

## REVIEW

# Trans fatty acids and weight gain

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Increasing rates of obesity have stimulated research into possible contributing factors, including specific dietary components such as *trans* fatty acids (TFAs). This review considers the evidence for an association between TFA intake and weight gain. It concludes that there is limited but consistent evidence from epidemiological studies, and from a primate model, that increased TFA consumption may result in a small additional weight gain. Data from a long-term study in a primate model suggest that TFA may have a greater adipogenic effect than *cis* monounsaturated fatty acids; however, there are currently inadequate mechanistic data to provide a comprehensive and plausible explanation for any such metabolic differences between the types of fatty acids. *International Journal of Obesity* (2011) 35, 315–324; doi:10.1038/ijo.2010.141; published online 20 July 2010

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### Introduction

Increasing rates of weight gain (and the follow-on effect of increasing rates of obesity) are a global concern, as higher body mass indices (BMIs) have been consistently associated with increased rates of cardiovascular disease, diabetes and hypertension. However, the various causes of the obesity epidemic that have been put forward by scientists and media are complex and numerous, ranging from genetic susceptibility<sup>1</sup> to fast food,<sup>2</sup> climate change<sup>3</sup> to lack of sleep,<sup>4</sup> unfriendly neighbourhoods<sup>5</sup> to driving to work,<sup>6</sup> and antidepressants<sup>7</sup> to having fat friends.<sup>8</sup> It is most likely that what we are seeing is the combined impact of a large number of factors that all individually have a relatively minor effect, and it is almost certain that changes in diet and nutrition have some role. A high-fat (HF) diet has often been associated with increased risk of weight gain,<sup>9</sup> presumably owing to the higher calorific density of fat than other food components. However, a recent review suggested that it may be not so much the amount of fat as the type of fat that should be considered.<sup>10</sup>

*Trans* fatty acids (TFAs) are monounsaturated fatty acids (MUFAs) or polyunsaturated fatty acids (PUFAs) that contain at least one double bond in the *trans* configuration, rather than the usual *cis* configuration found in most lipids. This configuration may occur either as a result of microbial

fermentation in the rumen (leading to the presence of TFA in dairy products or the meat of ruminants) or through the process of hydrogenation (giving rise to TFAs in spreadable fats that are commonly used in the baking industry).

The consumption of TFA has been associated with increased risk of coronary heart disease since reports from the early 1990s,<sup>11</sup> and subsequent research has investigated possible relationships between TFA intake and a wide range of disease states, including diabetes and cancer.<sup>12,13</sup> A small number of studies have also been published investigating the effect of TFA consumption on risk of obesity and/or weight gain. This review has been conducted by the authors commissioned by the United Kingdom's Scientific Advisory Committee on Nutrition (SACN), whose detailed report provided the basis for SACN's *Position Statement on TFA and Health* published in 2007.<sup>13</sup> The present review provides an updated assessment of the strength of the evidence relating to any putative relationship between TFA intake and weight gain, as well as attempting to put the potential size of any effect into context.

### Selection of papers

Papers were initially identified through keyword searches in the Medline and Pubmed database, followed by the inspection of citations. The SACN Framework for the Evaluation of Evidence<sup>14</sup> was used to assess the strength of the scientific evidence. A total of two case-control, one ecological and five prospective epidemiological studies were identified, along with three meal studies and one randomized controlled trial

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(RCT). Relevant cell and animal studies have also been included (1977–2009).

Three of the five prospective cohort studies are based on data from the Nurses' Health Study. Three meal studies evaluated the acute metabolic response to TFA during a single breakfast meal, whereas an RCT considered the longer-term effects during dietary replacement of FA for 4 weeks. Although weight change was not a primary outcome in the meal studies and the RCT, they reported changes in metabolic parameters that may influence body weight, such as fat oxidation, energy expenditure and appetite, and may thereby shed light on the potential mechanisms.

## Cell studies

The two cell studies are summarized in the first part of Table 1.

Potential differences in cellular metabolism of *cis* compared with TFA isomers were investigated using Swiss mouse fibroblast 3T3-L1 cells, a widely used adipocyte model.<sup>15</sup> At both the pre-adipocyte and differentiating adipocyte stages, less fat had accumulated in cells cultured in the presence of TFA ( $P < 0.05$ ), with a reduction in the total nonpolar lipid content of the cells. Comparisons of the total amounts of other FA in the cells suggested that TFA may have replaced MUFA in the nonpolar lipid fraction and saturated fatty acids (SFAs) in the polar lipid fraction. Similar experiments with rat adipocytes found that *trans* isomers caused a significant reduction in the amount of glucose converted to cell lipid ( $P < 0.01$ ) and in the oxidation of glucose to carbon dioxide ( $P < 0.05$ ), while increasing the rate of lipolysis.<sup>16</sup> A study using rat hepatocytes and isolated mitochondria found that liver peroxisomes exhibited a preference for oxidizing TFA as opposed to the *cis* equivalent FA.<sup>17</sup> There was also preferential incorporation of TFAs into hepatic phospholipids. The authors observed that the differences were not due to changes in the key enzymes of hepatic fatty acid metabolism, acetyl-CoA carboxylase and carnitine palmitoyltransferase I.

## Animal studies

Rodent and primate studies are summarized in the second part of Table 1.

### Rodent models

The addition of 5 wt% TFA to the diets of rats deficient in essential FA lowered their growth response to linoleic acid.<sup>18</sup> After 24 weeks, TFAs were found to have accumulated to relatively high levels in the serum and liver (up to 17.9% of FA). The TFAs impaired the conversion of oleic acid to eicosatrienoic acid and linoleic acid to arachidonic acid, and reduced the incorporation of eicosatrienoic acid into

