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The Relationship between Dietary Fat and Fatty Acid Intake and Body Weight, Diabetes, and the Metabolic Syndrome

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Introduction

Since the 1994 Food and Agriculture Organization/World Health Organization expert consultant report on fats and oils in human nutrition, substantially more evidence of the association between dietary fat and obesity, the metabolic syndrome and diabetes has emerged. Despite this progress, the role of dietary fat in body weight regulation and metabolic disease remains controversial. Other than for essential fatty acids (FAs), there is no definite lower limit of dietary fat intake for adults. It has been shown that humans have a significant ability for de novo lipogenesis under appropriate conditions [Strawford et al., 2004]. However, for body weight regulation and the associated conditions of diabetes and the metabolic syndrome, the optimal amount and type of dietary fat has not been fully elucidated. When diets of varying composition are evaluated together, what has been seen is that adherence to the diet per se, regardless of the composition, predicts weight loss [Dansinger et al., 2005]. The study by Dansinger et al. [2005] and other similar data have led to recommendations that for weight loss up to a year, either a low fat or a low carbohydrate energy-restricted diet might be effective [American Diabetes Association, 2008]. On the other hand, the only studies showing prevention of disease outcomes such as diabetes or atherosclerosis regression used lower fat diets (<30%) [Tuomilehto et al., 2001; Diabetes Prevention Program Research Group 2002; Ornish, 2005]. However, it is impossible to draw final conclusions from these studies in that they do not have a higher fat control group, they often incorporated additional lifestyle interventions, and there is difficulty in maintaining the very low fat diets, which leads to high drop out rates. Despite the findings of post hoc analyses of these trials that show that adherence to a high fiber, low fat diet is the strongest predictor of weight loss and decreased risk of type 2 diabetes (T2DM) [Lindstrom et al., 2006a], unified recommendations are difficult and the public is left with mixed messages [Bravata et al., 2003]. This review will endeavor to provide an update of the literature from 1993 to the present with respect to the role of dietary fat and obesity, metabolic syndrome and diabetes. Data from cross-sectional, prospective cohort and interventional studies will be evaluated, and emerging data on the role of genetic regulation of the response to dietary fat will be presented.

Total Fat

Consistent with other national and international guidelines, the 'Dietary Guidelines for Americans' recommend 20–35% of total calories from fat. From a biological plausibility standpoint, fat is more energy dense and thus there is a higher risk of overconsumption. However, obesity rates have increased despite of decreasing intakes of fat

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[Troiano et al., 2000; Marantz, 2008], which suggests that factors other than dietary fat may play a more important role in the increasing prevalence of obesity.

Obesity and Body Weight

The strength of evidence from studies considering obesity and body weight is outlined below.

Cross-Sectional Population and Cross-Population Studies

The vast majority of cross-sectional and cross-population studies – performed with a variety of methodologies, in multiple countries and in various age groups over the last 15 years – continue to show a correlation between higher fat intake (usually reported as percentage of caloric intake, but often also as total fat intake) and increases in weight (table 1). Obvious limitations to this type of data include the use of self-reported intake data in the majority of studies, and the inability to draw causal conclusions from the data. However, the large sample sizes, as well as the overall consistency of results, supports the hypothesis that higher fat diets are associated with higher weight.

Prospective Cohort Studies

Large-scale trials that have repeated data, such as repeated cross-sectional studies and prospective cohort studies have yielded mixed results. Repeated data in Framingham studies found that for both men and women, total calories and percentage of calories from fat decreased from the cohorts sampled in the 1950s and 1960s to the 1984–1988 cohort, while the prevalence of excess weight increased [Posner et al., 1995]. Likewise, in the British National Diet and Nutrition Survey, dietary fat intake (as percentage of calories) has fallen while obesity rates have increased [Swan, 2004]. In the Framingham Offspring and Spouse Cohort, when examining diet type, it was only the 'empty calorie' diet type (which was still high fat) but not the high fat cohort per se that was associated with increased weight [Quatromoni et al., 2002]. In the Health Professionals Follow-Up study of over 16,000 men, a higher total fat consumption was associated with increases in waist circumference; however, after controlling for changes in BMI, the effect of total fat on waist circumference disappeared, whereas effects of specific FAs (notably *trans* FAs, described below in depth) remained [Koh-Banerjee, 2003].

Conversely, in the Pound of Prevention prospective cohort study, with annual measures over 3 years, there was a positive correlation between dietary fat (either as amount or percentage) and weight gain [Sherwood et al., 2000]. In the NHANES I follow-up study, there was a positive relationship between percentage of dietary fat intake and obesity, but only in men, and only after excluding morbidity [Kant et al., 1995]. On the other hand, the NHANES I follow-up showed an even stronger inverse association between percent fat energy and weight gain [Kant et al., 1995].

In a 6-year follow-up of Swedish women, when controlled for total energy intake, dietary fat intake was associated with increased weight, but only in the sub-population defined as 'predisposed' (i.e. overweight at baseline and with an obese parent) and not in lean women with an obese parent or overweight women with a lean parent [Heitmann et al., 1995]. The Nurses' Health Study has shown a weak relationship between baseline percentage of calories from fat and subsequent weight change, but this change is such that the clinical significance is uncertain [Field et al., 2007a]. Interestingly, in the Nurses' Health Study, there was no clear association with those 'predisposed' to obesity; however, there was a stronger relationship between dietary fat and weight gain among overweight women [Field et al., 2007a].

In the diets of children and adolescents, using data from NHANES III and comparing to prior national surveys, the percentage of total fat had decreased during the 1990s [Troiano et al., 2000]. Similarly, a 1-year follow-up of children aged between 9 and 14 years at baseline found no significant effect of energy-adjusted dietary fat on weight [Berkey et al., 2000]. However, in a younger population (and with a much smaller sample size of only 70 children), Skinner et al. [2004] found that fat intake (and protein intake) in children aged between 2 and 8 years was a positive predictor of BMI at 8 years of age.

