

# Fats and Fatty Acid Requirements for Adults

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## Introduction

The FAO/WHO established criteria to describe the strength of evidence for developing dietary guidelines. The evidence is classified as convincing, probable, possible, and insufficient [Smit et al., 2009].

## Dietary Recommendations for Total Fat Intake

An overview of dietary recommendations for fat and fatty acid intake is provided in table 1. Fat has the highest energy value of all macronutrients. Protein and carbohydrate provide only about half of the energy per unit weight. Therefore, carbohydrate and protein can reduce the energy intake when they are eaten instead of fat (under the condition that the intake in grams is unchanged). Kilojoules from fat, protein and carbohydrates are not equal. Studies have demonstrated that fat has a reduced satiating influence compared to protein and carbohydrate [Prentice, 1998]. In addition, foods high in fat induce a lesser specific thermic response than meals high in carbohydrate or protein, and therefore, they are more efficiently stored in the body. An overconsumption of foods high in fat can also be induced by palatability [Schutz et al., 1989; Horton et al., 1995; Blundell and MacDiarmid, 1997; Westerterp et al., 1999]. Moreover, animal studies have shown that high-fat diets can increase the total number and size of the body's fat cells. After a switch from a high-fat to a low-fat diet, the fat cells can return to

normal size, but the increased number of fat cells may limit the successful reversal of obesity [Bray and Popkin, 1998].

## Overweight and Obesity

In most countries, the prevalence of obesity and overweight have increased severely [WHO, 2000].

Some prospective studies have demonstrated that foods high in fat and energy are associated with weight gain [Klesges et al., 1992; Schulz et al., 2002; Newby et al., 2003]. On the other hand, other prospective studies have yielded conflicting results on this topic [Colditz et al., 1990; Kant et al., 1995; Ludwig et al., 1999]. A randomized intervention trial of 48,835 postmenopausal women investigated the relationship between increasing obesity and low-fat and high-carbohydrate diets in the USA. The women (19,541) in the intervention group (29.8% fat from energy) reduced their body weight in the first year and kept a lower weight compared with the control group (38.1% fat from energy) during an average of 7.5 years of follow-up [Howard et al., 2006].

In another randomized study, the goal was to evaluate the effects of increased fruit and vegetable intake and reduced fat and sugar intake in families at risk of offspring obesity. The increase in fruit and vegetable consumption was associated with a lowered high-fat and high-sugar intake. The dietary changes resulted in a significant decrease in percentage of overweight in adults and prevented obesity in the children [Epstein et al., 2001].

**Table 1.** Dietary recommendations for fat and fatty acid intake

Total fat, %E	AMDR	20–35	con <sup>1</sup> ; pro <sup>2</sup> ; ins <sup>3</sup>
	MAL	35	
	MIL	15	
SFAs, %E	MAL	10	con <sup>4–7</sup> ; pro <sup>8,9</sup> ; ins <sup>10</sup>
MUFAs, %E	AMDR	by difference <sup>a,b</sup>	con <sup>4,11</sup> ; pos <sup>12</sup>
Total PUFAs, %E	AMDR (LA + ALA + EPA + DHA)	6–11	con <sup>4,7</sup>
	MAL	11	pos <sup>13</sup>
	MIL (to prevent deficiency)	3	con <sup>14</sup> ; pos <sup>15</sup>
	MIL (to prevent chronic diseases)	6	
n–6 PUFAs, %E	AMDR (LA)	2.5–9	con <sup>4,7</sup> ; pos <sup>15</sup>
	Average LA requirement	2	
	Individual LA level	2.5	con <sup>14</sup> ; pos <sup>15</sup>
n–3 PUFAs	AMDR (n–3 <sup>c</sup> ), %E	0.5–2	con <sup>14</sup> ; pos <sup>15</sup>
	Minimum requirement (ALA), %E	≥0.5	
	AMDR (EPA + DHA), g/day	0.250–2 <sup>d</sup>	con <sup>16</sup> ; pro <sup>17,18</sup> ; pos <sup>19</sup> ; ins <sup>20</sup>
	MAL <sup>e</sup> , g/day	3	
TFAs, %E	UL (from ruminants and industrially produced sources)	1	con <sup>6,21</sup> ; pro <sup>22</sup>

<sup>a</sup> Total fat [%E] – SFAs [%E] – PUFAs [%E] – TFAs [%E]; <sup>b</sup> can amount up to 15–20%E; <sup>c</sup> ALA + n–3 long-chain PUFAs; <sup>d</sup> for secondary prevention; <sup>e</sup> including supplements.

ALA =  $\alpha$ -Linolenic acid; AMDR = acceptable macronutrient distribution range; con = convincing; DHA = docosahexaenoic acid; E = energy; EPA = eicosapentaenoic acid; ins = insufficient; LA = linoleic acid; MAL = maximum level; MIL = minimum level; MUFAs = monounsaturated fatty acids; PUFAs = polyunsaturated fatty acids; pos = possible; pro = probable; SFAs = saturated fatty acids; TFAs = *trans* fatty acids; UL = upper level.

<sup>1</sup> con: Energy balance, dietary patterns, and optimal nutrient intakes are important for healthy body weight, apart from macronutrient distribution expressed in %E.

<sup>2</sup> pro: No relation with coronary heart disease (CHD) events, fatal CHD.

<sup>3</sup> ins: Association between total fat intake and body weight.

<sup>4</sup> con: Substituting SFAs (C12:0–C16:0) with PUFAs and MUFAs reduces LDL-cholesterol levels and the TC/HDL cholesterol ratio.

<sup>5</sup> con: Substituting SFAs (C12:0–C16:0) with mainly refined carbohydrates reduces LDL- and HDL-cholesterol levels, but has no effect on the TC/HDL-cholesterol ratio.

<sup>6</sup> con: Substituting SFAs (C12:0–C16:0) with TFAs decreases HDL-cholesterol levels and increases the TC/HDL-cholesterol ratio.

<sup>7</sup> con: ↓ Risk of CHD events when PUFAs replace SFAs.

<sup>8</sup> pro: Increased SFA intake results in increased weight.

<sup>9</sup> pro: Substituting SFAs with mainly refined carbohydrates does not impair the risk of CHD, but may support the development of metabolic syndrome.

<sup>10</sup> ins: Substituting SFAs with mainly whole grain carbohydrates does not impair the risk of CHD.

<sup>11</sup> con: Substituting carbohydrates with MUFAs raises HDL-cholesterol levels.

<sup>12</sup> pos: Substituting carbohydrates with MUFAs improves insulin sensitivity.

<sup>13</sup> pos: ↑ Lipid peroxidation with high consumption levels, especially when tocopherol intake is low.

<sup>14</sup> con: Essential.

<sup>15</sup> pos: Specific minimum required to prevent deficiency.

<sup>16</sup> con: Strong inverse relationship is present between n–3 LCPUFAs or fish intake and risk of CHD.