cholesteryl esters. C57Bl/6J mice fed a diet containing 5 wt% TFA had lower body weights (16 and 24 months of age), epididymal fat pad weights (8–24 months of age), perirenal fat weights, triacylglycerol to polar lipid ratios and adipose cell size than animals fed a control diet containing *cis* FA (all  $P < 0.05$ ).<sup>19</sup> Wistar rats fed diets containing 5.1% TFA had slightly lower weight gains after 30 days than rats fed similar amounts of SFA or *cis* FA, but the difference was not statistically significant.<sup>20</sup> Epididymal fat pads were significantly smaller in animals on the *cis* FA than TFA or SFA diets ( $P = 0.0007$ ). The apparent fat absorption was  $85.7 \pm 3.4$ ,  $93.1 \pm 0.4$  and  $96.7 \pm 1.1\%$  for the SFA, TFA and *cis* FA diets, respectively ( $P < 0.0001$ ). The efficiency of energy utilization varied between diets (SFA 15.2%, TFA 16.5% and *cis* FA 18.7%), but this difference was only statistically significant between SFA and *cis* FA. Wistar rats fed isoenergetic diets that included 0 or 4.5% energy (E) from TFAs for 16 weeks also showed no difference in weight gain between groups.<sup>21</sup> The rats receiving the TFA diet had lower leptin and higher adiponectin and resistin levels than the controls, but these differences did not result in any observed metabolic changes in the group. Male Wistar rats fed diets containing 9.5 wt% TFA for 14 days gained the same amount of weight as those on diets containing 18:0 or *cis* FA isomers, despite consuming significantly less feed.<sup>22</sup> Animals receiving the TFA showed impaired hepatic activity of carnitine palmitoyltransferase-I and 3-hydroxy-acyl-CoA dehydrogenase, and enhanced liver triacylglycerol by lowering the hepatic oxidation of fatty acids. However, male AKR/J mice gained significantly less weight over 8 weeks when fed a HF diet containing 20% of energy (% of E) from TFA than when fed an isoenergetic, HF diet containing no TFA.<sup>23</sup> The leptin levels of animals in the TFA group were significantly lower than those of the standard HF group after 8 weeks. There were no differences in total body weight or weight of intra-abdominal adipose tissue in groups of Wistar rats fed diets containing 4% of E from ruminant TFA, industrial TFA or oleic acid for 8 weeks.<sup>24</sup> There were also no differences in food intake or weight gain in groups of lean and obese JCR:LA-cp rats fed diets with and without 1.5% (wt wt<sup>-1</sup>) vaccenic acid (the predominant TFA in ruminant sources<sup>25</sup>) for 3<sup>26</sup> or 16 weeks.<sup>27</sup> Diets containing partially hydrogenated vegetable oil (1.05% of E from TFA), palm, canola or soy oil were fed to lactating female rats and then to their weaned male offspring until the males were 45 days old.<sup>28</sup> Animals on the partially hydrogenated vegetable oil and palm oil diets had higher total body weight and carcass fat content than their counterparts on the soy or canola diets, even though food intake was significantly lower in the partially hydrogenated vegetable oil group than in the other three groups. The lipogenesis rate (*de novo* synthesis of FA in white adipose tissue) was highest in those consuming the palm oil, but was also significantly higher in those on the partially hydrogenated vegetable oil diet than those consuming canola or soy oil. The second study fed Sprague-Dawley rats diets containing 10% SFA (low fat (LF)-SFA),

**Table 1** Cell and animal studies investigating the association of TFA with changes in body weight

Reference	Model	Study design	Types of fat used in study	Outcome
<i>Cell studies</i>				
Panigrahi and Sampugna <sup>15</sup>	Swiss mouse fibroblast 3T3-L1 cells (adipocyte model)	Cells cultured in growth media supplemented with FA complexed to bovine serum albumin	Mixture of FA, differing only in terms of C18 FA. Control: 0 wt% <i>trans</i> 18:1, 46 wt% <i>cis</i> 18:1, 6 wt% 18:0. Test: 18.6 wt% <i>trans</i> 18:1, 27.8 wt% <i>cis</i> 18:1, 8 wt% 18:0	Cells cultured in the presence of TFA had lower levels of polar and non-polar lipids accumulated in the cells ( $P < 0.05$ ), and higher ratios of linoleate:ARA ( $P < 0.05$ )
Cromer <i>et al.</i> <sup>16</sup>	Rat adipocytes	Cells incubated for 2 h in media containing FA	Purified oleic acid, <i>trans</i> 18:1, <i>n-9</i> and 18:1, <i>n-7</i>	The TFA reduced the conversion of glucose to cell lipid and the oxidation of glucose to carbon dioxide, while increasing the rate of lipolysis (all $P < 0.05$ )
Guzmán <i>et al.</i> <sup>17</sup>	Wistar rat hepatocytes and mitochondria isolated from hepatocytes	Cells or mitochondria incubated with various forms of the FA between 1 and 60 min, depending on specific analysis	Purified oleic acid and <i>trans</i> 18:1, <i>n-9</i>	The TFA was preferentially oxidized by hepatic peroxisomes, whereas the oleic acid was preferentially esterified
<i>Animal studies</i>				
Privett <i>et al.</i> <sup>18</sup>	Essential fatty acid-deficient rats	24 weeks fed a standard diet containing 10 wt% fat. In the control diets, the fat came solely from safflower oil or hydrogenated coconut oil; in the test diets 5% of the fat was substituted for purified TFA	Purified elaidate (18:1 $\omega$ 9) or linolelaidate (18:2 $\omega$ 9 $\omega$ 12)	TFA appeared to impair the interconversion of unsaturated FA and reduce the activity of lipoprotein lipase
Atal <i>et al.</i> <sup>19</sup>	Male C57Bl/6J mice	The animals were fed diets containing 10 wt% control or test fat for up to 24 months	Mixtures of fats were blended to produce two diets that were approximately the same, except that 50% of the <i>cis</i> 18:1 in the control diet was substituted for <i>trans</i> 18:1 in the test diet	The <i>trans</i> diet reduced the total body weight as well as the weight of epididymal fat pads and perirenal fat (all $P < 0.05$ ). The animals on the <i>trans</i> diet also had lower triacylglycerol:polar lipid ratios and adipose cell size (both $P < 0.05$ )
Colandre <i>et al.</i> <sup>20</sup>	Wistar rats	Fed diets containing 20% fat for 30 days. 17% of the fat was a maize oil-derived product that contained varying levels of <i>trans</i> , <i>cis</i> and SFA	Maize oil (0.66 wt% TFA, 13.94 wt% SFA, 85.40 wt% <i>cis</i> FA), hydrogenated maize oil (10.47 wt% TFA, 71.44 wt% SFA, 18.09 wt% <i>cis</i> FA), isomerized maize oil (30.00 wt% TFA, 14.38 wt% SFA, 55.62 wt% <i>cis</i> FA)	Energy utilization and apparent fat absorption were lower in TFA than in the <i>cis</i> diet ( $P = \text{NS}$ and $< 0.05$ , respectively), but were lowest in the SFA diet. Animals on the <i>cis</i> diet had significantly smaller epididymal fat pads ( $P = 0.0007$ ) and lower serum and hepatic TAG levels (both $P < 0.05$ )
Huang <i>et al.</i> <sup>21</sup>	Male Wistar rats	Fed diets containing TFA or no TFA for 16 weeks	TFA diet contained 201 g per kg margarine, resulting in a TFA level of 4.5%. Control diet used corn oil and water to achieve the same level of total fat	Animals fed the TFA diet had significantly lower leptin levels ( $16.1 \pm 4.5$ vs $21.5 \pm 4.8$ ng/ml) and higher adiponectin ( $14.1 \pm 1.7$ vs $12.3 \pm 1.0$ $\mu$ g/ml <sup>-1</sup> ) and resistin ( $18.9 \pm 6.7$ vs $16.0 \pm 3.9$ ng/ml <sup>-1</sup> ) levels (all $P < 0.05$ )
Giudetti <i>et al.</i> <sup>22</sup>	Male Wistar rats	Fed diets containing 200 g per kg fat for 14 days	Fat sources were hydrogenated soybean oil (diet contained 10.2 wt% 18:0, 5.0 wt% <i>cis</i> 18:1), olive oil (0.6 wt% 18:0, 14.1 wt% <i>cis</i> 18:1), or hydrogenated and fractionated soybean oil (0.8 wt% 18:0, 4.8 wt% <i>cis</i> 18:1, 9.5 wt% TFA)	There was no difference in growth between diets, despite significantly lower feed intake for the TFA animals. The TFA diet had a significantly lower feed efficiency value (grams of feed required for an animal to gain a gram of body weight) than the 18:0 diet. TFA reduced plasma cholesterol and inhibited carnitine palmitoyltransferase-1 and 3-hydroxyacyl-CoA dehydrogenase. Overall, TFA enhanced liver triacylglycerol by lowering the hepatic oxidation of fatty acids
Koppe <i>et al.</i> <sup>23</sup>	Male AKR/J mice	Fed high-fat diets containing 40% fat for 10 days, 4 or 8 weeks	Lard (16.2% SFA, 8.6% PUFA, 20.5% <i>cis</i> MUFA, 0% TFA) or shortening (10% SFA, 4.5% PUFA, 10.5% <i>cis</i> MUFA, 20% TFA). SFA:PUFA ratio 0.5 for both diets	After 8 weeks, rats on the standard high-fat diet had gained more weight than those on the high-TFA diet (approx. 55 vs 45%, respectively). Leptin levels of TFA group were