In summary, of the prospective cohort studies, the strengths include sample size (from 70 to over 41,000 participants) and their prospective nature as well as long duration and, as such, they are able to evaluate more chronic effects of diet. They are still limited by self-reported intake. Although many studies do show a positive relationship between dietary fat intake and weight gain, these data are overall inconclusive on the relationship between dietary fat and body weight.

Interventional Trials

Many smaller intervention studies examining the effect of dietary composition on weight loss have found that the lower carbohydrate, higher fat diets (based on the Atkins™ diet which is designed around limitation of dietary carbohydrate) often lead to more weight loss than either low fat or more traditional weight loss diets [Bravata et al.,

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Table 1. Recent studies that have considered the relationship between fat intake and weight gain

Population	n	Findings	Reference
Hispanic and non-Hispanic white women (Four Corners Breast Cancer Study)	871 Hispanic + 1,599 non-Hispanic	In non-Hispanic whites, fat as percent of energy intake associated with overweight and obesity; no association in Hispanics	Murtaugh et al., 2007
Adult men (Prostate Cancer Prevention Trial)	15,266	Total energy and energy from fat associated with obesity (31.4% in normal BMI to 34.3% in obese)	Satia-About, 2002
Iranians 10+ years old (Tehran Lipid and Glucose Study)	1,300	Energy intake from fat was positively associated with BMI in males of all ages and females of all ages, except from 10 to 18 years	Mirmiran et al., 2006
US- and Korea-born women of Korean descent	492	Obesity: 31.4% in US born and 9.4% in Korean born; US born had higher intakes of total fat and fat as percent of kcal	Park et al., 2005
South African urban (THUSA)	1,854	Migration from rural to urban increased percent energy from fat and protein and increased overweight and obesity	Vorster et al., 2005
Adults (Continuing Survey of Food Intakes by Individuals)	4,539 total, 1,932 'plausible'	Total fat (as percent of energy) associated with BMI in men and women in total sample, men only in plausible sample	Howarth et al., 2005
Japanese immigrants to Brazil aged 40–70 years	530	Obese and those with central adiposity consumed higher percentage of fat and lower percentage of carbohydrate; second generation only: total energy and all macronutrients significantly associated with BMI	Ferreira et al., 2002
Children and adolescents aged 4–16 years	181	Obese consumed more total calories, total fat (g), and saturated fat (g); total calories had the strongest influence	Gillis et al., 2002
Children aged 6–7 years	1,112	Cities with overweight and obesity also had increased intakes (by percent of calories) of fat, saturated fat and sugars	Rodríguez-Artalejo et al., 2002
Prepubertal children, obesity prone, obesity resistant and obese	114	Linear trend for percent fat and increased risk of obesity; percent fat related to body fat	McGloin et al., 2002
Middle-aged men (Seven Countries Study)	12,763	No correlation with fat (g/day) and BMI or skinfolds	Kromhout et al., 2001
Chinese adults aged 20–59 years (China Health and Nutrition Surveys)	5,783	Energy density associated with energy intake and overweight; fat was not a predictor of overweight	Stookey, 2001
African American vs. European American women	46 European + 44 African	More European Americans were overweight who used excessive fat; more African Americans were overweight who used appropriate fat	Cook et al., 2000
Women aged 25–64 years in India	3,212	Excess intake of fat weakly associated with central obesity	Singh et al., 1998
Cohorts (normal, over weight/ obese, severe obese)	150	Total fat (g/1,000 kcal) higher in severe obese, also higher SFA, MUFA and PUFA as a percent; energy intake was not associated with BMI	Alfieri et al., 1997
Children aged 9–10 years	262	Energy intake correlated with adiposity by skin folds, % of fat intake also correlated with adiposity	Tucker et al., 1997
Insulin Resistance and Atherosclerosis Study	1,173	Percent fat intake associated with insulin sensitivity and BMI; total fat (g/day) associated with insulin sensitivity in obese but not non-obese, consistent among fat sub-types	Mayer-Davis et al., 1997
Dietary and Nutrition Survey of British Adults, only LF (<35% fat) and HF (>45% fat) cohorts	134 LF + 191 HF	HF group ate more of all nutrients than the LF group; not all in HF were obese	Macdiarmid et al., 1996
Healthy men in Utah, USA, aged 21–71 years	203	Carbohydrate inversely associated with body fat (after control for energy intake), energy intake positively related to body fat; higher dietary fat in most obese	Nelson and Tucker, 1996
White and Native American children aged 4–7 years	56 white 15 Mohawk	Fat intake adjusted for non-fat intake; correlation between fat intake and fat mass in boys but not in girls after adjustment for physical activity energy expenditure	Nguyen et al., 1996
Spanish adolescents aged 15–17 years; overweight/obese vs. normal weight	64	Overweight/obese had greater proportion of energy from fat and protein but no differences in total energy intake	Ortega et al., 1995
Girls in the NHLBI Growth and Health Study aged 9–10 years	2,379	Black girls: percent energy from SFA helped explain BMI and skinfold adiposity variation; white girls: percent energy from total fat helped explain variation	Obarzanek et al., 1994
Normative Aging Study	878 males	SFA correlated with BMI, abdominal obesity and insulin level	Ward et al., 1994

LF = Low fat; HF = high fat; SFA = saturated fatty acids; MUFA = monounsaturated fatty acids; PUFA = polyunsaturated fatty acids.

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2003; Foster et al., 2003; Dansinger et al., 2005; Gardner et al., 2007]. A meta-analysis of randomized controlled trials of low carbohydrate diets (<60 g carbohydrate per day) without energy restriction versus low fat diets (<30% of total calories from fat) with energy restriction revealed greater weight loss at 6 months for the low carbohydrate diets, although there was no significant difference at 1 year [Nordmann et al., 2006]. It should be noted that the excess weight loss in the low carbohydrate diets has been attributed to a greater caloric reduction, and that the difference in weight loss is greatest at 6 months; by 1 year the significant differences in weight are often lost [Foster et al., 2003; Dansinger et al., 2005]. Finally, a recent 2-year randomized trial of low carbohydrate, Mediterranean, or low fat diets showed greater weight loss with the low carbohydrate and Mediterranean diets [Shai et al., 2008]. Limitations of these studies include the lack of specific comparison of dietary fat as the low carbohydrate diets are also higher in protein, and there is often a high attrition rate [Foster et al., 2003; Shai et al., 2008].