<sup>17</sup> pro: Fish intake probably decreases colorectal cancer risk.

<sup>18</sup> pro: n–3 LCPUFAs and fish oil have probable benefits for depression.

<sup>19</sup> pos: n–3 LCPUFAs and fish oil have possible benefits for bipolar disorder, cognitive decline, aggression, hostility, anti-social behavior and age-related maculopathy.

<sup>20</sup> ins: n–3 LCPUFAs and fish oil have insufficient benefits for Alzheimer's disease, schizophrenia, and Huntington's disease.

<sup>21</sup> con: ↑ Risk of CHD events.

<sup>22</sup> pro: ↑ Risk of fatal CHD and sudden cardiac death.

In the Women's Healthy Lifestyle Project Clinical Trial, the goal was to reduce the saturated fat and cholesterol intake and prevent weight gain during the perimenopausal to postmenopausal period in women by reducing energy and fat intake and increasing physical

activity. The intervention group participants (260) reduced their dietary fat intake to 25% of total energy, whereas in the control group the fat intake was about 30%E (percentage of energy). The investigation demonstrated that the 'lifestyle intervention group' was able to

maintain body weight, whereas the control group increased weight during the investigation period (4.5 years) [Kuller et al., 2001].

In a 2-year trial, 322 obese volunteers were randomly assigned to 1 of 3 diets: low-fat (~30%E), restricted-calorie (1,500–1,800 kcal/day); Mediterranean diet, restricted-calorie (1,500–1,800 kcal/day); or low-carbohydrate, non-restricted-calorie. 272 subjects completed the intervention, and the mean weight reductions were 2.9 kg (low-fat diet), 4.4 kg (Mediterranean diet), and 4.7 kg (low-carbohydrate diet). Diabetic subjects, who were assigned to the Mediterranean diet, improved fasting plasma glucose and insulin levels more favorably than those following the low-fat diet. All 3 diets reduced the ratio of total cholesterol (TC) to HDL-cholesterol, ranging from –0.6 (low-fat diet) to –1.1 (low-carbohydrate diet) [Shai et al., 2008].

A meta-analysis from 28 clinical trials [Bray and Popkin, 1998] investigated the effects of a reduction of fat in the diet. The reduction of 10%E from fat was associated with 16 g weight loss per day. This study concluded that dietary fat influences the development of obesity by enhancing passive overconsumption of energy by raising the energy density of the diet. A strategy used to reduce the prevalence of obesity is related to an increase in physical activity and a reduction in total energy intake by reducing the amount of fat [Bray and Popkin, 1998].

The relevance of studies demonstrating a relation between dietary fat and obesity has been questioned [Willett and Leibel, 2002]. In short-term intervention studies, deriving a lower percentage of energy from fat can lower body weight, but the efficacy of low-fat diets in free-living subjects on an ad libitum basis has been challenged. It has been suggested that fat intake within the range of 18–40%E has little effect on weight gain. This is supported by the fact that in the USA, the percentage of energy from fat has been reduced, but an increase in obesity has occurred [Willett and Leibel, 2002]. Therefore, the role of ad libitum low-fat diets in weight gain and obesity was investigated in a meta-analysis (16 studies) [Astrup et al., 2000]. The results demonstrated that a low-fat diet, high in protein and complex carbohydrates, had beneficial effects on blood lipids. Iso-energetic low-fat diets maintained weight in subjects with normal BMI, whereas overweight subjects reduced their weight [Astrup et al., 2000].

The review by Melanson et al. [2009] demonstrated that there is insufficient evidence for the association between total fat intake and body weight and probable evidence that increased SFA intake results in increased weight.

### *Type 2 Diabetes Mellitus*

The prevalence of diabetes is increasing. The major form is type 2 diabetes mellitus, which demonstrates a strong association with overweight and obesity. However, cohort studies have yielded conflicting results on total fat intake and the positive association with type 2 diabetes [Feskens et al., 1995; Meyer et al., 2001; Salmeron et al., 2001; van Dam et al., 2002; Harding et al., 2004].

On the other hand, there is convincing evidence that insulin sensitivity and characteristics of metabolic syndrome can be improved by regular physical activity and a reduction in body weight [Sanders, 2009].

### *Plasma Lipids and Cardiovascular Disease (CVD)*

A meta-analysis of 37 dietary intervention studies from the National Cholesterol Education Program's (NCEP) Steps I and II were carried out in free-living subjects [Yu-Poth et al., 1999]. The Step I diet was composed of ≤30% total energy as fat, ≤10%E as SFAs, and ≤300 mg dietary cholesterol/day, and the Step II diet had ≤7%E as SFAs and ≤200 mg dietary cholesterol/day. The goal of these dietary interventions was to lower elevated TC and LDL-cholesterol levels, and thereby reduce the risk of CVDs. The meta-analysis demonstrated that the total fat intake correlated positively with TC, LDL-, and HDL-cholesterol levels. In addition, for every 1 kg decline in body weight, triglycerides (TGs) were diminished by 0.011 mmol/l and HDL-cholesterol levels improved by 0.011 mmol/l. Exercise also improved the lipid profile by a reduction in TC, LDL-cholesterol, and TG, and maintenance in HDL-cholesterol [Yu-Poth et al., 1999].

Studies have yielded conflicting results on total fat intake and the positive association with coronary heart disease (CHD) because the total fat intake is very heterogeneous in consideration of the fatty acid pattern [Khaw and Barrett-Connor, 1987; Fehily et al., 1993; Ascherio et al., 1996; Hu et al., 1997; Laaksonen et al., 2005; Oh et al., 2005]. A few studies have found a significant positive association between the incidence of CVD and the proportion of dietary energy intake from total fat [Esrey et al., 1996; Boniface and Tefft, 2002]. On the other hand, several cohort studies found no association between total fat intake from energy and CHD [Khaw and Barrett-Connor, 1987; Fehily et al., 1993; Ascherio et al., 1996; Hu et al., 1997; Laaksonen et al., 2005; Oh et al., 2005]. In the Women's Health Initiative Dietary Modification Trial, a randomized controlled trial of 48,835 postmenopausal women, the intervention group (19,541) reduced the total fat intake (to 20%E) and increased intakes of vegetables

and fruits. This study demonstrated that the intervention group did not significantly reduce the risk of primary CHD over a mean of 8.1 years [Howard et al., 2006].

The meta-analysis by Skeaff and Miller [2009] demonstrated that high (38–47%E) compared with low (23–30%E) total fat consumption was not significantly related with diverse risk factors of CHD events.

In addition, investigations demonstrated that low-fat high-carbohydrate diets were associated with reduced LDL- and HDL-cholesterol, and an increase in fasting TGs [Katan et al., 1994; Mensink et al., 2003].