Table 1 (continued)

Reference	Model	Study design	Types of fat used in study	Outcome
Tardy <i>et al.</i> <sup>24</sup>	Male Wistar rats	8 weeks on diet enriched with oleic acid, ruminant TFA (R-TFA) or industrial TFA (I-TFA) at 4% of E	Ruminant fat enriched in vaccenic acid obtained from milk produced from cows supplemented with fish oil and soybean oil. Industrial fat enriched in elaidic acid was a mixture of partially hydrogenated vegetable oils	significantly lower than those of three standard high-fat group after 8 weeks ( $24.8 \pm 3.7$ vs $41.0 \pm 4.5$ ng ml <sup>-1</sup> , $P < 0.05$ ) Total body weight and weight of intra-abdominal tissue were slightly higher in animals fed either the R-TFA or I-TFA diets compared with the control diet, but none of these differences were statistically significant
Wang <i>et al.</i> <sup>26,27</sup>	Male JCR:LA-cp rats, either obese or lean	Fed diets with and without 1.5% (wt/wt) vaccenic acid for 3 <sup>25</sup> and 16 weeks <sup>26</sup>	Mixture of sunflower oil, flaxseed oil, soy tallow and olive oil used in both diets; vaccenic acid added to TFA diet. Total fat and ratio of PUFA:SFA maintained between diets	No difference in food consumption or weight gain between the diets after either 3 or 16 weeks
Silva <i>et al.</i> <sup>28</sup>	Male Wistar rats	Diets containing PHVO, palm, canola or soy oil were fed to lactating rats and male offspring until 45 days old	Diets contained blend of fats: PHVO = 6% PHVO+1% soy oil, palm = 5% palm+2% soy oil, canola = 6%, canola+1% soy oil, soy = 7% soy oil, PHVO diet had 1.05% of E as TFA	Total body weight and weight of carcass fat of rats on PHVO and palm diets were significantly higher than canola or soy, despite lower food intake in the PHVO group. There were also significant differences in the rate of <i>de novo</i> synthesis of FA: PHVO = 4.85 <sup>a</sup> , palm = 7.04 <sup>b</sup> , canola = 2.75 <sup>c</sup> , soy = 2.61 <sup>c</sup> (g fresh tissue per h)
Dorfman <i>et al.</i> <sup>29</sup>	Male Sprague-Dawley rats	Fed diets containing 10 or 45% total fat for 8 weeks	10% SFA diet (LF-SFA) and 45% SFA diet (HF-SFA) used a combination of soyabean oil and lard. LF- <i>Trans</i> diet was identical to the LF-SFA diet, but with the lard replaced by elaidic acid, giving 4.6% TFA	After 6 weeks, <i>in vivo</i> 1H-MR showed more adipose tissue in LF- <i>Trans</i> rats than those on LF-SFA diet ( $0.07 \pm 0.01$ vs $0.04 \pm 0.01$ g, $P < 0.05$ ). LF- <i>Trans</i> animals also had a higher proportion of visceral fat ( $P < 0.05$ )
Kavanagh <i>et al.</i> <sup>30</sup>	Male African green monkeys	Fed maintenance diets containing 35% of E as a fat blend enriched with either <i>cis</i> or TFA for 6 years. Overall, ~8% of E was from TFA	Blend of partially hydrogenated and non-hydrogenated oils that provided similar FA profiles, except that the <i>cis</i> diet contained 51.1% <i>cis</i> 18:1, whereas the <i>trans</i> diet contained 26.6% <i>cis</i> and 20.4% <i>trans</i> 18:1	Animals on TFA diet gained $7.20 \pm 2.70\%$ weight, those on the <i>cis</i> FA diet gained $1.78 \pm 1.95\%$ ( $P = 0.049$ ). The intra-abdominal:subcutaneous fat volume ratio was $1.67 \pm 0.14$ and $1.36 \pm 0.09$ for the <i>trans</i> and <i>cis</i> diets, respectively ( $P = 0.018$ ). The TFA diet also induced post-prandial hyperinsulinaemia ( $P = 0.015$ )

Abbreviations: ARA, arachidonic acid; E, energy; FA, fatty acid; PHVO, partially hydrogenated vegetable oil; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid; TAG, triacylglycerol; TFA, *trans* fatty acid. Means within columns with different superscript letters are significantly different,  $P < 0.05$ .

45% SFA (HF-SFA) or 4.6% TFA + 5.4% other FA (LF-*Trans*).<sup>29</sup> Rats on the HF-SFA and LF-*Trans* diets weighed significantly more than those on the LF-SFA after 6 weeks, but both the former groups had significantly higher cumulative food intakes than the LF-SFA group. After 6 weeks, *in vivo* 1H-MR showed that the LF-*Trans* and HF-SFA rats had accumulated significantly greater amounts of adipose tissue than the LF-SFA rats ( $0.07 \pm 0.01$  and  $0.08 \pm 0.02$  vs  $0.04 \pm 0.01$  g). The LF-*Trans* animals had a higher proportion of the fat in visceral regions compared with the other two groups, and had a significantly higher intrahepatic lipid level than the LF-SFA rats. There was no difference between LF-SFA and LF-*Trans* groups in terms of intramyocellular lipid content.

#### Primate models

A long-term intervention study was carried out, in which male African green monkeys ( $n = 42$ ) were fed maintenance diets containing 35% of E as fat.<sup>30</sup> This fat was composed of either *cis* MUFA (<1% of E from TFA) or a mixture of *cis* and *trans* isomers (~8% of E from TFA) for 6 years. The authors estimate that this period is equivalent to ~15 years in a human. The animals receiving the TFA diet gained an additional  $7.20 \pm 2.70\%$  body weight compared with  $1.78 \pm 1.95\%$  for those fed the *cis* FA diet ( $P = 0.049$ ). Assuming a linear relationship between weight gain and consumption of TFA, this would correspond to an increase of 0.42 or 0.55 kg over 6 years for a 1% increase in TFA in an

individual with an initial weight of 60 or 80 kg, respectively. The *trans* group also deposited more fat intra-abdominally for every cubic centimetre of fat gained, with an intra-abdominal:subcutaneous fat volume ratio of  $1.67 \pm 0.14$  and  $1.36 \pm 0.09$  for the *trans* and *cis* diets, respectively ( $P=0.018$ ). The TFA diet also induced significant post-prandial hyperinsulinaemia, with insulin concentrations being more than three times those of the animals fed the *cis* FA ( $P=0.015$ ).