Data from a recent very large (over 48,000 participants) intervention trial, the Women's Health Initiative (WHI), are supportive of a connection between lower fat intake and weight loss. This study was performed in cohorts to evaluate prevention of cancer and cardiovascular disease, and thus cohorts were prescribed a low fat diet but not with the intention of weight loss. Nonetheless, the low fat cohorts had significantly, albeit modestly, greater weight loss at 3–6 years of intervention (with a difference between groups of 0.8–1.3 kg) [Beresford et al., 2006; Howard et al., 2006; Prentice et al., 2006]. However, the aim of the intervention was prevention of cancer with no focus on caloric restriction or weight loss, and the participants were encouraged to maintain their body weight [Howard et al., 2006]. The weight loss can therefore be regarded as unintentional, and brought about by the ability of the low fat diets to reduce caloric intake per se, without any attempt to do so. However, the intervention group received a much greater intensity of intervention than did the control group, making these results less robust, and therefore the conclusion is supportive but certainly not sufficient to make a definitive conclusion.

In the Women's Health Trial Feasibility Study in Minority Populations, a prospective randomized trial that evaluated the effect of diet change and change in weight over 1 year in 351 control and 575 intervention participants, overall lowering of dietary fat and total energy intake resulted in greater weight loss. However, the only consistent predictor of weight loss was an increase in carbohydrate consumption [Bhargava and Guthrie, 2002].

A systematic review of dietary weight loss controlled trials suggests low fat calorically restricted diets are associated with significant and sustained weight loss; however, the control groups in the reviewed studies are not well matched, making specific conclusions on the role of total fat per se impossible [Avenell et al., 2004]. Although a few meta-analyses have been performed regarding the effects of total dietary fat on body weight, they have yielded mixed results. A meta-analysis of 16 trials comparing ad libitum low fat diet to habitual diet or moderate fat diet ad libitum found that a reduction in dietary fat without a prescribed restriction in calories resulted in more weight loss where the group difference was 3.2 kg (95% CI 1.9–4.5 kg) [Astrup et al., 2000]. This meta-analysis only included studies that compared low fat ad libitum diets with a control group consuming a habitual diet or a medium fat diet. The low fat diets produced a mean fat reduction of 10.8% with no change occurring in the control groups, and the percent fat did not differ between the groups at baseline. A more recently reported meta-analysis of 5 trials (n = 447 subjects) comparing the effect of low carbohydrate diets (without energy restriction) to low fat diets (with energy restriction) found no difference in weight loss between the 2 treatments after 1 year, although the low carbohydrate diets were more effective at 6 months (weighted mean difference 3.3 kg) [Nordmann et al., 2006].

With respect to weight maintenance after weight loss, the National Weight Control Registry using self-reported data, reports those maintaining a weight loss are eating a diet that is on average 24 ± 9% (SD) fat [Klem et al., 1997]. Dietary fat intake has been shown to correlate with weight regain in the 3 years following a weight loss intervention [Leser et al., 2002]. Other, prospective randomized studies have shown an ad libitum, low fat, high carbohydrate diet to be superior to a fixed energy intake for maintaining weight after a major weight loss [Toubro and Astrup, 1997]. At least one randomized trial comparing the effects of fat intake on weight regain has demonstrated lower weight regain in those randomized to the low fat diet, due to a lower total energy intake [Donnelly et al., 2008]. However, another study, which was quasi-experimental in design, showed that middle-aged adults had similar weight maintenance after weight loss using either a low fat or a high fat diet [Lecheminant et al., 2007].

Thus, the data from intervention studies are again inconsistent and therefore inconclusive on the role of total fat and weight regulation. Studies comparing the Atkins diet to other diets (with percentage of fat being the primary difference) and similar overall intensity of intervention tend to show a greater weight loss than lower fat

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diets. However, the differences in other macronutrients, and the high drop out rate limit these results. Larger intervention studies suggest lower dietary fat is associated with weight loss; however, the studies were not designed specifically to examine dietary fat and weight, and thus differences in intervention intensity make it impossible to make definitive conclusions from these results. Systemic studies of trials and meta-analyses do suggest lower fat calorie-restricted diets are associated with more weight loss, although these likewise are limited by the design of included studies. The data are too limited to make conclusions on weight maintenance. Thus, there is insufficient evidence around the relationship between total fat intake and body weight.

The results are not entirely unified and there are multiple possible explanations for this discrepancy. One major limitation is in determining the dietary composition. Most studies have used questionnaire evaluations of food intake, which is a methodology fraught with significant challenges, not least of which is under-reporting of both total intake and specific macronutrient intake, which increases as weight increases. Another consideration rarely accounted for is baseline physiological status or genetic variation. For example, some studies have shown that when participants are stratified by baseline insulin sensitivity, those that are more insulin resistant tend to lose more weight on a higher fat diet than those who are more insulin sensitive [Cornier et al., 2005; Ebbeling et al., 2007]. In addition, genetic variations such as those of the APOA5 gene [Corella et al., 2007] and carnitine palmitoyltransferase I [Robitaille et al., 2007] have been shown to interact with dietary fat intake to result in differences in weight.

