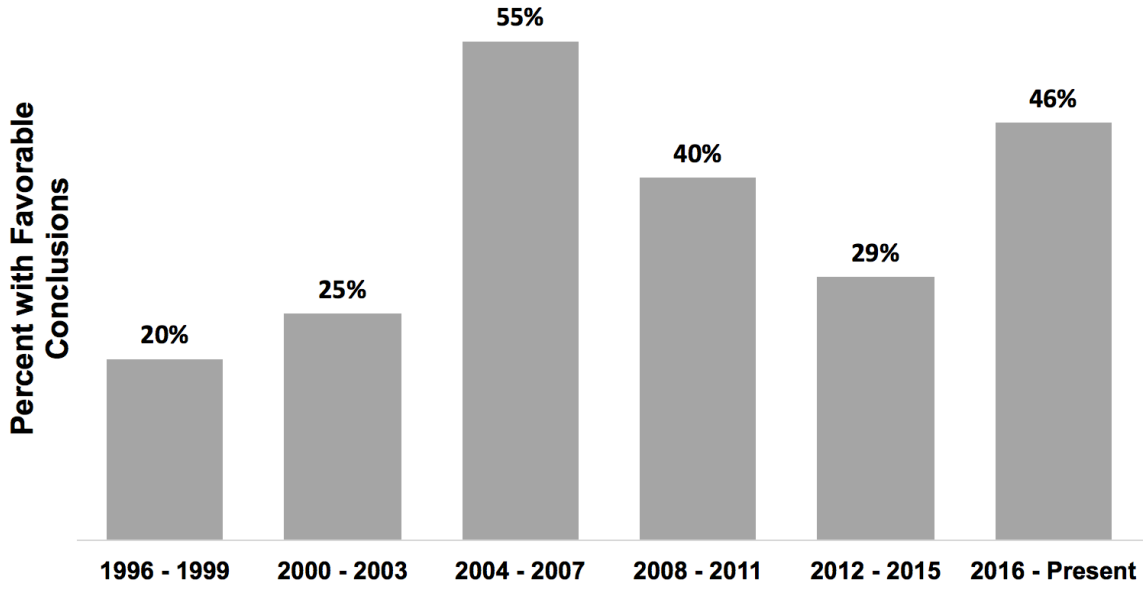

Figure 9. Percent of articles included reporting favorable conclusions by publication year

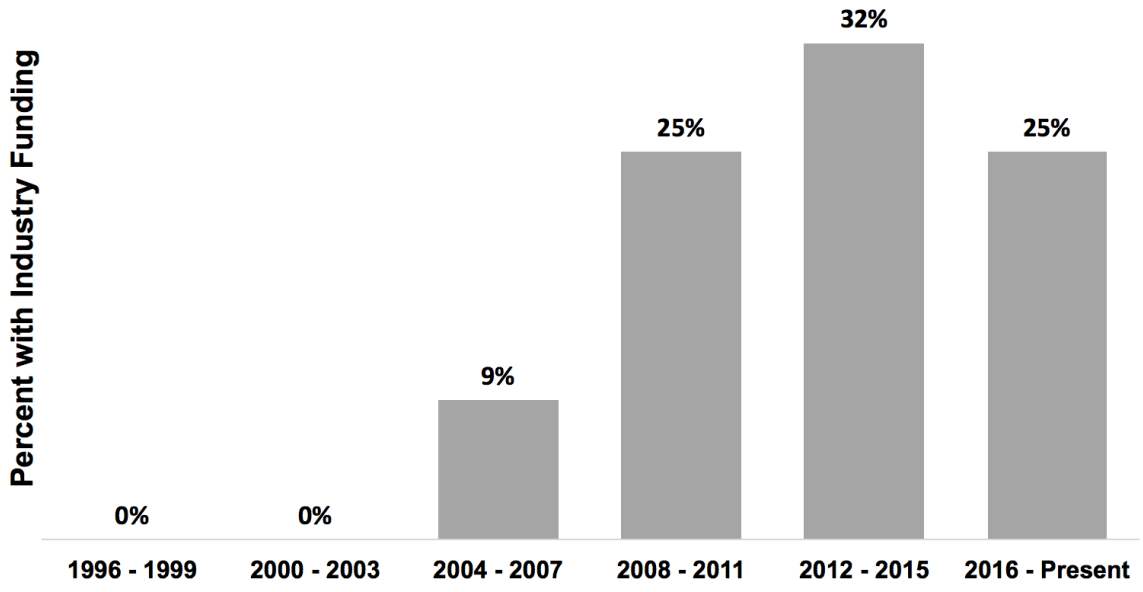

Figure 10. Percent of articles included with stated industry funding by publication year