## Human studies

### Measurement of TFA exposure levels in human studies

In the human studies, consumption of TFA was most commonly determined by assessing dietary TFA intakes through food frequency questionnaires (FFQ) or diet diaries, although a small number of more recent papers used the levels of TFA in blood or adipose tissue as a surrogate biomarker of TFA intakes.<sup>31,32</sup> Care must be taken when estimating TFA intake based on reported food intake, as it has been shown that different brands of food products can result in considerable variation in TFA content for the same diet – as much as  $1.4$ – $25.4$   $\text{g day}^{-1}$  in one example compiled in 1999.<sup>33</sup> There has been significant reduction in TFA content of most foods over the past decade,<sup>13</sup> and so it is important that composition databases have been updated to take this into account.

The most recent estimate of mean TFA intake in the United Kingdom is 1.0% of E ( $1.7$ – $2.4$   $\text{g day}^{-1}$ ).<sup>13</sup> This is similar to estimates for Western Europe (0.9–1.0% of E,  $2.0$ – $2.4$   $\text{g day}^{-1}$ )<sup>34</sup> and Australasia (0.5–0.6% of E,  $1.2$ – $1.6$   $\text{g day}^{-1}$ ),<sup>35</sup> but higher levels have been reported for Canada (2.2% of E,  $4.9$   $\text{g day}^{-1}$ )<sup>36</sup> and the United States ( $1.8$ – $2.2$   $\text{g day}^{-1}$ ).<sup>37</sup>

The details of all human studies are summarized in Table 2 (Epidemiological) and Table 3 (Meal studies).

### Population and case-control studies

A study using investigator-assessed waist-hip ratio as a measurement of abdominal obesity found no correlation with TFA intake in 617 Canadian volunteers of mixed ethnic origin.<sup>38</sup> The mean TFA intake for the group was  $0.43 \pm 0.52$   $\text{g day}^{-1}$ , which is at the lower end of intakes in most western countries. No adjustment was made for other dietary factors in the analysis. TFA intake and plasma TFA was not significantly different between a group of 34 obese children (>97 BMI percentile for age and sex) and 20 normal-weight controls.<sup>32</sup> The mean intake for both groups was <1 g TFA per day, and the adjustment included no apparent adjustment for either lifestyle or diet. A study in morbidly obese (BMI >40  $\text{kg m}^2$ ) and non-obese (BMI <30  $\text{kg m}^2$ ) Brazilian subjects also showed no correlation between BMI and TFA levels in adipose tissue, but, once again, there was no apparent adjustment for confounding factors.<sup>31</sup>

### Prospective cohort studies

An analysis of the change in body weight over 8 years (1976–1984) of 31 940 non-smoking women from the Nurses' Health Study found that age, relative weight and previous weight change were more strongly associated with recent weight change than were the intake patterns of specific nutrients.<sup>39</sup> All lipids other than vegetable fat were positively correlated with BMI, with the strongest association for TFA intake ( $\beta=0.191$ ,  $t=9.3$ ). This would correspond to an increase in weight of 0.52 or 0.62 kg over 8 years for an individual 1.65 or 1.8 m tall, respectively. However, when the effects of all nutrients studied were combined, they only explained 0.8% of the weight change over the 8-year period. No information on the levels of TFA consumption or additional statistical analysis was reported. Data from the Nurses' Health Study for another 8-year period (1986–1994) were also used to study the association between dietary fat and weight gain among 41 518 women.<sup>40</sup> Weight and diet were assessed using questionnaires at the baseline and at the end of the study period. Increases in MUFA and PUFA intake had no association with weight gain, but increases in animal fat, SFA and TFA were associated with an increase in weight. Among women who were overweight at the start of the study, increasing TFA intake by 1% of E resulted in an increase in weight of 2.3 lb (1.04 kg) over the 8 years (95% confidence interval, 1.80–2.86;  $P<0.0001$ ). The corresponding weight gain for women of normal weight was 1.2 lb (0.54 kg) ( $P<0.0001$ ). A further assessment of Nurses' Health Study data investigating the relationship between alcohol intakes and weight gain in 49 324 women (1991–1999) reported that weight gain associated with heavy drinking appeared to be more likely in women who consumed higher levels of TFA, although this interaction was not statistically significant ( $P=0.10$ ).<sup>41</sup>

Another large study examined dietary questionnaires and self-reported waist circumference (WC) of 16 587 men involved in the Health Professionals' Follow-up Study.<sup>42</sup> A validation study in a subset of participants found that the self-reported measures of WC were highly correlated with technician-assessed measurements ( $r=0.95$ ).<sup>43</sup> The analysis found that a substitution of 2% of E from carbohydrates or PUFA for TFA resulted in a 9-year increase in WC of 0.53 or 0.52 cm, respectively ( $P=0.007$  for both substitutions). Further adjustment of the data to compensate for discrepancies between reported and actual fat intake (as determined by a validation study) increased the effect for the substitution of PUFA to a 2.7-cm increase in WC over the 9-year period ( $P<0.001$ ).

The association between weight retention and diet and lifestyle factors was examined in 902 women at 6–12 months post-partum.<sup>44</sup> For every 0.5% of E from TFA, the odds ratio for retaining  $\geq 5$  kg at 12 months was 1.33. The odds ratio for weight retention by women who had TFA consumptions below the median was 0.23.

### Meal studies

The acute oxidation rates of different FA were examined using <sup>13</sup>C-FA in test meals given to four healthy male