Metabolic Syndrome

One way to evaluate the effect of dietary fat on treatment of insulin resistance is to use the data evaluating various interventions on the prevention of diabetes in those at risk. There have been at least 5 randomized studies and 2 meta-analyses that show that with lifestyle intervention including low fat diet (<30%), activity, and sometimes modest weight loss there is an overall 50% reduction in the incidence of diabetes in high risk individuals. In a post hoc analysis of the Finnish Diabetes Prevention Study, the low fat and high fiber portion of the intervention was found to be a significant predictor of both weight loss and prevention of progression to diabetes [Lindstrom et al., 2006b]. Although impossible to make definitive conclusions on the effect of dietary fat specifically based on these studies (as they do not directly compare fat and they are all part of a multifaceted intervention), these studies are consistent in that a lower fat diet was part of all interventions leading to the definitive outcome of diabetes prevention.

As noted above, several weight loss studies have suggested that participants with insulin resistance lose more weight on a higher fat diet [Cornier et al., 2005; Ebbeling et al., 2007], although other studies have found that in insulin resistant subjects, weight loss was similar when energy restriction was similar, regardless of percentage of dietary fat [McLaughlin et al., 2006]. There are noted genetic variations, for example, the insulin response to test meals of varying fat content varies with polymorphisms in the intestinal FA binding protein [Pratley et al., 2000].

Diabetes

The role of dietary advice in diabetes goes beyond weight regulation and must also incorporate changes in blood pressure, lipids, glycemic control, and other factors associated with risk for macrovascular outcomes. For a thorough review of the literature on the dietary advice in the treatment of diabetes, examination of the Cochrane review is recommended [Nield et al., 2007]. The summary conclusions by the authors of this review were that there were insufficient data to carry out any type of a meta-analysis, and that the only conclusion that could be drawn was that the addition of exercise improved outcomes at 6 months and 1 year [Nield et al., 2007].

Saturated Fats

The 'Dietary Guidelines for Americans' recommend that <10% of total calories should come from saturated fat (SFA). The primary purpose for limiting SFA has traditionally been with respect to improvements in dyslipidemia and decreasing the incidence of atherosclerotic vascular disease, and this is beyond the scope of this review relating to weight regulation and dietary fat intake.

Obesity and Body Weight

Several types of studies have examined obesity and body weight. These are outlined below.

Cross-Sectional Population and Cross-Population Studies

When cross-sectional studies examine fat subtypes including SFA, the data are overall consistent in showing an increase in obesity with an increase in SFA intake (see table 1 for specific study details). Again, it is not possible to draw causal relationships using these studies.

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Prospective Cohort Studies

Similar to data on total fat, using data from NHANES III and comparing them to prior national surveys, the percentage of SFA had also decreased in the 1990s [Troiano et al., 2000]. However, with respect to SFA specifically, Krachler et al. [2005] from Sweden found that despite significant decreases in SFA intake, obesity rates increased. Conversely, the Nurses' Health Study has shown a relationship between baseline percentage of calories from SFA and subsequent weight change [Field et al., 2007b].

Interventional Trials

The Women's Healthy Lifestyle Project Clinical Trial showed that reducing SFA consumption helped prevent weight gain through menopause, however, like most other studies including the WHI, this was part of a multifactorial intervention and the control group was assessment only [Kuller et al., 2001]. When examining intervention trials, it is important to consider the composition of the comparison or control diet. Thus, when a diet high in SFA is compared to a diet high in monounsaturated fatty acids (MUFAs), the MUFA diets have been shown to have an advantageous effect on body composition [Piers et al., 2002]; however, other studies have not demonstrated a similar effect [Christiansen et al., 1997; Clifton et al., 2004; Pelkman et al., 2004].

Metabolic Syndrome, Insulin Resistance and Diabetes

The lack of long-term data on dietary fat (including subtypes) and weight regulation with diabetes is discussed in the Cochrane review referenced above. A relationship between insulin resistance as measured by insulin levels and dietary SFA independent of obesity in men with coronary artery disease was shown by Maron et al. [1991]. In acute studies, SFA ingestion but not ingestion of monounsaturated fatty acids (MUFA) or polyunsaturated fatty acids (PUFAs) resulted in decreases in insulin sensitivity [Xiao et al., 2006]. A few studies have demonstrated that substituting SFA with n–6 PUFA improved directly measured insulin sensitivity [Heine et al., 1989; Summers et al., 2002]. In patients with T2DM, 6 weeks of a diet high in SFA versus a diet high in MUFA resulted in increases in insulinemia without changes in weight or glycemic control [Christiansen et al., 1997].

In summary, as all the evidence points to a negative effect of SFA on weight and insulin resistance, it is probable that SFA are deleterious and thus should be limited in intake. A large, well controlled randomized trial would be needed to make a definite conclusion.

Monounsaturated Fats

The primary dietary sources of MUFAs are vegetable oils (such as olive oil, canola oil, peanut oil, sunflower oil and sesame oil), avocados, nuts and seeds. It has been suggested that chain length, chemical structure, degree of unsaturation, and position and configuration of double bonds of different FAs cause differences in their rates of deposition and oxidation [Moussavi et al., 2008]. In the case of MUFAs, it has been proposed that increasing MUFA intake increases diet-induced thermogenesis and stimulation of the sympathetic nervous system [Moussavi et al., 2008]. However, a controlled 24-hour calorimetry study does not support any major difference in energy expenditure between a high MUFA and a low fat diet [Rasmussen et al, 2007]. Interest in the protective effect of a high MUFA diet stemmed from studies that demonstrated that regions with high intakes of MUFA also had low rates of death attributed to coronary heart disease (CHD) [Keys et al., 1986]. These seminal studies demonstrated that populations consuming a high MUFA diet had low levels of cholesterol despite a diet that was high in total fat (33–40% of total calories) but low in SFA (7–8% of calories). The primary source of MUFA in these diets, the so-called Mediterranean diets, is olive oil, of which the primary FA is oleic acid. Although the mechanisms are not entirely clear, it is believed that oleic oil provides protection against CHD through its effects on blood lipids or its antioxidant capacity, but data also suggest that MUFAs decrease platelet aggregation [Sirtori et al., 1986] and increase fibrinolysis [Lopez-Segura et al., 1996].