*The FAO/WHO Expert Consultation (2008) agreed on the fact that there is convincing evidence that energy balance, dietary patterns, and optimal nutrient intakes are important for healthy body weight, apart from macronutrient distribution expressed in energy percentage.*

#### *Dietary Recommendations for Total Fat Intake*

The acceptable macronutrient distribution range (AMDR) for total fat intake can vary between 20 and 35%E (maximum: 35%E; minimum 15%E). While for most individuals with moderate physical activity 30%E is recommended, for those with high physical activity levels this can reach 35%E. The maximum level (MAL) of total fat intake is considered to be 35%E, with regard to energy balance and diet quality. However, high fat intakes are habitually accompanied by increased saturated fat, cholesterol, and energy density.

The dietary guidelines for Americans recognize that low-fat diets of <20%E can elevate the risk of inadequate intakes of essential fatty acids and fat-soluble vitamins, and may encourage changes in HDL-cholesterol levels and TGs [Department of Health and Human Services, 2005]. On the one hand, for some population groups, this aim ( $\geq 20$ –30%E) cannot be reached immediately due to their socioeconomic status. On the other hand, an increase in dietary fat intake of 15 to 20–30%E can also have adverse effects [Suh et al., 2001; Bourne et al., 2002; Vorster et al., 2005; Pieters and Vorster, 2008]. For instance, among urban blacks in Africa in the past 50 years, the dietary fat intake was increased from 16.4 to 26.2%E, while the proportion of carbohydrates has decreased from 69.3 to 61.7% of total energy. These changes to a 'Western' diet can also be observed among rural Africans. In 1998, the South African Demographic and Health Survey observed that 31.8% of African women (>15 years) were obese and that a further 26.7% were overweight, whereas 6.0% men were obese and 19.4% overweight [Bourne et al., 2002]. For this reason, promoting a dietary fat intake between 20 and 30 or even 35%E without hav-

ing a special focus on energy balance may not be favorable for all population groups and should be done with caution, especially when there are no obvious signs of deficiency. Therefore, the minimum level (MIL) of fat intake should not be less than 15%E, while paying attention to the adequate intake of essential fatty acids and energy needs. Nevertheless, it has to be considered that this lower limit of fat intake for adults is difficult to define because only a few investigations have addressed this topic [Walker and Walker, 1978; Jequier, 1999; Bourne et al., 2002].

### **Dietary Recommendations for SFAs**

#### *Plasma Lipids and CVD*

Different effects of SFAs on plasma cholesterol concentrations were observed in the mid-1950s. Short-(C4:0–C6:0) or medium-chain fatty acids (C8:0–C12:0) have little effects on plasma cholesterol levels due to the direct absorption into the portal circulation [Lichtenstein, 2006]. SFA intake raises atherogenic LDL- and antiatherogenic HDL-cholesterol levels compared with starch under iso-caloric replacement and lowers fasting TGs in blood plasma [Katan et al., 1994].

Individual SFA have different effects on plasma cholesterol levels. Lauric (C12:0), myristic (C14:0), and palmitic (C16:0) acids increase LDL- and HDL-cholesterol [Hegsted et al., 1993; Katan et al., 1994; Clarke et al., 1997; Yu-Poth et al., 1999], which can be explained by the observed reduction in LDL receptor activity, protein, and amount of mRNA [Fernandez and West, 2005]. Stearic acid decreased LDL-cholesterol relative to other SFA (lauric, myristic, and palmitic acids) and *trans* monounsaturated fatty acids (MUFAs) [Mensink, 2005]. The different mechanism is attributed to the high conversion rate of C18:0 to C18:1 (oleic acid) [Lichtenstein, 2006]. Stearic acid accounts for about a quarter of dietary saturated fats [Clarke et al., 1997].

LDL-cholesterol is a major risk factor for CHD. An animal study with monkeys demonstrated that polyunsaturated fatty acids (PUFAs) and MUFAs had similar effects on plasma LDL-cholesterol levels, whereas SFAs significantly raised LDL levels. Animals fed a MUFA-rich diet developed equivalent amounts of coronary artery atherosclerosis as those fed a diet rich in SFAs, but monkeys fed a PUFA-rich diet demonstrated less progression of atherosclerosis [Rudel et al., 1995]. Prospective cohort studies are especially useful in determining connections between diet and CHD. SFA intake was di-

rectly associated with CHD in several prospective epidemiological studies [McGee et al., 1984; Kromhout et al., 1985; Esrey et al., 1996; Kabagambe et al., 2003]. On the other hand, in some studies no association was found between the risk of CHD and SFAs [Yano et al., 1978; Pietinen et al., 1997]. In addition, the Health Professionals Follow-up Study demonstrated no strong relationship between the intake of SFA and risk of CHD, but SFA can raise blood cholesterol levels and therefore influence the risk of CHD [Ascherio et al., 1996]. Heterogenous results were obtained by Boniface and Tefft in 2002. Analyses demonstrated that women had a significantly higher CHD death rate associated with SFA intake. This trend was similar but weaker in men, and therefore not significant [Boniface and Tefft, 2002]. Jakobsen et al. [2004] obtained similar results, which demonstrated that SFA intake was associated with a greater risk of CHD among women, but not men. However, age influenced the results because among young men, the intake of saturated fat was positively associated with CHD [Jakobsen et al., 2004]. The Nurses' Health Study demonstrated that the risk of CHD can be reduced by replacing SFAs and *trans* fatty acids with *cis* MUFAs and PUFAs, and that especially the ratio of PUFAs to SFAs was strongly and inversely associated with the risk of CHD [Hu et al., 1997, 1999a; Oh et al., 2005].

The meta-analysis by Skeaff and Miller [2009] demonstrated that the relative risk of CHD death in the highest (14–18%E) category of SFA consumption was not significantly different from that in the lowest (7–11%E) category. High compared with low SFA consumption was not significantly related with diverse risk factors of CHD events.

A meta-analysis investigated the effects of the NCEP Steps I and II on major CVD risk factors [Yu-Poth et al., 1999]. In total, 37 dietary intervention studies from free-living subjects published between 1981 and 1997 were evaluated. The aim of the NCEP is to normalize cholesterol levels, and thereby lower CHD. The changes in the lifestyle should be implemented in 2 steps. Both diets (Step I and Step II) are planned to progressively reduce dietary SFAs and cholesterol, and to encourage weight loss, if required, through diet and regular physical activity. The Step I diet was characterized by  $\leq 30\%$ E as fat,  $\leq 10\%$ E as SFAs, and  $\leq 300$  mg dietary cholesterol/day; the Step II diet had  $\leq 7\%$ E as SFAs and  $\leq 200$  mg dietary cholesterol/day. The Step I diet reduced TC (10%), LDL-cholesterol (12%), TGs (8%), and TC to HDL-cholesterol (10%). The Step II diet reduced TC (13%), LDL-cholesterol (16%), TGs (8%), and TC to HDL-cholesterol (7%).