**Table 2** Epidemiological studies investigating the association of TFA with changes in body weight

Reference	Subject population	Measure of exposure	TFA intake/level (median of group, unless otherwise specified)	Adjusted relative risk or odds ratio (95% CI)	Trend	Factors adjusted for in analysis
Bortolotto <i>et al.</i> <sup>31</sup> Case-control Brazil	~ 33 cases/18 controls (paper not clear) Morbidly obese and non-obese	Adipose tissue TFA	% TFA of total FA in adipose tissue Level of total TFA for quartiles not given TFA in visceral adipose tissue of whole population (mean $\pm$ SD): Cases 8.74 $\pm$ 0.29% Controls 9.29 $\pm$ 0.59%	Not reported. There was no difference between the case and control groups	NS	Not reported
Larque <i>et al.</i> <sup>32</sup> Case-control Spain	34 obese (23 M), 20 normal weight (11 M) 6-13 years of age	FFQ and a 72-h dietary survey; individual interviews of parents and children	g TFA per day Obese: 0.97 $\pm$ 0.09% Control: 0.81 $\pm$ 0.15% % of E from TFA Obese: 0.43 $\pm$ 0.04% Control: 0.46 $\pm$ 0.08%	Not reported. There was no difference between the obese and control groups	NS	Not reported
Merchant <i>et al.</i> <sup>38</sup> Population study Canada	617 M+F 35-75 years of age 1996-2000	FFQ, validated by comparison with 7- to 14-day food records	g TFA per day 0.43 $\pm$ 0.52	Correlation between TFA intake and HR $\beta$ = -0.00247	$P$ = 0.62	Age, energy intake, height, physical activity, BMI, sex, smoking, alcohol intake and ethnicity
Colditz <i>et al.</i> <sup>39</sup> Prospective cohort (NHS) USA	31 940 F 1976-1984	Dietary TFA assessed by FFQ	% of E from TFA Intake of TFA for cohort not reported	Intake of TFA was related to changes in BMI over 8 years with a coefficient ( $\beta$ ) of 0.191 ( $t$ = 9.3)	Not reported	Age and total calorie intake
Field <i>et al.</i> <sup>40</sup> Prospective cohort (NHS) USA	41 518 F 1984-1996	Dietary TFA assessed by FFQ	% of E from TFA Mean intake of TFA for cohort 1.7 $\pm$ 0.5%	Change in body weight (lb) for a 1% increase in the percentage of calories from TFA: Normal weight women +1.22 (CI not reported) Overweight women +2.33 (1.80-2.86)	$P$ < 0.0001 $P$ < 0.0001	Age, BMI in 1986, activity level in 1986, menopausal status, smoking status, time spent sitting, protein intake, $\Delta$ protein intake, intake of different fat types
Wannamethee <i>et al.</i> <sup>41</sup> Prospective cohort (NHS) USA	49 324 F 1991-1999	Dietary TFA assessed by FFQ	% of E from TFA TFA intake of cohort or individual tertiles not reported	OR for weight gain 5 kg stratified by alcohol intake (0 g day <sup>-1</sup> alcohol used as reference level for OR calculations): Alcohol 0.1-4.9 g day <sup>-1</sup> T1 = 0.93 (0.66-0.99) T2 = 0.91 (0.84-0.98) T3 = 0.96 (0.90-1.03) Alcohol 30 g day <sup>-1</sup> T1 = 0.91 (0.71-1.16) T2 = 1.21 (0.86-1.70) T3 = 1.24 (0.85-1.81)	$P$ for interaction = 0.10	Age, cigarette smoking, level of physical activity, race, initial weight, previous weight change, height, spousal education at 1999, total non-alcohol calorie intake, TFA, SFA, total fibre, protein and sucrose
Koh-Banerjee <i>et al.</i> <sup>42</sup> Prospective cohort (HPFS) USA	16 587 M 1987-1996	Dietary TFA assessed by FFQ	% of E from TFA Mean intake of TFA for cohort 1.3 $\pm$ 0.6%	9-year $\Delta$ waist circumference as a result of changing the source of 2% of energy to TFA: Replacing carbohydrates = 0.53 cm $\pm$ 0.19 Replacing PUFA = 0.52 cm $\pm$ 0.19 Replacing PUFA = 2.7 cm	$P$ = 0.007 $P$ = 0.007 $P$ < 0.001	Age, baseline waist circumference, baseline and $\Delta$ BMI, baseline and $\Delta$ total calories, baseline and $\Delta$ alcohol consumption, baseline and $\Delta$ total physical activity, $\Delta$ smoking, baseline and $\Delta$ intakes of total fat. Replacement of carbohydrates analysis also adjusted for baseline and $\Delta$ intakes of protein and all

Table 2 (continued)

Reference	Subject population	Measure of exposure	TFA intake/level (median of group, unless otherwise specified)	Adjusted relative risk or odds ratio (95% CI)	Trend	Factors adjusted for in analysis
Oken et al. <sup>44</sup> Prospective cohort (Project Viva) USA	902 F, post-partum 1999–2003	Dietary TFA assessed by FFQ	% of E from TFA Median intake of TFA at 6 months post-partum Those who retained 5 kg at 12 months: 1.3 ± 0.6 Those who retained <5 kg at 12 months: 1.1 ± 0.5	OR for retaining 5 kg at 12 months post-partum: per 0.5% increase in E from TFA: 1.33 (1.09–1.62) if consumed below the median level of TFA: 0.23 (0.08–0.66)	Not reported	fat subtypes Further adjustment for measurement errors in significant predictors Maternal age, race/ethnicity, parity, education, household income, parity, pre-pregnancy BMI, gestational weight gain, breastfeeding and smoking

Abbreviations: BMI, body mass index; CI, confidence interval; Δ, changes in; E, energy; F, female; FA, fatty acid; FFQ, food frequency questionnaire; HPFS, Health Professionals' Follow-up Study; M, male; NHS, Nurses' Health Study; NS, not significant; OR, odds ratio; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid; TFA, trans fatty acid; WHR, waist-hip ratio.

volunteers.<sup>45</sup> After consumption of each test meal, breath samples were collected for 9 h, and the oxidation of each FA assessed by measuring the amount of liberated <sup>13</sup>CO<sub>2</sub> in the breath. There was no significant difference between *cis* and *trans* isomers. A longer-term feeding study compared three 4-week diets in 25 healthy subjects with normal (BMI <25 kg m<sup>-2</sup>) or heavier (BMI 25–30 kg m<sup>-2</sup>) body weights.<sup>46</sup> Each diet contained 7–9% of E from *trans* 18:1, *cis* 18:1 or 16:0 FA, and body weight was maintained at a constant level throughout the study. Rates of fat and carbohydrate oxidation were measured at the end of each diet phase, with subjects oxidizing significantly less fat on the MUFA diet (26.0 ± 1.5 g day<sup>-1</sup>) than on the TFA diet (31.4 ± 1.5 g day<sup>-1</sup>) (*P* = 0.02). Fat oxidation on the SFA diet was not significantly different from either of the other diets (29.0 ± 1.5 g day<sup>-1</sup>). There was no significant effect of diet on carbohydrate oxidation, although, as expected, the trend was in the opposite direction to that of fat oxidation. A single isoenergetic meal containing 10% of E as either *cis* or *trans* 18:1 was given to moderately overweight but generally healthy individuals.<sup>47</sup> No difference was observed in fat or carbohydrate oxidation between the two meals.

The effect of different C18 isomers on appetite and energy expenditure was assessed in 19 overweight young men given three isoenergetic test meals (0–32% of E from TFA).<sup>48</sup> The energy content of the meal was adjusted so that each participant consumed 0.8 g of fat per kg body weight. Energy efficiency (respiratory gas exchange) was measured continuously, and appetite rated by visual analogue scales. After 5 h, an *ad libitum* meal was served. There were no differences in acute post-prandial appetite, *ad libitum* energy intake or energy efficiency between the test meals.

## Summary – TFA and weight gain

An overall summary of the data is presented in Table 4. There are limited data available on which to base an assessment of the risk of obesity or increased weight gain associated with TFA consumption. Animal and cell studies have reported conflicting results with regard to the effect of TFA on glucose and lipid oxidation and on body weight and composition. *In vitro* and *ex vivo* studies of adipose tissue have generally found TFA to inhibit lipid synthesis and reduce lipid deposition. The majority of the studies performed using rodent models have reported that diets containing TFA have resulted in the same or lower body weights than control diets containing *cis* FA.<sup>18,20,21,23,24,26</sup> However, the two studies that measured hormones associated with appetite and weight gain reported lower leptin<sup>21,23</sup> and higher adiponectin and resistin levels<sup>21</sup> in animals fed diets containing 4.5 or 20% TFA than animals on *cis* MUFA-based control diets, despite there being no differences in weight between groups. Leptin, adiponectin and resistin are hormones secreted by adipose tissue.<sup>49</sup> Leptin levels are correlated with the amount of adiposity, and reduce during caloric restriction.<sup>49</sup> Rodent studies have suggested that resistin levels increase in obese animals, and may be involved in the development of insulin resistance, but that higher adiponectin levels are associated with improved weight and glycaemic control.<sup>50</sup> Two groups did find differences in body weight; one observed increased body weight, carcass fat and *de novo* synthesis of FA in animals fed 1.05% TFA, despite the rats consuming less food than those on control diets containing no TFA.<sup>28</sup> The second study fed diets containing 4.6% of E as TFA and also reported increased weight, although this was most likely due to increased food consumption.<sup>29</sup> However, irrespective of body weight, the TFA-fed group had a higher proportion of