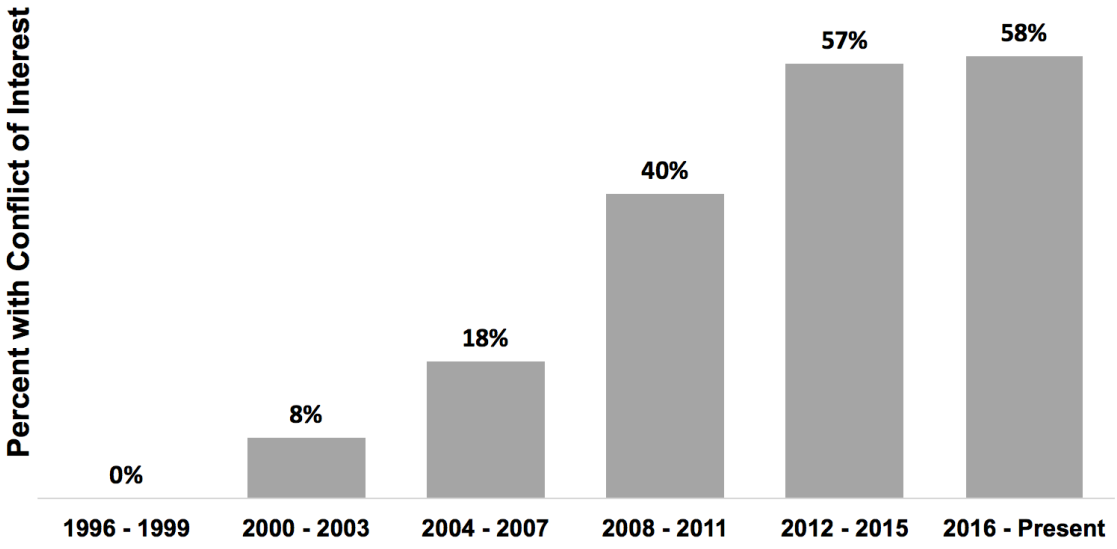

Figure 11. Percent of articles included with stated conflict of interest by publication year

Discussion

The main finding of this thesis is that food industry funding does not significantly affect conclusion favorability in nutrition-related scientific articles on foods high in saturated fat. While studies funded by the food industry or with conflict of interest appear to report more favorable conclusions, this trend is not significant. This is different from Lesser's findings that scientific articles on commonly consumed beverages funded entirely by industry are four to eight times more likely to be favorable to the financial interests of the sponsors. Lesser noted that his team could not be certain whether his findings are generalizable to all areas of nutrition[1]. This analysis suggests that Lesser's findings might not be translated to all nutrition studies.

This thesis also identified several secondary findings. First, there appear to be inconsistencies in results of studies related to saturated fat independent of the funding source. Second, industry antagonist funding from polyunsaturated fat companies may produce more unfavorable conclusions contributing to the inconsistent results. Third, industry funding and conflict of interest appear to be increasing over time.

Inconsistent Conclusions

This analysis suggests that there is a general variability in conclusions of saturated fat studies, independent of industry funding source. Of the 100 studies included, 37% of the conclusions were classified as favorable, 20% were classified as neutral and 42% were classified as unfavorable. This variation appeared regardless of funding source. In studies funded by the food industry, 37% of the conclusions were classified as unfavorable. This figure is similar to the 45% unfavorable conclusions in studies without industry. While there appears to be a slight trend in the food industry publishing studies with more favorable conclusions, the data analyzed in this

thesis do not suggest that this variability is significantly associated with funding source. Rather the varying conclusions could stem from the difficulties in isolating saturated fat and the methodological challenges in nutrition research.

The effects of saturated fatty acids are difficult to isolate; even when studies are meticulously designed randomized control trials. For example, one study included in this analysis compared the effects of polyunsaturated fatty acids with saturated fatty acids on liver fat, and inflammation and adipose tissue expression of inflammatory and lipogenic genes[43]. The study randomly assigned subjects to a diet high in polyunsaturated fats or saturated fats keeping the overall macronutrient balance constant. The polyunsaturated fat group received foods rich in n-6 linoleic acid including scones baked in sunflower oil, margarine, sunflower seeds, and sunflower oil. The saturated fat group received foods rich in saturated fatty acids including scones baked in butter. Despite being randomized and controlled, the effects of polyunsaturated fatty acids versus saturated fatty acids were not isolated. Sunflower oil is not purely polyunsaturated fatty acids - it can often contain up to 20% saturated fatty acids[44]. Likewise, butter is approximately 61% saturated fatty acids and 33% unsaturated fatty acids[44]. Because it is difficult to isolate saturated fatty acids, it is also difficult to measure their direct effects on metabolism and health outcomes. This difficulty exists regardless of whether a study is funded by the food industry or not. This could explain some of the inconsistencies in study conclusions.