Obesity and Body Weight

There is insufficient evidence regarding the effect of MUFAs on body weight. Among cross-sectional studies, some studies showed a positive association between MUFA consumption and risk of obesity [Doucet et al., 1998] and others have observed no association [Trichopoulou et al., 2002, 2005; Bes-Rastrollo et al., 2006; Sanchez-Villegas et al., 2006]. In the Nurses' Health Study, there was no difference in BMI at baseline across tertiles of MUFA intake [Hu et al., 1997]. Studies of the effects of increasing MUFA on body weight are few and have yielded mixed results. In a recent well-designed study using an energy-restricted Mediterranean dietary plan that included MUFA, both the Mediterranean and high fat diet showed superior weight loss compared to the low fat diet [Shai et al., 2008]. In contrast, another recent study showed no differences in weight regain or fat regain between a MUFA diet, a low fat diet and a control diet over 6 months [Due et al., 2008]. How-

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ever, the sample size in this latter study was small (n = 46) and the percentage of total fat intake was high (30–45% of total intake). Some evidence suggests that a diet rich in MUFA results in less fat deposition than a diet high in SFA [Piers et al., 2002], but this finding is not universal [Christiansen et al., 1997; Clifton et al., 2004; Pelkman et al., 2004]. There is also some evidence that a diet high in MUFA conserves lean mass when energy intake is restricted [Clifton et al., 2004], but again, other studies find no differences [Due et al., 2008]. It is interesting to note that the amount of MUFAs and n–3 FAs in adipose tissue are inversely related to central obesity in humans, whereas the association with PUFAs is positive [Garaulet et al., 2001].

Metabolic Syndrome

There is probable evidence for a beneficial effect of high MUFA intake on the components of the metabolic syndrome. Evidence from several large epidemiological studies has demonstrated an inverse relationship between MUFA intake and risk of CHD [Gillman et al., 1997; Hu et al., 1997; Panagiotakos et al., 2002; Trichopoulou et al., 2003] and ischemic stroke [Hu et al., 1997; Trichopoulou et al., 2003]. In addition, a recent meta-analysis concluded that diets high in MUFAs are associated with lower blood pressures when compared to high carbohydrate, low fat diets [Shah et al., 2007]. Evidence from intervention studies suggest that exchanging dietary SFA with MUFA (primarily in the form of olive oil) lowers low-density lipoprotein (LDL) cholesterol [Rivellese et al., 2003; Shai et al., 2008], lowers triglyceride [Grundy, 1986; Kris-Etherton et al., 1999], reduces post-prandial lipemia [Thomsen et al., 1999], lowers blood pressure [Alonso and Martinez-Gonzalez, 2004; Rasmussen et al., 2006; Shai et al., 2008], improves endothelial function [Mata et al., 1997; Carluccio et al., 1999; Serrano-Martinez et al., 2005], and reduces inflammatory markers [Chrysohoou et al., 2004; Shai et al., 2008]. The evidence regarding the effects on high-density lipoproteins (HDL) are mixed, with some studies showing an increase when SFA are substituted with MUFA [Martinez-Gonzalez and Bes-Rastrollo, 2006; Shai et al., 2008], but others showing that HDL are maintained [Grundy, 1986]. The maintenance of HDL levels would still be considered to have a beneficial effect against CHD.

Diabetes

There is insufficient evidence regarding the effects of MUFAs on diabetes.

Very few studies have considered the effects of MUFA intake on diabetes risk or markers of glucose metabolism. A few studies have demonstrated that diets high in MUFAs promote improvements in indexes of insulin sensitivity [Perez-Jimenez et al., 2001; Vessby et al., 2001; Esposito et al., 2004; Paniagua et al., 2007; Due et al., 2008]. In the recent study of Shai et al. [2008], among the subjects with diabetes, changes in fasting glucose, fasting insulin and insulin sensitivity assessed using the HOMA model were more favorable in those assigned to the energy-restricted Mediterranean diet than those assigned to either the energy-restricted low fat or energy-restricted low carbohydrate diets. In those without diabetes, fasting insulin decreased in all groups, but there were no significant changes in fasting glucose in any group. How the composition of dietary FAs influence insulin action is not completely understood, but it is believed that the composition of FAs in cell membranes affects cellular functions [Storlien et al., 1996].

n–3 Polyunsaturated Fatty Acids

The major classes of dietary n–3 FAs are long-chain FAs [eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)] derived from cold-water fish (e.g. salmon, mackerel) and the shorter-chain α-linolenic acid (ALA) derived from plant sources (e.g. flaxseed and nuts including almonds). Although a substantial body of literature discussing the effects of n–3 FAs exists, ALA has been less well studied. Thus, our summary is primarily limited to the effects of n–3 FAs. The cardioprotective effects of n–3 FAs are believed to be derived from its anti-arrhythmic, anti-thrombotic, anti-hypertensive, and anti-inflammatory effects. They are also believed to improve endothelial function, decrease triglycerides, and possibly slow the growth of atherosclerotic plaques [Balk et al., 2006; Giugliano et al., 2006].

Obesity and Body Weight

There is insufficient evidence regarding the effect of n–3 on body weight. Very few studies have considered the effects of n–3 PUFAs on body weight. A negative association between fish oil intake and BMI has been reported in a British cross-sectional study [Williams et al., 2000]. Some studies report that fish oil induces weight loss in humans [Couet et al., 1997; Krebs et al., 2006; Kunesova et al., 2006] but others do not [Awad et al., 1990]. One study reported enhanced weight loss in women on an energy-restricted diet supplemented with fish oil compared to the non-supplemented group [Kunesova et al., 2006]. Another study found that addition of fatty fish or fish oil

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to an energy-restricted diet induced greater weight loss in men, but not in women [Thorsdottir et al., 2007]. The mechanism via which high intake of n–3 PUFAs may decrease deposition of fat is not known.