**Table 3** Meal studies investigating the association of TFA with changes in body weight

Reference	Subject population (M/F)	Design	Time period for study	Test diet/meal	Fatty acid composition (% of daily/meal E)				Lipid oxidation	Other parameters
					S	M	P	T		
DeLany <i>et al.</i> <sup>45</sup>	4/0 Healthy, normal weight	X	7 days baseline diet prior to first test meal; test meal every 2–4 days with baseline diet for remaining meals throughout the study	Laurate Palmitate Stearate Oleate Elaidate Linoleate Linolenate	10 mg per kg body weight of the specified <sup>13</sup> C-labelled fatty acid, 98% chemically pure				40.6 ± 7.0 <sup>a</sup> <sup>13</sup> CO <sub>2</sub> /9 h 15.8 ± 2.8 <sup>c,d</sup> 13.0 ± 4.7 <sup>d</sup> 17.9 ± 3.8 <sup>c,d</sup> 20.5 ± 3.0 <sup>b,c</sup> 19.8 ± 5.4 <sup>b,c</sup> 27.0 ± 7.0 <sup>b</sup>	NA
Lovejoy <i>et al.</i> <sup>46</sup>	13/12 Healthy but some overweight	X	4 weeks per diet	SFA MUFA TFA	11.3 5.8 7.3	9.3 15.2 8.4	6.4 6.3 4.0	0.0 0.0 7.3	29.0 ± 1.5 <sup>a,b</sup> g day <sup>-1</sup> 26.0 ± 1.5 <sup>a</sup> 31.4 ± 1.5 <sup>b</sup>	No changes in insulin metabolism (see Diabetes section)
Lefevre <i>et al.</i> <sup>47</sup>	10/12 Healthy but overweight	X	16 days baseline diet, test breakfast meal on days 10 and 16	<i>Cis</i> 18:1 <i>Trans</i> 18:1	15 15	20 10	15 15	0 10	16.0 ± 1.2 kJ/8 h kg <sup>-1</sup> 16.9 ± 1.5	Acute insulin resistance and hyperinsulinaemia on TFA diet
Flint <i>et al.</i> <sup>48</sup>	19/0 Healthy but overweight	X	Free-living situation, test breakfast meal given after overnight fast, 3-day washout between meals	PUFA* MUFA TFA	6.5 4.6 18.1	10.3 49.8 8.1	42.1 NR NR	0.6 1.44 32.4	Not measured	No changes in post-prandial appetite, <i>ad libitum</i> energy intake or energy efficiency

Abbreviations: E, energy; MUFA, monounsaturated fatty acid; NA, not applicable; NR, not reported; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid; TFA, trans fatty acid; X, cross-over or Latin square design. \*Fatty acid composition of the diets was reported as a function of specific fatty acids (16:0, 18:0, 18:1, 18:1t, 18:2t, 18:2, 18:3), and thus included the category 'other', which made up 0.9% of PUFA diet, 7.0% of the MUFA diet and 2.4% of the TFA diet. Means within columns with different superscript letters are significantly different,  $P < 0.05$ .

visceral adipose tissue. This possible change in fat distribution was also noted by a recent long-term study in monkeys, which reported that animals consuming 8% of E as TFA had increased weight gain and intra-abdominal fat deposition, as well as marked post-prandial hyperinsulinaemia.<sup>30</sup>

All five prospective cohort studies have found statistically significant correlations between TFA intake and weight gain or retention. The three reports based on data from the Nurses' Health Study showed a small positive association,<sup>39–41</sup> with a weight increase over 8 years of approximately 0.5–1.0 kg for a 1% of E increase in TFA. Data from the Health Professionals' Follow-up Study showed that an increase of 2% of E from TFA was associated with a 2.7-cm increase in WC over 9 years,<sup>42</sup> and a small study reported increased post-partum weight retention in women consuming higher levels of TFA.<sup>44</sup> It is interesting to include the primate study here as a reference point, as it is obviously a much more closely controlled situation, but in monkeys rather than humans.<sup>30</sup> The relative weight gain of the TFA-fed monkeys compared with the *cis* FA group is  $\approx 0.68\%$  over 8 years for a 1% increase in E from TFA. Assuming this result is transferable to humans, the weight gain associated with 1% E from TFA would be around 0.45 kg for a 65-kg woman over 8 years, which is very similar to the results obtained in the reports from the Nurses' Health Study.

There are no long-term RCTs that have evaluated the impact of TFA intakes on weight change, but a small number of meal studies have investigated the potential metabolic effects of TFA compared with SFA and MUFA: three using acute meal challenges and one using 4-week dietary inter-

ventions. Two studies reported that TFAs were oxidized more rapidly than *cis* isomers,<sup>45, 47</sup> but a third found no significant difference.<sup>46</sup> Another meal study that evaluated the effect of TFA on appetite, energy intake and energy efficiency failed to observe any difference between diets.<sup>48</sup>

The results of the prospective cohort and primate studies do seem to tell a cohesive story, but there is a lack of supporting data from meal studies or RCTs, and conflicting results in the cell and rodent models. It is also difficult to identify a clear mechanism for an effect of TFA on weight gain. However, even if there is indeed a positive relationship between weight gain and TFA intake, the effect appears to be very small—possibly around 60–125 g per year for an increase in TFA consumption of 1% of E. However, it is important to consider the possibility that some groups may be more susceptible to weight gain (or metabolic effects) owing to TFA consumption, potentially because of age, gender, genetics or other physiological factors. It should be noted that in one analysis of the Nurses' Health Study, the combination of all nutrients studied, including TFA, only contributed 0.8% to the variation in weight gain over the 8-year period, with age, relative weight and previous weight gain making the largest contributions.<sup>39</sup> Associations between dietary variables and body weight or weight gain are likely to be confounded by a very large number of other variables, some of which have not been measured and therefore cannot be adjusted for, and it cannot be ruled out that such a small increase in weight may be simply because of a confounding factor that has not been accounted for.