The investigation demonstrated that for each 1% reduction in SFAs (%E), total cholesterol levels decreased by 0.056 mmol/l and LDL-cholesterol by 0.05 mmol/l. In addition, for each 1 kg reduction in body weight, TGs decreased by 0.011 mmol/l and HDL-cholesterol was raised by 0.011 mmol/l. Regular physical activity reduced TC, LDL-cholesterol, and TGs, whereas HDL-cholesterol levels were maintained [Yu-Poth et al., 1999].

*The FAO/WHO Expert Consultation (2008) came to the following agreements:*

- *Individual SFA lauric (C12:0), myristic (C14:0), palmitic acids (C16:0), and stearic acid (C18:0) have different effects on plasma cholesterol levels. Lauric, myristic, and palmitic acids increase LDL-cholesterol levels compared with stearic acid.*
- *There is convincing evidence that substituting SFAs C12:0–C16:0 with PUFAs reduces LDL-cholesterol levels and the TC/HDL-cholesterol ratio. This effect can also be observed, but to a lesser extent, by substituting these SFAs with MUFAs.*
- *There is convincing evidence that exchanging SFAs (C12:0–C16:0) with mainly refined carbohydrates reduces LDL- and HDL-cholesterol levels, but has no effect on the TC/HDL-cholesterol ratio.*
- *There is convincing evidence that substituting (C12:0–C16:0) with trans fatty acids decreases HDL-cholesterol levels and increases the TC/HDL-cholesterol ratio.*

*Based on the results of epidemiological studies and trials on CHD (events and death) it was also agreed that:*

- *There is convincing evidence that substituting SFAs with PUFAs reduces the risk of CHD.*
- *There is probable evidence that substituting SFAs with mainly refined carbohydrates does not impair the risk of CHD, but may support the development of metabolic syndrome.*
- *There is insufficient evidence that substituting SFAs with mainly whole grain carbohydrates does not impair the risk of CHD.*

#### *FAO/WHO Dietary Recommendations for SFAs*

The intake of SFA should not exceed a MAL of 10%E to keep cholesterol levels in a normal range and to reduce the risk of CHD.

#### **Dietary Recommendations for MUFAs**

Oleic acid is the major MUFA, but there are also minor amounts of C16:1, C17:1 and C22:1 in the diet. Plant oils are good sources of MUFAs and PUFAs as well as nonsaponifiable compounds (e.g. phytosterols) that affect plasma cholesterol levels [Truswell and Choudhury, 1998].

### Plasma Lipids and CVD

High-carbohydrate diets and MUFA-rich diets have similar effects on plasma TC and LDL-cholesterol levels. Substituting MUFAs for SFAs (8%E) can reduce plasma TC (-9%) and LDL-cholesterol levels (-19%). Therefore, the energy-balanced reference diet has to be taken into consideration in the interpretation of the effects. On the other hand, MUFAs raise plasma TC and LDL-cholesterol levels compared with PUFAs [Katan et al., 1994; Kris-Etherton and Yu, 1997]. This effect was not confirmed by a meta-analysis, which selected a minority of the reports [Gardner and Kraemer, 1995]. The increase in postprandial TGs is higher from MUFAs than from SFAs and PUFAs [Nielsen et al., 2002; Koutsari et al., 2004].

Two strictly controlled diets, one high in complex carbohydrates and the other high in MUFAs, were used to investigate the effects on serum lipids. With both diets, serum cholesterol levels (TC) fell. HDL-cholesterol was reduced only in the carbohydrate diet and increased in the MUFA diet. Serum TGs were increased in the carbohydrate diet and decreased slightly in the MUFA diet. The results demonstrated that a high-complex carbohydrate diet can affect blood lipids ( $\downarrow$ TC,  $\downarrow$ HDL and  $\uparrow$ TG), while a diet rich in MUFAs did not demonstrate this effect ( $\downarrow$ TC,  $\uparrow$ HDL and  $\downarrow$ TG) [Mensink and Katan, 1987].

Prospective cohort studies demonstrated diverse results on the relationship between MUFAs and coronary events. Two Italian rural cohorts of the Seven Countries Study on CVD demonstrated that subjects with coronary deaths had significantly lower intakes of MUFAs than survivors, although confounders due to the study design cannot be excluded [Farchi et al., 1989]. The Framingham cohort study showed in the younger group (aged 45–55 years) significant positive associations between the incidence of CHD and the dietary intake of total fat and MUFAs [Posner et al., 1991]. Similar results were obtained by a cohort study [Esrey et al., 1996], where increased %E intakes as total fat, SFAs, and MUFAs were significantly associated with CHD mortality among 30- to 59-year-olds.

The US Nurses' Health Study showed a significant negative association of MUFAs with CHD after several adjustments, and demonstrated that the risk of CHD can be reduced by replacing saturated and *trans* fatty acids with *cis* MUFAs and PUFAs [Hu et al., 1997]. Other studies demonstrated no significant association between the intake of MUFAs and the risk of CHD [Pietinen et al., 1997; Oh et al., 2005].

The FAO/WHO Expert Consultation (2008) came to the following agreements:

- There is convincing evidence that substituting carbohydrates with MUFAs raises HDL-cholesterol levels.
- There is possible evidence that substituting carbohydrates with MUFAs improves insulin sensitivity.
- There is convincing evidence that substituting SFAs (C12:0–C16:0) with MUFAs lowers LDL-cholesterol levels and the TC/HDL-cholesterol ratio.

### FAO/WHO Dietary Recommendations for MUFAs

MUFA intake is calculated by: total fat intake (MIL 15%E, MAL 35%E) minus SFAs (MAL 10%E) minus PUFAs (MIL 3%E; MAL 11%E) minus TFAs (UL 1%E). For this reason, MUFA intake can show a wide range depending on the total fat intake and dietary fatty acid pattern.

### Dietary Recommendations for PUFAs

#### Plasma Lipids and CVD

When PUFAs replace carbohydrates, they lower TC and LDL-cholesterol [Clarke et al., 1997]. Compared with SFAs, PUFAs also reduce TC, LDL-cholesterol, and (slightly) HDL-cholesterol concentrations [Kris-Etherton and Yu, 1997]. The predominant PUFA is linoleic acid (LA) followed by  $\alpha$ -linolenic acid (ALA).

A high intake of PUFAs has been suggested to have cardioprotective effects. The diet and heart study demonstrated a significant inverse association between a high PUFA/SFA ratio and CHD mortality after 5 years. However, this result was not sustained after 10 years of follow-up [Morris et al., 1977]. Two Italian cohorts of the Seven Countries Study demonstrated that survivors had a significant higher intake of PUFAs compared to subjects who died from CHD [Farchi et al., 1989]. Similar results were observed by Laaksonen et al. [2005]. The Nurses' Health Study demonstrated an inverse relationship of a high PUFA/SFA ratio with cardiovascular outcomes [Hu et al., 1997, 1999b]. These observations were confirmed after 20 years [Oh et al., 2005].