Additionally, the difficulty with isolating the effects of saturated fatty acids is magnified in observational studies. For example, a study included in this analysis investigated the association of saturated fatty acids compared to unsaturated fatty acids and carbohydrates with fatalities from coronary heart disease[45]. The study administered food frequency questionnaires to 84,628 women and 42,908 men every four years. These food frequency questionnaires asked

how often participants had consumed specific foods in the past year. Participants were also asked to specify the types of fat or oil used for baking and frying. Similar to randomized control trials, no food is made up of purely unsaturated or saturated fatty acids. At the same time, these memory dependent questionnaires may not yield accurate results being that participants are providing estimates. The study's investigators even noted that the observational study could not prove causality. Further, the investigators explained that it is difficult to rule out residual confounding factors, despite careful control for these lifestyle factors (e.g., exercise, socioeconomic status, access to health insurance)[45]. The methodological challenges in isolating the effects of a single nutrient in observational studies might also explain the variation in conclusions among the studies analyzed.

The complex cellular and metabolic functions of saturated fatty acids likely add to the inconsistencies in conclusions. One review of the functions of saturated fatty acids claims that saturated fatty acids should no longer be considered a single group[4]. This review cites studies demonstrating that individual saturated fatty acids, such as myristic acid and stearic acid, each have different physiological and metabolic functions. For example, myristic acid is thought to regulate polyunsaturated fat bioavailability and stearic acid is thought stimulate secretion of lipoproteins involved in lipogenesis. It is argued that this variety in functionality demonstrates that saturated fatty acids should not be considered one group in terms of structure, metabolism and biological functions. The complex functions of saturated fatty acids might lead to different health outcomes in different individuals and in different environments.

Beyond the challenges specific to studying saturated fatty acids, there are several methodological challenges in all nutrition research. For one, it is difficult to gather the 'gold standard' of evidence as outlined by evidence-based medicine through nutrition research. In the

evidence-based medicine model, highest quality of evidence is gathered from the well-conducted and suitably powered multinational double-blind placebo-controlled randomized trial[46]. In this type of study, the control group is a placebo that allows participants, investigators and study staff to be blinded. In these studies, the data can demonstrate causality. While many clinical trials investigating pharmaceuticals and biologics can meet this gold standard, the same is not feasible for investigating macronutrients or specific foods. There is no believable 'placebo' for palm oil, coconut oil, butter or meat. Therefore, nutritional research often uses comparison groups in interventional studies. This was the case with many studies included in this analysis. For example, several evaluated the effects of olive oil versus coconut oil. These comparison groups make it difficult to isolate the effect of a single nutrient. For example, in the individuals that consumed olive oil, it is difficult to separate the effects caused by the addition of polyunsaturated fatty acids in olive oil or caused by the absence of saturated fatty acids in coconut oil.

Another challenge in nutrition research stems from the principle of energy balance in nutrition and metabolism. Assuming the body expends consistent energy to sustain life and perform physical work, caloric intake must remain constant to maintain body weight. Therefore, in most nutrition studies, when the intake of one nutrient is increased another nutrient is generally increased. This is not the same case in pharmaceutical research, where a clear dose-dependent relationship can be measured. Pharmaceutical products can be given in high doses without changing diet because consuming a drug does not increase calorie intake. This is not the same for consuming meat or dairy. For example, if someone is given a high-fat diet intervention (e.g., adding butter to their diet), the individual is likely to replace other nutrients such as carbohydrates (e.g., reduction of bread eaten). Thus, it is difficult determine whether changes from the baseline occur due to an increase in fat, a reduction in carbohydrates, or the two

combined. Overall, while industry funding and conflict of interest might influence the inconsistent conclusions on saturated fatty acids, methodological challenges are likely the greater factor.