**Table 4** Overall summary of human and primate studies assessing impact of TFA intake on aspects of weight gain

Paper	Population	TFA intake	Outcome measures	Significant negative effect of TFA
<i>Population and case-control studies (human)</i>				
Merchant et al. <sup>38</sup>	Canada N = 617, M+F	0.43 ± 0.52 g day <sup>-1</sup>	Waist:hip ratio	X
Larque et al. <sup>32</sup>	Spain Obese (N = 34) and non-obese (N = 20), M+F children	< 1 g TFA per day	Plasma TFA between obese and normal weight	X
Bortolotto et al. <sup>31</sup>	Brazil Morbidly obese and non-obese (N = NR), M+F	NR	Correlation between BMI and TFA in adipose tissue	X
<i>Prospective cohort studies (human)</i>				
Colditz et al. <sup>39</sup>	USA, Nurses' Health Study N = 31 940, W, 8 years	NR	Association between BMI and TFA intake	✓
Field et al. <sup>40</sup>	USA, Nurses' Health Study N = 41 518, W, 8 years	Mean for cohort 1.7 ± 0.5%	Association between increases in TFA intake and weight gain	✓
Wannamethee et al. <sup>41</sup>	USA, Nurses' Health Study N = 49 324, W, 8 years	NR	Association between TFA intake and weight gain in heavy drinkers	X
Koh-Banerjee et al. <sup>42</sup>	USA, HPFS N = 16 587, M	Mean for cohort 1.3 ± 0.6% of E	Waist circumference	✓
Oken et al. <sup>44</sup>	USA N = 902, F, post-partum	Median intake 1.1–1.3% of E	Post-partum weight retention	✓
<i>RCT and meal studies (human and primate)</i>				
Kavanagh et al. <sup>30</sup>	Male African green monkeys N = 42, 6-year diet	~ 8% of E as <i>cis</i> or <i>trans</i> 18:1	Weight gain Post-prandial insulin levels Volume of intra-abdominal:subcutaneous fat	✓ ✓ ✓
DeLany et al. <sup>45</sup>	N = 4, M, isoenergetic meals	<sup>13</sup> C-labelled FA at 10 mg per kg body weight	FA oxidation	X
Lovejoy et al. <sup>46</sup>	N = 25, M+F, 4-week diets	7–9% of E as <i>cis</i> or <i>trans</i> 18:1	Fat oxidation	X
Lefevre et al. <sup>47</sup>	N = 22, M+F, isoenergetic meals	10% of E as <i>cis</i> or <i>trans</i> 18:1	Carbohydrate oxidation	X
Flint et al. <sup>48</sup>	N = 19, M, isoenergetic meals	0–32% of E from TFA	Fat oxidation Carbohydrate oxidation Acute post-prandial appetite <i>Ad libitum</i> energy intake Energy efficiency	X X X X X

Abbreviations: BMI, body mass index; E, energy; F, female; FA, fatty acid; HPFS, Health Professionals' Follow-up Study; M, male; NR, not reported; TFA, *trans* fatty acids. 'X' means that there is no negative effect of TFA. The tick marks indicate that the study did show a negative effect of TFA.

## Conclusion

Epidemiological studies provide limited but consistent evidence to support a weak association between TFA consumption and a small increase in weight gain. There are conflicting data from animal studies, but a recent long-term and well-controlled study in a primate model has produced data that support a greater adipogenic effect of TFA than *cis* MUFA, with the size of the effect being similar to that reported in human studies. The strength of this evidence needs to be considered against the background of the lack of a plausible biological mechanism that can explain differences in energy utilization or fat deposition between different dietary FA.

## Conflict of interest

The authors declare no conflict of interest.

## References

- Vimaleswaran KS and Loos RJF (2010). Progress in the genetics of common obesity and type 2 diabetes. *Expert Rev Mol Med* 2010; 12: e7.
- Rosenheck R. Fast food consumption and increased caloric intake: a systematic review of a trajectory towards weight gain and obesity risk. *Obesity Rev* 2008; 9: 535–547.
- Farmer SR. Obesity: be cool, lose weight. *Nature* 2009; 458: 839–840.
- Patel SR, Hu FB. Short sleep duration and weight gain: a systematic review. *Obesity* 2008; 16: 643–653.
- Rundle A, Roux AVD, Freeman LM, Miller D, Neckerman KM, Weiss CC. The urban built environment and obesity in New York City: a multilevel analysis. *Am J Health Promot* 2007; 21 (Suppl 4): 326–334.
- Lindström M. Means of transportation to work and overweight and obesity: a population-based study in southern Sweden. *Prev Med* 2008; 46: 22–28.
- Garland E, Remick R, Zis A. Weight gain with antidepressants and lithium. *J Clin Psychopharmacol* 1988; 8: 323–330.
- Cohen-Cole E, Fletcher JM. Is obesity contagious? Social networks vs environmental factors in the obesity epidemic. *J Health Econ* 2008; 27: 1382–1387.