However, the cohort studies within the meta-analysis by Skeaff and Miller demonstrated that high (6–10%E) compared with low (3–4%E) PUFA diets were not significantly related to different risks of CHD events. A 5% increase in PUFA consumption was related with a significant fall in the relative risk of CHD events, but there was no significant relationship with CHD death [Skeaff and Miller, 2009].

In addition, several prospective studies did not find an inverse association between PUFA intake and the risk of CHD [Yano et al., 1978; McGee et al., 1984; Ascherio et al., 1996; Pietinen et al., 1997].

However, some intervention studies demonstrated a cardioprotective effect when foods rich in SFA were partly replaced by those rich in PUFAs [Christakis et al., 1966; Turpeinen, 1979].

The meta-analysis by Skeaff and Miller demonstrated that the restriction of the studies where PUFA/SFA diets significantly reduced mean serum cholesterol levels in the treatment group significantly lowered the risk of fatal CHD, whereas the relative risk of CHD events did not achieve statistical significance [Skeaff and Miller, 2009].

In summary, outcomes from epidemiologic studies and controlled clinical trials have shown that replacing SFAs with unsaturated fat (including *cis* MUFA and PUFA) is more successful in reducing the risk of CHD than simply reducing total fat consumption. These results are the basis for important changes in the recommendations for dietary fat intake [Hu et al., 2001; Sacks and Katan, 2002].

*The FAO/WHO Expert Consultation (2008) considered that there was convincing evidence showing that substituting SFAs with PUFAs reduces the risk of CHD [see p. 60].*

#### *Dietary Recommendations for n-6 and n-3 PUFA Intake*

The minimum intake levels for essential fatty acids are 2.5%E LA plus 0.5%E ALA to prevent deficiency symptoms. Effective intake levels for chronic disease prevention lie between 6 and 11%E, which is considered to be the acceptable range for total PUFAs (n-6 and n-3 fatty acids). The minimum intake level (3%E) corresponds to the prevention of deficiency symptoms, whereas the range of medium (6%E) to high (11%E) intakes can form part of a healthy heart diet by lowering TC and LDL-cholesterol levels, and therefore decreasing the risk of CHD. However, 11%E are also regarded as the MAL for total PUFAs due to a decrease in bioavailability of vitamin E leading to a higher risk of lipid peroxidations, especially when tocopherol supply is not increased accordingly [Elmadfa and Schwalbe, 1989]. High amounts (>11%E) of PUFAs (especially n-6 fatty acids) are recognized to increase the susceptibility of LDL oxidation compared with diets high in SFAs and MUFAs [Berry et al., 1991; Abbey et al., 1993; Kratz et al., 2002].

## **Dietary Recommendations for n-6 Fatty Acids**

### *Dietary Recommendations for LA*

#### *Prevention of Deficiency*

In 1929, Burr and Burr discovered the deficiency syndromes of essential PUFAs by feeding rats a fat-free diet. The observed deficiency signs included scaliness of skin, necrosis of the tail, reduced growth, degeneration of kidneys, and failure to reproduce. The syndromes were only attributed to LA. It was observed that LA enhanced growth and prevented dermatitis when it was additionally fed to rats receiving a fat-free diet [Holman, 1978, 1998].

Further investigations have demonstrated that both LA and ALA are essential for humans. This has been clearly demonstrated in hospitalized patients getting lipid-free total parenteral nutrition. On average, the onset of a deficiency of essential fatty acids is obvious within 4–6 weeks of fat-free parenteral nutrition with dextrose as the single caloric substrate. In addition, malabsorption of essential fatty acids (LA, ALA), low dietary intake and increased physiological requirements (such as growth) promote biochemical signs of essential fatty acid deficiency within days to weeks and increase the risk of manifestations of clinical deficiency symptoms [Jeppesen et al., 1998].

A study on parenteral nutrition (12 patients) investigated the effect of intravenously administered essential fatty acids. The newer threshold triene-tetraene ratio of  $\geq 0.2$  was used for an essential fatty acid deficiency (Holman index). Therefore, the intravenous essential lipids were increased by the amount of lipids delivered in total nutrient admixtures in biweekly doses. They estimated that the subjects who required 1.2 g fat per kg of body weight every 14 days reached about 1.7% of their total caloric requirement by LA. It is also suggested that a dose of 1.8 g LA per kg body weight per 14 days can be estimated to about 2.5% of their total caloric requirements. Most subjects needed 1.2–1.8 g of LA/kg body weight/biweekly to correct the triene-tetraene ratio in adults, whereas deficiency signs of dermatitis for example were not obvious for the whole duration of the observation period. In this study, the focus on the establishment of the minimum requirement was centered around biochemical improvements in the Holman index [Mascioli et al., 1996].

On the other hand, the daily requirement was also estimated by the measurement of clinical deficiency signs (e.g. reduced growth, scaliness of skin, necrotic tail) and

biochemical deficiency in rats. Therefore, the results from animal and human studies differ slightly, but demonstrate an estimated daily requirement of 1–2% LA of total energy [Hansen et al., 1963; Mohrhauer and Holman, 1963; Holman, 1978, 1998; Wollbeck et al., 1981; Anderson and Connor, 1989; Strijbosch et al., 2008]. Severe LA deficiency signs (e.g. necrotic tail, scaly feet) appeared at less than 0.6%E in almost all animals [Mohrhauer and Holman, 1963]. The D-A-CH reference intakes consider a recommended intake of LA fatty acid of 2.5% (includes 15% coefficient of variation) from total energy. This recommendation is based on the average requirement of a young healthy adult, who needs 6.5 g LA/day to prevent biochemical deficiency symptoms (decrease in LA content of blood cholesterol esters). This amount corresponds to about 2%E of LA [Deutsche Gesellschaft für Ernährung, 2000].

The Institute of Medicine (IOM) states that due to the lack of data on the n–6 fatty acid requirement in healthy individuals, an estimated average requirement (EAR) cannot be set based on correction of a deficiency. Therefore, the adequate intake (AI) for LA is set at 17 g/day for young men and 12 g/day for young women. This is based on the median intake in the USA, where a LA deficiency is not known in ‘healthy’ individuals. It is also stated that intake levels much lower than the AI are observed without the presence of a deficiency (e.g. rough and scaly skin and dermatitis). No upper level has been set by the IOM due to insufficient evidence [IOM, 2002].

Tables 2 and 3 demonstrate that an AI for LA is also difficult to establish for different populations, because the intake differs widely between population groups. For instance, the LA intake varies between 6.8 g/day in French women and 22.5 g/day in Austrian vegans. In India, the LA intake ranges from 2 to 17%E. Especially in poor population groups, a very low LA intake of 2%E can be observed [Ghafoorunissa, 1998; Goyal et al., 2005]. In addition, there is also a wide variation between different dietary groups, and it has to be considered that the data are only an excerpt.