Polyunsaturated Fat Industry Antagonism

Several of the studies included in this analysis were funded by companies that would benefit from distinguishing the health effects caused by polyunsaturated versus saturated fatty acids. Moreover, these companies would benefit from consumers replacing saturated fatty acids (e.g., butter) with polyunsaturated fatty acids (e.g., vegetable oils). Some of the industry antagonistic funding sources included Kewpie Corporation (soybean oil) and the California Walnut Commission. Of the 5 studies with industry antagonist funding, 100% reported conclusions classified as 'unfavorable' to saturated fatty acids, but 'favorable' to the products of the funding source. For example, California Walnut Commission would benefit from consumers choosing 'healthy' polyunsaturated fatty acids in nuts over 'unhealthy' saturated fatty acids fats in cheese. This thesis only included a small sampling of studies funded by companies' with interest in polyunsaturated fatty acids. Further research should be performed to better understand this relationship.

Rise in Conflict of Interest

This analysis found a trend in increasing conflict of interest and industry funding within nutrition studies over time. Likely contributing to this are the cuts in the NIH budget, now funding only 1 out of 6 grant applications - the lowest rate in NIH history[33]. Industry funding of nutrition research will likely continue to increase, therefore, researchers and journals should take precautions in order to ensure integrity of nutrition research.

This analysis identified cases that suggest the food industry sponsors research teams that have a record of publishing results favorable to the sponsor. For example, the meta-analysis performed by Siri Tarino et. al in January 2010 questioned the negative perception of saturated fat stated that none of the investigators had a conflict of interest[21]. However, in November 2010, the same team published a scientific commentary on saturated fatty acids. The disclosure statement, just ten months later, stated that one of the investigators, Dr. Krauss, received grants from the National Dairy Council, National Cattlemen's Beef Association, Robert C. and Veronica Atkins Foundation, and the National Institutes of Health[47]. Similarly, Dr. Siri-Tarino received a grant from the National Dairy Council[47]. This change in disclosure statements suggests that industry sponsors saw the potential for Siri-Tarino's team to publish research beneficial to their products, and began sponsoring follow-up research. Therefore, while industry sponsored research and conflict of interest might not be the cause of the variation of scientific conclusions, companies might strategically invest in research by investigators likely to publish results beneficial to the product of interest.

Methodological Strengths and Weaknesses

This thesis had several methodological strengths. First and foremost, this thesis modified the methods of Lesser's previously published paper and built follow-up research into the study. This allowed for a systematic methodological approach. This thesis used Lesser's study as a baseline model for data collection and took the analysis in a different direction. It built off substantial previous literature to investigate a different area of nutrition - saturated fatty acids as opposed to sweetened beverages - over a greater period of time. Additionally, this study was performed over a decade after the study by Lesser, therefore, many more studies disclosed

funding source and conflict of interest. Only 13 out of the 100 studies included in this analysis did not disclose funding source, whereas 95 of Lesser's 206 studies included did not disclose funding.

At the same time, this study had several methodological weaknesses. Unlike Lesser's study, this thesis was written with one investigator and without the consultation of a medical librarian. Therefore, conclusions and funding sources were classified with one, rather than two investigators' opinion. While the creation of a locked tab, randomly numbered spreadsheet helped mitigate potential biases, this analysis was missing a key secondary opinion. Lesser, on the other hand, required the agreement of two investigators for discrete 'favorable' and 'unfavorable' conclusion classifications, otherwise the conclusion would be classified as 'neutral'[1]. Additionally, this study looked at saturated fatty acids, rather specific food products. Lesser looked at juice, milk and soda. The search algorithm identified articles on both specific saturated fatty acids (e.g., palmitic acid, lauric acid) and food sources that are generally high in saturated fatty acids (e.g., dairy, butter). Therefore, there was a greater range of studies that were included in this thesis. Some studies measured the impact of specific saturated fatty acids on cholesterol levels. Other studies looked at the association between diets high in saturated fat and mortality using estimates with nutrition questionnaires. This range was exacerbated because saturated fatty acids exist in a variety of different food products and their effects are generally more difficult to isolate. For example, dairy products are high in dietary saturated fatty acids, but also high in micronutrients like calcium and vitamin D. Therefore, the effects of saturated fat on overall well-being is generally harder to isolate than the effects of consuming a sugary beverage. Finally, the sample included in this study might have obscured underlying relationships. Of the studies included, 21 were fully funded by the industry and 57 were not funded by the industry.

Since the number of studies in each category were not tracked during the collection, these figures were not known until after the data analysis. The sample of studies funded by the industry might have been too small to accurately represent the full population.