- 9 Boltri J, House A, Nelson R. Clinical inquiries. Which strategies work best to prevent obesity in adults? *J Fam Pract.* 2009; **58**: 668–676.
- 10 Moussavi N, Gavino V, Receveur O. Could the quality of dietary fat, and not just its quantity, be related to risk of obesity? *Obesity* 2009; **16**: 7–15.
- 11 Mann GV. Metabolic consequences of dietary *trans* fatty acids. *Lancet* 1994; **343**: 1268–1271.
- 12 Mozaffarian D, Aro A, Willett WC. Health effects of *trans*-fatty acids: experimental and observational evidence. *Eur J Clin Nutr* 2009; **63** (Suppl 2): S5–S21.
- 13 SACN. *Update on Trans Fatty Acids and Health. Position Statement by the Scientific Advisory Committee on Nutrition (SACN)*. HMSO: London, 2007.
- 14 SACN. A Framework for evaluation of evidence that relates food and nutrients to health. [http://www.sacn.gov.uk/pdfs/sacn\\_02\\_02a.pdf](http://www.sacn.gov.uk/pdfs/sacn_02_02a.pdf) 2002.
- 15 Panigrahi K, Sampugna J. Effects of *trans* fatty acids on lipid accumulation in 3T3-L1 cells. *Lipids* 1993; **28**: 1069–1074.
- 16 Cromer KD, Jenkins TC, Thies EJ. Replacing *cis* octadecenoic acid with *trans* isomers in media containing rat adipocytes stimulates lipolysis and inhibits glucose utilization. *J Nutr* 1995; **125**: 2394–2399.
- 17 Guzmán M, Klein W, Gómez del Pulgar T, Geelen M. Metabolism of *trans* fatty acids by hepatocytes. *Lipids* 1999; **34**: 381–386.
- 18 Privett OS, Phillips F, Shimasaki H, Nozawa T, Nickell EC. Studies of effects of *trans* fatty acids in the diet on lipid metabolism in essential fatty acid deficient rats. *Am J Clin Nutr* 1977; **30**: 1009–1017.
- 19 Atal S, Zarnowski MJ, Cushman SW, Sampugna J. Comparison of body weight and adipose tissue in male C57Bl/6J mice fed diets with and without *trans* fatty acids. *Lipids* 1994; **29**: 319–325.
- 20 Colandre ME, Diez RS, Bernal CA. Metabolic effects of *trans* fatty acids on an experimental dietary model. *Br J Nutr* 2003; **89**: 631–638.
- 21 Huang Z, Wang B, Pace RD, Yoon S. *Trans* fat intake lowers total cholesterol and high-density lipoprotein cholesterol levels without changing insulin sensitivity index in Wistar rats. *Nutr Res* 2009; **29**: 206–212.
- 22 Giudetti AM, Beynen AC, Lemmens AG, Gnoni GV, Geelen MJH. Hepatic fatty acid metabolism in rats fed diets with different contents of C18:0, C18:1 *cis* and C18:1 *trans* isomers. *Br J Nutr* 2003; **90**: 887–893.
- 23 Koppe SWP, Elias M, Moseley RH, Green RM. *Trans* fat feeding results in higher serum alanine aminotransferase and increased insulin resistance compared with a standard murine high-fat diet. *Am J Physiol Gastrointest Liver Physiol* 2009; **297**: G378–G384.
- 24 Tardy A-L, Giraudet C, Rousset P, Rigaudiere J-P, Laillet B, Chalancou S *et al*. Effects of *trans* MUFA from dairy and industrial sources on muscle mitochondrial function and insulin sensitivity. *J Lipid Res* 2008; **49**: 1445–1455.
- 25 European Food Safety Authority. Opinion of the scientific panel on the dietetic products, nutrition and allergies on a request from the Commission related to the presence of *trans* fatty acids in foods and the effect on human health of the consumption of *trans* fatty acids. *EFSA J* 2004; **81**: 1–49.
- 26 Wang Y, Lu J, Ruth MR, Goruk SD, Reaney MJ, Glimm DR *et al*. *Trans*-11 vaccenic acid dietary supplementation induces hypo-lipidemic effects in JCR:LA-cp rats. *J Nutr* 2008; **138**: 2117–2122.
- 27 Wang Y, Jacome-Sosa MM, Ruth MR, Goruk SD, Reaney MJ, Glimm DR *et al*. *Trans*-11 vaccenic acid reduces hepatic lipogenesis and chylomicron secretion in JCR:LA-cp rats. *J Nutr* 2009; **139**: 2049–2054.
- 28 Silva APS, Guimarães DED, Mizurini DM, Maia IC, Ortiz-Costa S, Sardinha FL *et al*. Dietary fatty acids early in life affect lipid metabolism and adiposity in young rats. *Lipids* 2006; **41**: 535–541.
- 29 Dorfman SE, Laurent D, Gounarides JS, Li X, Mullarkey TL, Rocheford EC *et al*. Metabolic implications of dietary *trans*-fatty acids. *Obesity* 2009; **17**: 1200–1207.
- 30 Kavanagh K, Jones KL, Sawyer J, Kelley K, Carr JJ, Wagner JD *et al*. *Trans* fat diet induces abdominal obesity and changes in insulin sensitivity in monkeys. *Obesity* 2007; **15**: 1675–1684.
- 31 Bortolotto JW, Reis C, Ferreira A, Costa S, Mottin CC, Souto AA *et al*. Higher content of *trans* fatty acids in abdominal visceral fat of morbidly obese individuals undergoing bariatric surgery compared to non-obese subjects. *Obes Surg* 2005; **15**: 1265–1270.
- 32 Larque E, Gil-Campos M, Ramirez-Tortosa MC, Linde J, Canete R, Gil A. Postprandial response of *trans* fatty acids in prepubertal obese children. *Int J Obes Relat Disord* 2006; **30**: 1488–1493.
- 33 Innis SM, Green TJ, Halsey TK. Variability in the *trans* fatty acid content of foods within a food category: implications for estimation of dietary *trans* fatty acid intakes. *J Am Coll Nutr* 1999; **18**: 255–260.
- 34 van de Vijver LPL, Kardinaal AFM, Couet C, Aro A, Kafatos A, Steingrimsdottir L *et al*. Association between *trans* fatty acid intake and cardiovascular risk factors in Europe: the TRANSFAIR study. *Eur J Clin Nutr* 2000; **54**: 126–135.
- 35 Food Standards Australia New Zealand. Intakes of *trans* fatty acids in New Zealand and Australia. [http://www.foodstandards.gov.au/\\_srcfiles/TFAs\\_intakes\\_2009.pdf](http://www.foodstandards.gov.au/_srcfiles/TFAs_intakes_2009.pdf) 2009.
- 36 Health Canada. TRANSforming the Food Supply, Report of the Trans Fat Task Force. [http://www.hc-sc.gc.ca/fnan/nutrition/gras-trans-fats/tf-gt/tf-gt\\_rep-rap\\_e.html](http://www.hc-sc.gc.ca/fnan/nutrition/gras-trans-fats/tf-gt/tf-gt_rep-rap_e.html) 2006.
- 37 Lemaitre RN, King IB, Patterson RE, Psaty BM, Kestn M, Heckbert SR. Assessment of *trans*-fatty acid intake with a food frequency questionnaire and validation with adipose tissue levels of *trans*-fatty acids. *Am J Epidemiol* 1998; **148**: 1085–1093.
- 38 Merchant AT, Anand SS, Vuksan V, Jacobs R, Davis B, Teo K *et al*. Protein intake is inversely associated with abdominal obesity in a multi-ethnic population. *J Nutr* 2005; **135**: 1196–1201.
- 39 Colditz GA, Willett WC, Stampfer MJ, London SJ, Segal MR, Speizer FE. Patterns of weight change and their relation to diet in a cohort of healthy women. *Am J Clin Nutr* 1990; **51**: 1100–1105.
- 40 Field AE, Willett WC, Lissner L, Colditz GA. Dietary fat and weight gain among women in the Nurses' Health Study. *Obesity* 2007; **15**: 967–976.
- 41 Wannamethee S, Field A, Colditz G, Rimm E. Alcohol intake and eight year weight gain in women; a prospective study. *Obes Res* 2004; **12**: 1386–1396.
- 42 Koh-Banerjee P, Chu N-F, Spiegelman D, Rosner B, Colditz G, Willett W *et al*. Prospective study of the association of changes in dietary intake, physical activity, alcohol consumption, and smoking with 9-y gain in waist circumference among 16 587 US men. *Am J Clin Nutr* 2003; **78**: 719–727.
- 43 Rimm EB, Stampfer MJ, Colditz GA, Chute CG, Litin LB, Willett WC. Validity of self-reported waist and hip circumferences in men and women. *Epidemiology* 1990; **1**: 466–473.
- 44 Oken E, Taveras EM, Popoola FA, Rich-Edwards JW, Gillman MW. Television, walking, and diet: associations with postpartum weight retention. *Am J Prev Med* 2007; **32**: 305–311.
- 45 DeLany JP, Windhauser MM, Champagne CM, Bray GA. Differential oxidation of individual dietary fatty acids in humans. *Am J Clin Nutr* 2000; **72**: 905–911.
- 46 Lovejoy JC, Smith SR, Champagne CM, Most MM, Lefevre M, DeLany JP *et al*. Effects of diets enriched in saturated (palmitic), monounsaturated (oleic), or *trans* (elaidic) fatty acids on insulin sensitivity and substrate oxidation in healthy adults. *Diabetes Care* 2002; **25**: 1283–1288.
- 47 Lefevre M, Lovejoy JC, Smith SR, DeLany JP, Champagne C, Most MM *et al*. Comparison of the acute response to meals enriched with *cis*- or *trans*-fatty acids on glucose and lipids in overweight individuals with differing FABP2 genotypes. *Metabolism* 2005; **54**: 1652–1658.
- 48 Flint A, Helt B, Raben A, Trouero S, Astrupa A. Effects of different dietary fat types on postprandial appetite and energy expenditure. *Obes Res* 2003; **11**: 1449–1455.
- 49 Das UN. Is obesity an inflammatory condition? *Nutrition* 2001; **17**: 953–966.
- 50 Ouchi N, Ohishi M, Kihara S, Funahashi T, Nakamura T, Nagaretani H *et al*. Association of hypoadiponectinemia with impaired vasoreactivity. *Hypertension* 2003; **42**: 231–234.