#### *Plasma Lipids and CVD*

LA is the most potent fatty acid for lowering TC and LDL levels in the plasma. Both are well-known CHD risk factors. n–6 Fatty acids reduce LDL and TC compared with SFAs, which raise cholesterol levels [Mensink and Katan, 1992; Katan et al., 1994; Howell et al., 1997]. Iso-caloric replacement of 1%E SFAs by PUFAs reduces HDL-cholesterol levels by about 0.2 mg/dl [Kromhout et al., 1985; Mensink and Katan, 1992; Kris-Etherton and

Yu, 1997]. On the other hand, compared with stearic acid (C18:0), LA reduces LDL and TC levels and increases HDL-cholesterol [Kris-Etherton and Yu, 1997].

Prospective cohort studies demonstrated that opposed or no associations between intake of LA and the risk of CHD [Ascherio et al., 1996; Pietinen et al., 1997].

Prospective studies demonstrated that higher dietary markers of LA intake (e.g. LA in adipose tissue, serum LA) are negatively associated with lower risk of CHD [Miettinen et al., 1982; Laaksonen et al., 2005]. The Nurses’ Health Study showed significant inverse associations of PUFAs, or LA, with CHD [Hu et al., 1997; Oh et al., 2005].

Dietary intervention studies demonstrated that the replacement of SFAs by plant oils high in LA reduced plasma cholesterol levels and the risk of CHD [Christakis et al., 1966; Turpeinen, 1979].

In addition, the Dietary Guidelines for Australian Adults recommends an intake of n–6 PUFA (LA) between 6 and 8%E due to the strong evidence that n–6 PUFAs can reduce LDL and TC levels, even when the oil increases the total fat intake [NHMRC, 2003].

#### *FAO/WHO Dietary Recommendations for LA Intake*

It is recognized that only few data on humans are available for the establishment of the LA requirement, which has the effect that most authorities do not set an average LA requirement. However, animal and human studies have demonstrated that the prevention of deficiency signs (e.g. in rats reduced growth, scaliness of skin, necrotic tail) occurs by an estimated daily requirement of 1–2% LA of total energy. Therefore, an average LA requirement of 2%E and an individual LA level of 2.5%E are given. On the one hand, this requirement seems to be very low, but on the other hand, the requirement of a young healthy adult is around 6.5 g LA/day [Deutsche Gesellschaft für Ernährung, 2000] corresponding to about 2%E of LA, which can be very close to the intake in a normal diet (6.8 g/day French women) [Burdge and Calder, 2005b]. Under the condition that the maximum intake levels of PUFAs (MAL 11%E) and n–3 fatty acids (MAL 2%E) are taken into consideration, the resulting acceptable range for n–6 fatty acids (LA) can range between 2.5 and 9%E. The lower value (2.5%E) corresponds to the prevention of deficiency symptoms, whereas the higher value can be part of a healthy heart diet by lowering LDL and TC levels, and therefore the risk for CHD.



**Table 2.** Consumption of fat and LCPUFA among adults in different countries

	Total fat		SFA		MUFA		PUFA		LA		AA	
	male	female	male	female	male	female	male	female	male	female	male	female
AT(a)	37%	37%	14.3 g	14.8 g	13.0 g	12.3 g	7.8 g	8.1 g	7.1%	7.2%	0.28 g	0.22 g
	91.0 g	75.6 g							16.7 g	14.1 g		
AT(b) <sup>a</sup>	36.8%		18.2%		11.1%		4.5%		7.9 g		0.21 g	
AT(b) <sup>b</sup>	36.9%		16.4%		12.4%		6.6%		15.0 g		0.03 g	
AT(b) <sup>c</sup>	33.2%		12.4%		11.2%		8.6%		22.5 g		0.05 g	
AU(a)	32.4%	32.5%	12.7%	12.7%	11.9%	11.7%	4.9%	5.0%				
	98.5 g	67.6 g	39.0 g	26.7 g	36.2 g	24.3 g	14.7 g	10.4 g				
AU(b)							15.1 g	10.6 g	13.2 g	9.4 g	0.07 g	0.04 g
BE(a)	38.9%	37.0%	15.7%	15.6%	14.1%	13.4%	7.1%	6.7%				
BE(b)		34.3%		13.7%		13.1%		6.0%		5.3%		0.03%
		77.6 g		30.9 g		29.6 g		13.4 g		11.9 g		0.06 g
CA	31.4%	31.4%	10.2%	10.2%	12.7%	12.4%	5.5%	5.7%				
CM (rural)	43.8% <sup>1</sup>	43.8% <sup>1</sup>										
	215.8 g <sup>1</sup>	197.7 g <sup>1</sup>	67.3 g	63.9 g	82.2 g	77.5 g	28.4 g	27.7 g				
CM (urban)	42.0% <sup>1</sup>	42.1% <sup>1</sup>										
	80.1 g <sup>1</sup>	156.2 g <sup>1</sup>	61.9 g	53.4 g	69.9 g	59.9 g	25.0 g	21.7 g				
DE(a)	35.8%	34.8%										
	102.0 g	73.8 g										
DE(b)	36.0%	36.6%	15.1%	15.7%	12.6%	12.3%						
(Heidelberg)	110.9 g	78.0 g	42.4 g	33.7 g	35.3 g	26.5 g	-	-	14.3 g	10.9 g	0.23 g	0.16 g
DE(b)	40.3%	37.4%	16.5%	15.6%	13.7%	12.6%						
(Potsdam)	116.8 g	76.1 g	48.1 g	31.9 g	39.8 g	25.6 g	-	-	18.6 g	11.6 g	0.23 g	0.14 g
DK									12.0 g	9.0 g		
ES										21.6 g		
FR(a)									8.3 g	6.8 g		
FR(b)	36.3%	38.1%							4.1%	4.2%	0.08%	0.08%
	94.1 g	73.6 g							10.6 g	8.1 g	0.20 g	0.15 g
IN(a)	30%		7-24%						2-17%			
(urban)			16-58 g						5-42 g			
IN(a)	18%		2-10%						2-9%			
(rural)			6-22 g						5-20 g			
IN(b)		25.8%	16.7 g		9.8 g		5.8 g		3.0%			
(semi-urban)		44.0 g							5.2 g			
IN(b)		27.6%	18.9 g		10.5 g		5.2 g		2.3%			
(urban)		45.8 g							4.5 g			
IT									14.5 g			
JP	49.2 g	46.2 g	13.9 g	14.4 g	19.2 g	18.3 g			12.9 g	10.7 g	0.16 g	0.15 g
MX	55.0 g	46.1 g	15.7 g	13.3 g	15.7 g	12.7 g	9.6 g	7.8 g				
NG	51.0%	50.5%	26%	25%								
(rural)	93 g	81 g	47 g	40 g								
NG	35.6%	39.5%	5.4%	5.9%								
(urban)	79 g	78 g	12 g	12 g								
NL									19.0 g	13.2 g		
NO	31.5%	30.6%										
	97.4 g	67.0 g	12.3%	12.2%	11.1%	10.7%	5.7%	5.3%	13.5 g	8.8 g	0.17 g	0.12 g
NZ	35%	35%	15%	15%	12%	11%	5%	5%				
	114 g	75 g	49 g	32 g	38 g	25 g	16 g	10 g				
PH	18%											
TZ	15.2%	15.0%										
(rural)	49 g	44 g	10 g <sup>2</sup>	10 g <sup>2</sup>	15.5 g <sup>2</sup>	13 g <sup>2</sup>	12.5 g <sup>2</sup>	12.5 g <sup>2</sup>				
TZ	12.5%	12.2%										
(urban)	40 g	37 g	20.5 g <sup>2</sup>	18 g <sup>2</sup>	14 g <sup>2</sup>	13.5 g <sup>2</sup>	12 g <sup>2</sup>	12 g <sup>2</sup>				
UK(a)	35.8%	34.9%	13.4%	13.2%	12.1%	11.5%						
	86.5 g	61.4 g	32.5 g	23.3 g	29.1 g	20.2 g						
UK(b)	81 g	67 g	29.5 g	24.1 g	26.8 g	22.2 g	14.2 g	11.8 g	12.3 g	10.3 g	0.10 g	0.10 g
USA	98.1 g	69.4 g	31.8 g	22.0 g	36.4 g	25.3 g	19.5 g	14.3 g	17.1 g	12.8 g	0.16 g	0.11 g