While Lesser's research provided a great baseline for the methods in this thesis, their work received some criticism. Professor Martijn B Katan at the Free University of Amsterdam writes that "an association between funding and outcome does not by itself prove bias"[48]. Katan notes that five of the papers included in Lesser's analysis that did not have industry funding dealt with outbreaks of food poisoning. This strengthened the correlation of unfavorable outcomes with the absence of industry funding. He also suggests that industry funding tends measure positive health outcomes and that there might be cancellation or delay in publication when the results are disappointing to the sponsor. Therefore, Katan argues that the relationship between industry funding and nutrition research conclusions goes beyond publicly available data. Katan disagrees with the general condemnation of industry-supported research[48]. He cites his own experience working on research sponsored by Unilever that discovered the effects of trans-fatty acids and a study sponsored by Nestle discovering the cholesterol-raising factor in unfiltered coffee. Despite this, using Lesser's methods as a baseline generally strengthened this thesis.

Implications and Future Directions

In the future, one could investigate the influence of industry funding in studies related to both sugar, as in Lesser's research, and dietary fatty acids. There is evidence that specific food industries sponsor research to point the blame at a potential substitute product. For example, a company that sells soda would benefit from the public perceiving fat as more harmful than sugar, as this could influence customers to choose a soda over a milkshake. Likewise, the meat industry

would benefit from the public perceiving high fat, low carbohydrate diets as better for weight loss. This way, more consumers might replace calories from carbohydrates with saturated fat.

There is evidence to suggest that industry antagonism from the sugar industry contributed to the negative perception of saturated fat. In fact, the Sugar Research Foundation played a key role in forming the diet-heart hypothesis. During the same time Ancel Keys identified total fat, saturated fat and cholesterol as a potential causal hypothesis for heart disease, another researcher championed sugar as a potential cause[49]. A recent historical review looked at records from the Sugar Research Foundation, and determined that the foundation initiated coronary heart disease research in 1965[50]. The SRF sponsored a review titled "Dietary Fats, Carbohydrates and Atheroslerotic Disease"[51]. The review concluded that the dietary intervention required to prevent coronary heart disease was reducing dietary cholesterol and replace saturated fat with polyunsaturated fat. This research downplayed early warning signals that sucrose consumption was a risk factor for heart disease and pointed the blame at saturated fatty acids. This suggests that the review sponsored by the Sugar Research Foundation played a key role in shaping public perceptions and influencing federal policy.

Food industry funding and conflict of interest might influence conclusion favorability across different nutrients and food products. Therefore, the relationship between food industry funding and scientific conclusions might be more complex that the relationship this thesis or any other research has identified. In the future, it could be interesting to look at overall industry dollar spending on scientific research across different food industries (soda, dairy, meat, oil) and public perception of the healthfulness of the products. The degree to which the food industry uses nutrition research as a product promotion strategy is unclear, and this thesis suggests that there might be variation across industries. For instance, the sweetened beverage industry that

Lesser investigated might sponsor more research than the Palm Oil Board, or other companies with a vested interest in the perception of saturated fatty acids.

At the same time, this study suggests that companies selling products high in saturated fat could be funding studies to point the blame back at sugars and complex carbohydrates. Several studies included in this thesis concluded that saturated fatty acids had favorable health outcomes when compared to carbohydrates. For example, one study investigated the impact of saturated fatty acids in butter and cheese heavy diets on LDL and HDL cholesterol concentrations. Diets high in polyunsaturated fats and carbohydrates were used as comparisons. The study concluded that saturated fatty acids have similar effects on HDL cholesterol to the other diets and that saturated fatty acids from dairy products have no significant effects cardio metabolic risk factors[52].

Therefore, studies with industry funding and conflict of interest should be evaluated critically before being used to inform dietary recommendations and health policy. Because the need for industry funding in nutrition funding is increasing, investigators, journals and policy makers should continue thinking up ways to ensure the integrity of scientific research.

Conclusion

Overall, this thesis did not uncover a statistically significant relationship between industry funding and favorability of conclusions in studies on foods high in saturated fat. However, the odds of a study performed by an investigator with a disclosed conflict of interest was 2.67 times more likely to report a favorable conclusion than those with no conflict of interest. Additionally, there were several secondary findings. Studies on saturated fat have inconsistent and conflicting conclusions independent of funding source, industry antagonistic funding studies be associated with more unfavorable conclusions on saturated fat and there appears to be a rise in food industry conflict of interest. More research should be performed to better understand conflict of interest in nutrition research. For the time being, nutrition-related scientific articles on saturated fatty acids should be critically evaluated before being used to inform dietary recommendations.