Metabolic Syndrome

There is probable evidence for a beneficial effect of n–3 PUFAs on the components of the metabolic syndrome, and there is convincing evidence that n–3 PUFAs decrease triglycerides and improve blood pressure. A recent systematic review concluded that fish oil consumption results in a decrease in triglycerides, increases in HDL and LDL cholesterol, and has no effect on total cholesterol [Balk et al., 2006]. An increase in fish oil intake of 1 g/day was associated with an 8 mg/dl decrease in triglycerides, but the effects were greater (19 mg/dl) in those individuals with higher baseline triglycerides. Evidence suggests that reduced risk of CHD and sudden cardiac death occur at a dose of approximately 250 mg/day EPA/DHA [Mozaffarian and Rimm, 2006]. Another recent systematic review concluded that consumption of n–3 FA from fish or fish oil supplements, but not ALA, reduces the risk of all-cause mortality, cardiac and sudden death, and possibly stroke [Wang et al., 2006]. Only 1 trial has directly compared the effects of ALA and fish oil, but there are concerns about the validity of these results [Wang et al., 2006]. However, some studies have shown lower rates of CHD with higher intakes of ALA [Baylin et al., 2003]. The evidence for benefits was stronger in secondary rather than primary prevention trials, but this was driven by the results of 1 large randomized controlled trial [Wang et al., 2006]. A very recent cross-sectional study of 5,488 adults reported that intake of n–3 PUFA is inversely related to subclinical atherosclerosis as measured by common-carotid intima thickness [He et al., 2008]. Another systematic review concluded that fish oil consumption is associated with a reduction in both systolic and diastolic blood pressure [Geleijnse et al., 2002]. The effects of fish oil on inflammation, thrombosis and endothelial function are not conclusive [Balk et al., 2006].

Diabetes

There is insufficient evidence regarding the effects of n–3 FAs on diabetes.

Very few studies have considered the effects of n–3 FA intake on diabetes risk or markers of glucose metabolism. A systematic review concluded that fish oil consumption has small effects on fasting glucose and HbA_{1c} [Balk et al., 2006]. The only trial to directly determine the effect of n–3 FA on insulin sensitivity showed no effect [Vessby et al., 2001], and there is some evidence that high doses of n–3 FAs impair insulin action in subjects with T2DM [Mostad et al., 2006].

n–6 Polyunsaturated Fatty Acids

The primary dietary sources of n–6 PUFAs are safflower, sunflower and corn oils. Linoleic acid (LA) accounts for the majority of n–6 FAs in the diet.

Obesity and Body Weight

There is insufficient evidence regarding the effect of n–6 FAs on body weight. Studies of the effects of n–6 FAs on body weight are limited. In the Nurses' Health Study, there was no difference in BMI across tertiles of PUFA intake [Hu et al., 1997]. In contrast, a recent review has presented data from both animal and human models suggesting that increased n–6 PUFA intake is associated with an increased adipose tissue development [Ailhaud et al., 2006]. We are not aware of any intervention study that has directly assessed the effects of n–6 PUFA intake on body weight.

Metabolic Syndrome

There is possible evidence of the effect of n–6 FAs on the components of the metabolic syndrome. The specific effects of n–6 FAs have been less well studied than the effects of n–3 FAs. A high LA intake is associated with a lower risk of CHD [Shekelle et al., 1981; Hu et al., 1997; Sacks and Katan, 2002]. There is evidence that increasing the intake of n–6 FAs reduces the risk of CHD [Dayton and Pearce, 1969; Leren, 1970; Turpeinen et al., 1979], but all of these trials were performed prior to 1980. A meta-analysis by Mensink and Katan [1992] demonstrated that replacement of SFA with PUFA reduced total cholesterol and raises the HDL to LDL ratio. The results were confirmed in a recently reported meta-analysis that showed that, compared to carbohydrate, a high PUFA diet (which is primarily LA) reduces LDL, increases HDL, and reduces triglycerides [Mensink et al., 2003]. n–6 FAs have anti-inflammatory properties [De Caterina et al., 2000; Sacks and Campos, 2006], and higher intakes of n–6 FAs are associated with lower plasma levels of inflammatory markers [Pischon et al., 2003].

Diabetes

There is insufficient evidence regarding the effects of n–6 FAs on diabetes. There are limited data on the effects

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of n–6 FAs on diabetes risk or insulin action. Intake of LA is inversely related to incidence of T2DM [Hu et al., 2001; Salmeron et al., 2001]. A few studies have demonstrated that substituting SFA with n–6 PUFA improved directly measured insulin sensitivity [Heine et al., 1989; Summers et al., 2002].

Trans Saturated Fatty Acids

Trans fatty acids (TFAs) are created through the transformation of PUFAs from their natural *cis* form to the *trans* form. TFAs are formed during partial hydrogenation of vegetable oils, which converts the oils to semi-solid fats, and is a useful process in extending shelf life, increasing the stability during frying, and palatability of baked goods and sweets. Small amounts of TFA occur naturally in dairy products and the meat of ruminant animals, but this makes up a small proportion of the total TFA intake. In the US, intake of TFA is estimated to be <7% of dietary fat and approximately 3% of total energy intake [Mozaffarian et al., 2004a]. Concern has been raised that TFA from industrial sources may increase the risk of CHD and the incidence of T2DM and obesity.

Obesity and Body Weight

There is insufficient evidence regarding the effect of TFA on body weight. In a recent prospective study of 16,587 American men, a 2% increment in energy intake from TFA was significantly associated with a 0.77-cm waist gain over 9 years [Koh-Banerjee et al., 2003]. This is the only known study that specifically addressed the association between TFA intake and adiposity in humans. Conversely, although TFA is associated with increased risk of CHD [Oh et al., 2005] and T2DM [Salmeron et al., 2001], BMI did not differ according to TFA intake in these studies. No intervention studies have been conducted in humans to determine the effects of TFA on visceral adiposity. However, in non-human primates, replacing *cis*-monounsaturated fats with an isoenergetic amount of TFA resulted in a 5% greater weight gain and a 33% greater increase (not significant) in intra-abdominal fat deposition measured by CT compared to monkeys fed a low TFA diet [Kavanagh et al., 2007].