Studies referred to can be found by cross-referencing with table 3. Units: % = %E; g = g/day. <sup>a</sup> Omnivores; <sup>b</sup> Vegetarians; <sup>c</sup> Vegans.

<sup>1</sup> High fat intake may be due to high energy requirement, but may also be overestimated due to the use of palm oil in recipes, which is extremely difficult to calculate. <sup>2</sup> Estimated from graphic.

ALA		EPA		DHA		LA/ALA	
male	female	male	female	male	female	male	female
0.51%	0.57%	0.09 g	0.07 g	0.19 g	0.18 g		
1.2 g	1.1 g						
	1.2 g	0.05 g		0.23 g			
	1.7 g	0.004 g		0.07 g			
	2.6 g	0.006 g		0.03 g			
1.4 g	1.0 g	0.07 g	0.05 g	0.13 g	0.09 g		
	0.64%		0.04%		0.06%		
	1.4 g		0.08 g		0.13 g		
1.6 g	1.3 g	0.10 g	0.07 g	0.19 g	0.14 g		
2.3 g	1.5 g	0.13 g	0.08 g	0.21 g	0.14 g		
2.2 g	2.1 g					5.5	4.3
	0.8 g					27.0	
0.6 g	0.5 g					13.8	13.6
0.36%	0.38%	0.06%	0.06%	0.11%	0.12%		
0.9 g	0.7 g	0.15 g	0.12 g	0.27 g	0.23 g	11.5	11.1
	0.2–1.8%					2–69	
	0.6–4.0 g						
	0.1–1.5%					3–54	
	0.3–3.4 g						
	0.44%					7.0	
	0.75 g						
	0.43%						
	0.71 g					6.3	
	0.8 g					18.1	
2.0 g	1.6 g	0.36 g	0.31 g	0.63 g	0.57 g		
1.7 g	1.2 g					11.2	11.0
1.8 g	1.2 g	0.41 g	0.27 g	0.59 g	0.40 g		
1.4 g	1.0 g	0.09 g	0.11 g	0.13 g	0.16 g	9.5	10.7
1.7 g	1.3 g	0.05 g	0.04 g	0.09 g	0.07 g		

### Dietary Recommendations for Arachidonic Acid (AA)

#### Function of AA

Essential fatty acids have different roles, especially in immune cells. Long-chain PUFAs (n-6 and n-3 LC-PUFAs) are precursors for the synthesis of bioactive lipid mediators like prostaglandins, leukotrienes, lipoxins, and resolvins. Essential fatty acids are important components of structural lipids, where they ensure optimal environmental conditions for membrane protein function, maintaining membrane fluidity and normal epithelial cell function. Alterations of the phospholipid composition influence cell function in different ways, which include changes in the regulation of gene expression either through effects on receptor activity, on intracellular signaling processes, or on transcription factor activation. As a consequence, the transcription factor activation and gene expression are changed [Calder, 2007, 2008]. Due to major dietary changes over the last 150 years, n-6 LC-PUFAs, derived from LA, form the majority of PUFAs [Simopoulos, 2008]. When n-6 fatty acids are partly replaced by n-3 fatty acids in the diet, the essential fatty acid shift can also be observed in the membranes of practically every single cell (e.g. immune cells or erythrocytes) [Calder, 2007].

Prostanoids (prostaglandins, prostacyclins, thromboxanes), leukotrienes, lipoxins, and resolvins released from dihomo- $\gamma$ -linolenic acid (DGLA), AA, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) have a key role in modulating inflammation, cytokine formation, immune response, platelet aggregation, vascular reactivity, and thrombosis [Simopoulos, 2002; Das, 2006].

It has recently been discussed that especially this balance between n-6 and n-3 LCPUFAs could be involved in various pathological processes like atherosclerosis, CHD, cancer, diabetes mellitus, bronchial asthma, inflammatory bowel disease, and several other inflammatory conditions [Das, 2006].

For instance, DGLA produces prostaglandins of the 1 series, which mostly inhibit inflammatory cells. One reason is that DGLA cannot be converted to leukotrienes, but it can form a 15-hydroxyl derivative that inhibits the transformation of AA to leukotrienes [Belch and Hill, 2000]. Although these anti-inflammatory effects are known, most investigations have focused on AA, which produces prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) and thus raises the cardinal signs of inflammation, including fever, vascular permeability, and vasodilatation, and enhances pain and edema caused by other agents like bradykinin and hista-