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Appendix

Title	Number Code	Author(s)	Year	Study Type (linked to 'Conclusion Classification')	Conclusion Text	Conclusion Classification (linked to 'Conclusion Classification')	Fat Source (linked to 'Conclusi
Palm Oil Consumption Increases LDL Cholesterol Compared with Vegetable Oils Low in Saturated Fat in a Meta-Analysis of Clinical Trials.	5662	Sun et. al	2015	Literature Review	Palm oil consumption re	Unfavorable	Palm Oil
					Results: Behenate oil pr		
Behenic Acid is a cholesterol raising saturated fatty	5852	Cater and Denke	2001	Interventional	Conclusions: Despite its	Unfavorable	Palm Oil
					Pooled relative risk estir		
Food Sources of Saturated Fat and the Association With Mortality: A Meta-analysis	5757	O'Sullivan et. al	2013	Literature Review	Associations varied by f	Neutral	Various
Effects of oils and solid fats on blood lipids: a syster	5732	Schwingshackl et. al	2018	Literature Review	The aim of this network	Unfavorable	Various
Palm olein increases plasma cholesterol moderatel	5845	Tholstrup et. al	2011	Literature Review	The current study did no	Favorable	Palm Oil
Effects of dietary palm olein on the cardiovascular r	5925	Lv. et al	2018	Interventional	Therefore, partial replac	Favorable	Palm Oil
					Results: During 14 y of		
Dietary saturated fats and their food sources in rela	5790	Hu et. al	1999	Observational	Conclusion: A distinctio	Unfavorable	Various
					Treatments resulted in s		
					Conclusions		Soybean Oil (low SFA,
Comparing effects of soybean oil- and palm olein-b	5927	Karupiah et. al	2016	Randomized Control Trial	Daily use with 20 g of lir	Unfavorable	PALM OIL AS CONTRC
Comparison of the impact of SFAs from cheese and butter on cardiometabolic risk factors: a randomized control trial	5847	Brassard et. al	2017	Randomized Control Trial	Conclusions: The result	Favorable	Dairy - butter and chee
Butter increased total and LDL cholesterol compared with olive oil but resulted in higher HDL cholesterol compared with a habitual diet.	5812	Engel and Tholstrop	2015	Randomized Control Trial	Conclusions: Moderate	Unfavorable	Butter
Multi-Country analysis of palm oil consumption and cardiovascular disease mortality for countries at different stages of economic development: 1980-1997	5849	Chen et. al	2011	Observational	Increased palm oil cons	Unfavorable	Palm Oil
					Compared with control		
Health effects of saturated and trans-fatty acid intake in children and adolescents: Systematic review and meta-analysis	5789	Morenga and Montez	2017	Literature Review	Advice to reduce satura	Unfavorable	Varies
Evidence of Health Benefits of Canola Oil	5785	Lin et. al	2013	Literature Review	Canola oil-based diets r	Unfavorable	Canola Oil (low SFA, hi SFA ad control)

Figure 11. A segment of the Raw Data Tab

The title, number code, authors, year, conclusion raw text, funding raw text and conflict of interest raw text (columns in navy) were entered into the spreadsheet.

='Raw Data '!F2

A	B	C	D
Number Code	**Study Type**	**Conclusion Text (linked to 'Raw Data')**	**Conclusion Classification (for saturated fat)**
5662	Literature Review	Palm oil consumption results in higher LDL cholesterol than do vegetable oils low i	Unfavorable
5852	Interventional	Results: Behenate oil produced mean concentrations of total cholesterol (5.87 ± 0. Conclusions: Despite its low bioavailability compared with oleic acid, behenic acid i	Unfavorable
5757	Literature Review	Pooled relative risk estimates demonstrated that high intakes of milk, cheese, yogu Associations varied by food group and population. This may be because of factors	Neutral
5732	Literature Review	The aim of this network meta-analysis (NMA) is to compare the effects of different	Unfavorable

Figure 12. A segment of the Conclusion Classification tab

The conclusion text (column in purple) showed the conclusion raw text from the Raw Data tab. From this text study type, conclusion favorability and saturated fat source (columns in navy) were classified. These categorizations linked back to the study type, conclusion classification and fat source (columns in purple) on the Raw data tab shown in Figure 11.