Metabolic Syndrome

There is probable evidence regarding a positive association between TFA intake and components of the metabolic syndrome. Data from randomized controlled trials indicate that TFAs cause harmful changes in serum lipids, systemic inflammation and endothelial function, and prospective studies have demonstrated positive associations between TFA intake and the risk of myocardial infarction, CHD, and sudden death [Hu et al., 1997; Pietinen et al., 1997; Ascherio et al., 1999; Oomen et al., 2001; Lemaitre et al., 2002; Mozaffarian and Willett, 2007]. A possible limitation of these studies is the accuracy of measuring TFA in the diet. Indeed, the association of CHD risk is stronger with adipose tissue TFA levels than with dietary TFA, suggesting that measurement errors dampen this association [Mozaffarian and Willett, 2007]. TFAs take on similar properties to SFAs, but because they are consumed in lower quantities, they may be more atherogenic. TFAs increase LDL cholesterol similarly or more than SFAs, decrease HDL cholesterol, and possibly increase triglycerides [Mensink and Katan, 1990; Mensink and Katan, 1992; Ascherio et al., 1999; Lichtenstein et al., 1999; Dyerberg et al., 2004; Mozaffarian et al., 2006]. TFAs also increase levels of Lp(a) and reduce the particle size of LDL, which may further increase the risk of CHD [Mozaffarian et al., 2006]. Replacement of SFA with TFA decreased flow-mediated vasodilation by 29% [de Roos et al., 2001]. Intake of TFAs is positively associated with levels of TNF-α [Mozaffarian et al., 2004b] and C-reactive protein [Mozaffarian et al., 2004a].

Diabetes

There is insufficient evidence that TFA increases diabetes risk. Data from human studies is limited and mixed. Intakes of TFAs were positively associated with an increased risk of T2DM in the Nurses' Health Study [Salmeron et al., 2001], but not in the Health Professionals Follow-Up Study [van Dam et al., 2002], or in the Iowa Women's Health Study [Meyer et al., 2001]. Possible reasons for these discrepant findings include low overall intake of TFA [van Dam et al., 2002] or self-reported diagnosis of T2DM [Meyer et al., 2001]. In smaller experimental trials, increasing intake of TFAs has inversely affected insulin resistance and glucose metabolism in some [Christiansen et al., 1997; Lovejoy et al., 2002; Lefevre et al., 2005] but not all studies [Louheranta et al., 1999]. However, all but one of these studies were performed in lean, healthy, young adults; only the study of Christiansen et al. [1997] was performed in obese adults with T2DM. Although no study has attempted to address the mechanism by which TFAs impair glucose metabolism, it is hypothesized that systemic inflammation induced by TFAs may reduce insulin sensitivity [Odegaard and Pereira, 2006].

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Conjugated Linoleic Acid

Conjugated linoleic acid (CLA) is a group of positional and geometric isomers of conjugated dienoic derivatives of LA. The major source of CLA in the human diet is ruminant meats and dairy products. The average daily intake in humans is approximately 0.5–1.5 g/day. The major isomer in natural food is *cis*-19,*trans*-11 (c9,t11), and commercial preparations contain approximately an equal mixture of c9,t11 and *trans*-10,*cis*-12 (t10,c12) isomers. Increased CLA consumption, specifically of the t10,c12 isomer, has been shown to have anti-obesity, anti-atherogenic and anti-diabetic effects in animals, which has raised interest in using this FA to treat these conditions in humans. However, concern has been raised that increasing CLA intake may result in insulin resistance or induce inflammation in humans.

Obesity and Body Weight

There is insufficient evidence regarding the effect of CLA on body weight. Animal studies have shown dramatic effects of CLA supplementation on body weight and body fat (particularly the t10,c12 isomer), with mice being the most responsive model to treatment [Whigham et al., 2007]. Marked reductions in both white and brown adipose tissue are evident at doses as low as 0.5% in the diet [Wang and Jones, 2004]. The decrease in fat mass is generally accompanied by an increase in body protein, also attributable to the t10,c12-isomer [Wang and Jones, 2004]. The mechanism by which CLA exerts its anti-obesity effect is not clear, but possible reasons are decreases in energy intake, increases in energy expenditure with concomitant increases in the expression of uncoupling protein 2, inhibition of lipogenesis, and increases in fat oxidation [Wang and Jones, 2004]. Some evidence suggests that these mechanisms operate in animals [Li et al., 2008], but human data are lacking.

The effects of CLA on body weight and body fat in humans are inconsistent and less substantial than in animals. Significant effect of CLA supplementation on body weight have been demonstrated in some studies [Basu et al., 2000b; Blankson et al., 2000; Mougios et al., 2001; Riserus et al., 2001], but other studies have shown no effect of CLA on body weight in healthy obese or non-obese individuals [Zambell et al., 2000; Mougios et al., 2001; Smedman and Vessby, 2001; Larsen et al., 2006]. Possible reasons for discrepancy include a wide variation in doses (<0.5 up to 6.8 g/day) and duration of treatment. A recent meta-analysis concluded that CLA at a dose of 3.2 g/day produces a modest weight loss (–0.024 kg/g CLA/week compared to placebo) and fat loss (0.09 kg/week compared to placebo) [Whigham et al., 2007]. Eighteen eligible studies were identified, with 3 being single-isomer studies. It was concluded that 10 of the studies that showed no significant effect of CLA on fat mass were too short; most of the studies included in the meta-analysis were ≤12 weeks in duration. Of the single-isomer studies, the t10,c12 isomer reduced body fat mass by approximately 1 kg in groups receiving ≥2.4 g/day. Unlike in animals, consumption of CLA by humans does not have any affect on energy intake or expenditure [Basu et al., 2000a, 2000b; Zambell et al., 2000; Mougios et al., 2001; Belury et al., 2003]. CLA also does not alter fat oxidation in humans at rest or during exercise [Zambell et al., 2000].

Metabolic Syndrome

There is insufficient evidence regarding the effect of CLA on either the components of or risk of acquiring the metabolic syndrome. No long-term or prospective studies have been performed to determine if CLA supplementation increases the risk of acquiring the metabolic syndrome, and no epidemiological studies exist. Likewise, no human intervention studies have examined the effects of CLA supplementation on the components of or risk of acquiring the metabolic syndrome. One study has reported a decrease in HDL with CLA supplementation [Riserus et al., 2002]. It has been reported that CLA slightly increases biomarkers of inflammatory disease such as C-reactive protein [Riserus et al., 2002], white blood cells [Gaullier et al., 2005], and blood and urinary isoprostanes [Riserus et al., 2002]. However, in animals, CLA exhibits anti-inflammatory effects [Whigham et al., 2007].

Diabetes

There is insufficient evidence to determine whether increasing CLA increases diabetes risk. No long-term or prospective studies have been performed to determine if CLA supplementation increases the risk of T2DM, and no epidemiological studies exist. There is some evidence that CLA supplementation alters glucose metabolism. Several small studies have reported that CLA supplementation increases insulin resistance, although these studies are typically short in duration [Moloney et al., 2004], or notably, used single isomers [Riserus et al., 2002, 2004a, 2004b]. An increase in fasting glucose has also been observed [Riserus et al., 2002]. Many studies have not found significant changes in fasting glucose or insulin or in measures of insulin sensitivity [Basu et al., 2000a; Smedman and Vessby, 2001; Belury et al., 2003; Whigham, et al., 2004; Gaullier, et al., 2005] and some have noted an im-

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provement [Eyjolfson et al., 2004; Larsen et al., 2006]. Evidence that CLA induces fatty liver has been reported in C57BL/6J mice [Tsuboyama-Kasaoka et al., 2000], and CLA-induced fatty liver is associated with hyperinsulinemia [Clement et al., 2002]. Such effects have not been studied in humans.

Reasons for Discrepant Results

A possible reason for the discrepant findings regarding the effects of different dietary fats on the outcomes reviewed above is the fact that almost all of the studies used some form of dietary record or recall. These methods notoriously produce underestimation of the total energy and macronutrient intake. Some studies have used carefully validated instruments, for example, the food frequency questionnaire used in the Nurses' Health Study [Hu et al., 1997] and the Men's Health Professionals Study [Koh-Banerjee et al., 2003], whereas many studies do not address this issue. However, whether even these instruments provide valid reports of fat intake has been questioned [Johnson et al., 1998]. More recently developed instruments may be more sensitive to measuring dietary fat. For example, a survey developed for use in the European Prospective Investigation of Cancer and Nutrition Norfolk Study demonstrated a positive association between SF intake and breast cancer risk, whereas in the same cohort the association using the food frequency questionnaire from the Nurses' Health Study did not show a significant association [Bingham et al., 2003]. Some studies have adjusted for energy intake in multivariate analyses, but it may be argued that this approach is invalid because it assumes that the variance in macronutrients and fats is the same as the variance in energy intake [Johnson et al., 1998]. Finally, when interpreting the results of epidemiological studies, one should be mindful of control for potential covariates such as age, physical activity level, smoking status, BMI or other measures of adiposity, consumption of alcohol and use of hormonal contraceptives. As in the case of dietary records, methods of estimating physical activity level are prone to reporting errors.

Interpreting studies that have examined the specific fats must consider whether the comparison diets were isoenergetic. For example, addition of MUFAs to the diet (in the form of peanut oil) promoted an increase in weight of 2.4 kg over 8 weeks [Coelho et al., 2006]. Another potential problem is the fact that major food sources of monounsaturated fat can also be high in SFA, *trans*-unsaturated FA or PUFA [Hu et al., 1997].

Summary

In this review, we have summarized studies published between 1993 and the present that have addressed the associations between dietary fat intake and obesity, the metabolic syndrome and diabetes.

With regard to obesity, although there is a substantial body of data suggesting that there is an association between total fat and saturated fat intakes and body weight, there are nearly as much data suggesting that there is no association. Thus, we conclude that the data on the association between total fat intake and saturated fat intake and body weight remain inconclusive. Interventional randomized studies comparing the Atkin's diet to other regimes – with percentage of fat being the primary difference and similar overall intensity of intervention – tend to show a greater weight loss than lower fat diets. However, the usefulness of these results is limited by differences in other macronutrients and high drop-out rates. Larger intervention studies suggest that lower dietary fat is associated with weight loss; however, the studies were not designed to specifically examine dietary fat and weight, and thus differences in intervention intensity make it impossible to draw definitive conclusions from these results.

Systemic studies of trials and meta-analyses suggest that diets lower in fat and with calorie restriction are associated with greater weight loss, but these interventions have typically been of limited duration or involved additional lifestyle changes (e.g. an increase in physical activity). Although many prospective cohort studies show a positive relationship between dietary fat intake and weight gain, these data are also inconclusive. From our review, we also conclude that there is insufficient evidence – due to the small number of studies – to determine whether there is a relationship between intake of MUFAs or PUFAs and body weight.

We also conclude that there is insufficient evidence at this time to determine the association between diabetes risk and intake of total fat or of any particular type of fat. However, there are a sufficient number of studies that suggest that total fat and saturated fat intakes increase the risk of having components of the metabolic syndrome, and that higher intakes of MUFAs and PUFAs have a beneficial effect in reducing this risk.

Disclosure Statement

Dr. Melanson and Dr. Donahoo have no disclosures. Dr. Astrup is an advisor or member of advisory boards for a number of food producers (e.g. European Almond Advisory Board, Communications and Scientific Advisory Board of The Global Dairy Platform, Chicago), and recipient of honoraria as speaker for a wide range of Danish and international concerns. He is also an Executive Board member of the Beer Knowlegde Institute, The Netherlands, and the Nordic Food Lab, Copenhagen, Denmark.

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