A	B	C
Number Code	**Funding Text (linked to 'Raw Data')**	**Funding Source**
5662	None	None
5852	Supported by NIH Endocrinology and Metabolism training grant 5 T32 OK07307 (to NBC), NIH-NIHLBI Clinical Investigator Award N	Nonindustry
5757	This study was supported by the National Health and Medical Research Council (grant 572742). We would like to thank Eve Blair, PhD, and Sonya Girdler, PhD, for sharing their knowledge on systematically reviewing literature an Note. T. O. S. was previously awarded a Dairy Innovation Australia grant (DHNC-MetX06-2011) separate to this project.	Nonindustry
5732	This work was supported by NutriAct–Competence Cluster Nutrition Research Berlin-Potsdam funded by the German Federal Minist	Nonindustry
5845	Supported by Malaysian Palm Oil Board, No. 6, Persiaran Institusi, Bandar Baru Bangi, Kajang, Selangor.	Industry
5925	We are grateful to the canteen of Capital Medical University for providing the diets. This work was supported by Mutual fund of the C	Mixed
5790	None	None
5927	This study was supported by a grant (NN-188-2010) received from Kewpie Corporation, Japan.	Industry
5847	Supported by grants from the Dairy Research Cluster Initiative (Agriculture and Agri-Food Canada, Dairy Farmers of Canada, the Ca	Industry
5812	Supported by the Danish Dairy Research Foundation. Butter was provided by Arla Foods, Denmark, and olive oil was provided by A	Mixed
5849	Dr. Chen was supported by the Walter S. Shorenstein Asia Pacific Research Center's Postdoctoral Fellowship in Comparative Healt	Nonindustry

Figure 13. A segment of the Funding Source and Conflict of Interest tab

The funding text and conflict of interest text (columns in purple), showed the respective raw texts from the Raw Data tab. From this, funding source and declared conflict of interest (columns in navy) were classified. These categorizations linked back to funding source and declared conflict of interest (columns in purple) on the Raw data tab shown in Figure 11.

The following 100 studies were included in the analysis:

Appel, L. J. *et al.* Effects of protein, monounsaturated fat, and carbohydrate intake on blood pressure and serum lipids: results of the OmniHeart Randomized Trial. (2005).

Ascherio, A. *et al.* Dietary fat and risk of coronary heart disease in men: cohort follow up study in the United States. (1996).

Astrup, A. Yogurt and dairy product consumption to prevent cardiometabolic diseases: epidemiologic and experimental studies. (2014).

Azadbakht, L., Mirmiran, P., Esmaillzadeh, A. & Azizi, F. Dairy consumption is inversely associated with the prevalence of the metabolic syndrome in Tehranian adults. (2005).

Berglund, L. *et al.* Comparison of monounsaturated fat with carbohydrates as a replacement for saturated fat in subjects with a high metabolic risk profile: studies in the fasting and postprandial states. (2007).

Bjermo, H. *et al.* Effects of n-6 PUFAs compared with SFAs on liver fat, lipoproteins, and inflammation in abdominal obesity: a randomized controlled trial. (2012).

Brassard, D. *et al.* Comparison of the impact of SFAs from cheese and butter on cardiometabolic risk factors: a randomized controlled trial. (2017).

Casas, R. *et al.* Long-Term immunomodulatory effects of a mediterranean diet in adults at high risk of cardiovascular disease in the PREvención con DIeta MEDiterránea (PREDIMED) randomized controlled trial. (2016).

Cater, N. B. & Denke, M. A. Behenic acid is a cholesterol-raising saturated fatty acid in humans. (2001).

Chen, B. K., Seligman, B., Farquhar, J. W. & Goldhaber-Fiebert, J. D. Multi-Country analysis of palm oil consumption and cardiovascular disease mortality for countries at different stages of economic development: 1980-1997. (2011).

Cheng, P., Wang, J., Shao, W., Liu, M. & Zhang, H. Can dietary saturated fat be beneficial in prevention of stroke risk? A meta-analysis. (2016).

Chiu, S., Williams, P. T. & Krauss, R. M. Effects of a very high saturated fat diet on LDL particles in adults with atherogenic dyslipidemia: A randomized controlled trial. (2017).

Chowdhury, R. *et al.* Association of dietary, circulating, and supplement fatty acids with coronary risk: a systematic review and meta-analysis. (2014).

Clarke, R., Frost, C., Collins, R., Appleby, P. & Peto, R. Dietary lipids and blood cholesterol: quantitative meta-analysis of metabolic ward studies. (1997).

de Oliveira Otto, M. C. *et al.* Dietary intake of saturated fat by food source and incident cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis1234. (2012).

de Souza, R. J. *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. (2015).

Dehghan, M. *et al.* Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): a prospective cohort study. (2017).

Engel, S. & Tholstrup, T. Butter increased total and LDL cholesterol compared with olive oil but resulted in higher HDL cholesterol compared with a habitual diet. (2015).

Ericson, U. *et al.* Food sources of fat may clarify the inconsistent role of dietary fat intake for incidence of type 2 diabetes. (2015).

Eyres, L., Eyres, M. F., Chisholm, A. & Brown, R. C. Coconut oil consumption and cardiovascular risk factors in humans. (2016).

Faghihnia, N., Mangravite, L. M., Chiu, S., Bergeron, N. & Krauss, R. M. Effects of dietary saturated fat on LDL subclasses and apolipoprotein CIII in men. (2012).

Fattore, E., Bosetti, C., Brighenti, F., Agostoni, C. & Fattore, G. Palm oil and blood lipid–related markers of cardiovascular disease: a systematic review and meta-analysis of dietary intervention trials. (2014).

Forouhi, N. G. *et al.* Differences in the prospective association between individual plasma phospholipid saturated fatty acids and incident type 2 diabetes: the EPIC-InterAct case-cohort study. (2014).

Forsythe, C. E. *et al.* Limited Effect of Dietary Saturated Fat on Plasma Saturated Fat in the Context of a Low Carbohydrate Diet. (2010).

Guasch-Ferré, M. *et al.* Total and subtypes of dietary fat intake and risk of type 2 diabetes mellitus in the Prevención con Dieta Mediterránea (PREDIMED) study. (2017).

Gillman, M. W., Cupples, L. A., Millen, B. E., Ellison, R. C. & Wolf, P. A. Inverse association of dietary fat with development of ischemic stroke in men. (1997).

Hamley, S. The effect of replacing saturated fat with mostly n-6 polyunsaturated fat on coronary heart disease: a meta-analysis of randomized controlled trials. (2017).

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Haub, M. D., Wells, A. M. & Campbell, W. W. Beef and soy-based food supplements differentially affect serum lipoprotein-lipid profiles because of changes in carbohydrate intake and novel nutrient intake ratios in older men who resistive-train. (2005).

He, K. *et al.* Dietary fat intake and risk of stroke in male US healthcare professionals: 14 year prospective cohort study. (2003).

Hooper, L., Martin, N., Abdelhamid, A. & Davey Smith, G. Reduction in saturated fat intake for cardiovascular disease. (2015).

Howard, B. V. *et al.* Low-fat dietary pattern and risk of cardiovascular disease: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. (2006).

Hu, F. B. *et al.* Dietary saturated fats and their food sources in relation to the risk of coronary heart disease in women. (1999).

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Huth, P. J., Fulgoni, V. L. & Larson, B. T. A systematic review of high-oleic vegetable oil substitutions for other fats and oils on cardiovascular disease risk factors: implications for novel high-oleic soybean oils. (2015).

Imamura, F. *et al.* Effects of saturated fat, polyunsaturated fat, monounsaturated fat, and carbohydrate on glucose-insulin homeostasis: a systematic review and meta-analysis of randomized controlled feeding trials. (2016).

Ivey, K. L. *et al.* Association between yogurt, milk, and cheese consumption and common carotid artery intima-media thickness and cardiovascular disease risk factors in elderly women. (2011).

Jakobsen, M. U. *et al.* Major types of dietary fat and risk of coronary heart disease: a pooled analysis of 11 cohort studies. (2009).

Jakobsen, M. U. *et al.* Intake of carbohydrates compared with intake of saturated fatty acids and risk of myocardial infarction: importance of the glycemic index. (2010).

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Khaw, K.-T. *et al.* Randomised trial of coconut oil, olive oil or butter on blood lipids and other cardiovascular risk factors in healthy men and women. (2018).

Kim, E. H. J. *et al.* Dietary Fat and Risk of Postmenopausal Breast Cancer in a 20-year Follow-up. (2006).

Kralova Lesna, I., Suchanek, P., Kovar, J., Stavek, P. & Poledne, R. Replacement of dietary saturated FAs by PUFAs in diet and reverse cholesterol transport. (2008).

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Li, Y. *et al.* Saturated Fat as Compared With Unsaturated Fats and Sources of Carbohydrates in Relation to Risk of Coronary Heart Disease: A Prospective Cohort Study. (2015).

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