**Table 3.** Description of the studies used

	Country	Survey	Method	n	Age, years	References
AT(a)	Austria	Austrian Nutrition Survey 2009; is representative; collected data from 2004–2005; data presented in means	24-hour recall	males 778 females 1,345	19–64	Elmadfa, 2009
AT(b)	Austria	Vegetarian study; is not representative; omnivores; vegetarians; vegans; collected data from 2003; data presented in means	24-hour recall	n = 85	19+	Kornsteiner et al., 2008
AU(a)	Australia	Australian Nutrition Survey 1995; is not representative; collected data from 1995; data presented in means	24-hour recall	males 3,742 females 4,236	19+	McLennan and Podger, 1995
AU(b)	Australia	Australian Nutrition Survey 1995; is not representative; collected data from 1995; data presented in means	24-hour recall	males 2,840 females 3,178	19–64	Meyer et al., 2003
BE(a)	Belgium	Belgian National Food Consumption Survey (BNFS) 2004; data presented in means	24-hour recall, food frequency questionnaire	males 1,623 females 1,622	15+	Devriese et al., 2004
BE(b)	Belgium	Large epidemiological survey; randomly selected from the population register of Ghent; included the Dutch-speaking; northern part of Belgium women of reproductive age; data presented in means	2 × 24-hour record	female 641	18–39	Sioen et al., 2006
CA	Canada	Canadian community health survey cycle 2.2; representative survey; collected data from 2004; data presented in means	24-hour recall	males 8,470 females 10,350	19+	Health Canada, 2004
CM	Cameroon	Habitual diet study of rural and urban subjects in Cameroon; rural subjects (3 villages in Evoudoula); urban subjects (Cité Verte Housing District; Yaoundé); data presented in means	food frequency questionnaire and 24-hour recall	male 307 female 436 male 458 female 584	24–74	Mennen et al., 2000
DE(a)	Germany	National Nutrition Survey II (NVSII); representative; collected data from 2005–2006; data presented in means	2 × 24-hour recall	male 7,093 female 8,278	14–80	Bell et al., 2008
DE(b)	Germany	German cohorts participating in the European Prospective Investigation into Cancer and Nutrition (EPIC); subjects from Heidelberg; subjects from Potsdam; data is not representative; data presented in means	24-hour recall	<i>Heidelberg</i> male 1,013 female 1,078 <i>Potsdam</i> male 1,032 female 898	35–65	Linseisen et al., 2003
DK	Denmark	Summary of LA and ALA intake without descriptions of the methods	–	–	–	Burdge and Calder, 2005a
ES	Spain	Summary of LA and ALA intake without descriptions of the methods	–	–	–	Burdge and Calder, 2005a
FR(a)	France	Summary of LA and ALA intake without descriptions of the methods	–	–	–	Burdge and Calder, 2005a
FR(b)	France	French Survey 1994–1995; from all regions of France; data presented in means	6 × 24-hour recall	male 2,099 female 2,785	35–63	Astorg et al., 2004
IN(a)	India	Computations from National Nutrition Monitoring Bureau; urban; rural	–	both	–	Ghafoorunissa, 1998
IN(b)	India	Fat intake among urban and semi-urban women of Punjab; semi-urban subjects from Dhuri; urban subjects from Sangrur; non-lactating and non-pregnant were selected using non-stratified random sampling technique	3 × 24-hour recall	<i>semi-urban</i> female 100 <i>urban</i> female 100	30–60	Goyal et al., 2005
IT	Italy	Summary of LA and ALA intake without descriptions of the methods	–	–	–	Burdge and Calder, 2005a
JP	Japan	Cross-sectional study; samples from Japanese dietitians; data presented in means	7-day weighed dietary records	male 15 female 79	male 45.3 female 47.2	Kuriki et al., 2003
MX	Mexico	Mexican Health and Nutrition survey (MHNS) 2006; is representative; data presented in medians	food frequency questionnaire	male 5,898 female 10,053	19–69	Bakewell et al., 2006

**Table 3** (continued)

Country	Survey	Method	n	Age, years	References	
NG	Nigeria	Study of urban and rural dweller in northern Nigeria; rural subjects were of the Fulani ethnic group; urban subjects were recruited in the city of Jos (north-central Nigeria); Fulani are semi-nomadic pastoralists; data presented in means	<i>rural</i> food frequency questionnaire, 7-day dietary record <i>urban</i> 4-day dietary recall	<i>rural</i> male 42 female 79 <i>urban</i> males 55 females 77	<i>rural</i> males 33.8 females 31.9 <i>urban</i> males 41.2 females 39.8	Glew et al., 2004
NL	Netherlands	Summary of LA and $\alpha$ -LA intake without descriptions of the methods	–	–	–	Burdge and Calder, 2005a
NO	Norway	National dietary survey (NORKOST); representative random sample	food frequency questionnaire	n = 3,144	16–79	Johansson et al., 1998
NZ	New Zealand	New Zealand National Nutrition Survey (NNS97); representative sample of 4,636 New Zealanders; collected data from 1996–1997; data presented in means	24-hour recall, food frequency questionnaire	n = 4,636	15+ (total)	Ministry of Health, 1999
PH	Philippines	Summary without descriptions of the methods	–	–	–	FAO, 2006
TZ	Tanzania	Food consumption in rural and urban Tanzania; rural subjects (Msongola village); urban subjects (Kariakoo area in central Dar-es-Salaam; data presented in means	24-hour recall	<i>rural</i> male 41 female 34 <i>urban</i> male 13 female 17	35–44	Mazengo et al., 1997
UK(a)	United Kingdom	The National Diet & Nutrition Survey; national sample; collected data from 2000–2001; data presented in means	7-day dietary record	n = 1,724	19–64	Henderson et al., 2003
UK(b)	United Kingdom	Study is not representative; data presented in means	food frequency questionnaire	male 13 female 23	18–35	Bakewell et al., 2006
USA	United States of America	WWEIA (What we eat in America)/NHANES (National Health and Nutrition Examination Survey) 2001–2002; nationwide dietary intake survey; data presented in means	24-hour recall	males 2,250 females 2,494	20 +	NHANES, 2001–2002

mine. AA induces thromboxane A<sub>2</sub> (a powerful platelet aggregator and vasoconstrictor) as well as prostacyclin I<sub>2</sub> (vasodilator and inhibitor of platelet aggregation). Leukotriene B<sub>4</sub> (LTB<sub>4</sub>) is produced via lipoxygenase from AA, which is a potent inducer of inflammation, leukocyte chemotaxis and adherence. Conversely, investigations have demonstrated that prostaglandin E<sub>2</sub> inhibits lipoxygenase and so reduces the formation of LTB<sub>4</sub> and encourages the formation of lipoxins, which have anti-inflammatory effects. A decreased production of AA-derived mediators which can be achieved by fish oil consumption has led to thoughts that fatty fish has anti-inflammatory effects and that it may be useful in the prevention and therapy of inflammatory conditions [Simopoulos, 2002; Calder, 2005].

LA can be converted to  $\gamma$ -linolenic acid (GLA; C18:3n–6) by the action of the enzyme  $\Delta$ 6-desaturase, and further elongated into DGLA (C20:3n–6) and desaturated into AA (C20:4n–6) by the action of the enzyme

$\Delta$ 5-desaturase. Further conversion into adrenic acid (C22:4n–6) and docosapentaenoic acid (C22:5n–6) involves the addition of 2 carbons to produce C22:4n–6 and the desaturation to form C22:5n–6 [Elmadfa and Leitzmann, 2004; Nicolaou and Kokotos, 2004; Calder, 2005]. Analysis of erythrocyte phospholipids demonstrated that vegans and vegetarians have increased contents of LA in the phosphatidylethanolamine fraction compared with omnivores. There are similar erythrocyte phospholipid contents of the elongation products of C18:3n–6 and C20:3n–6 between the dietary groups, whereas AA tended to be higher in omnivores. Nevertheless, especially vegans and vegetarians showed significant higher contents of C22:4n–6 compared with omnivores. Therefore, it is suggested that vegetarians and vegans, who have low intakes in preformed AA in their diet, meet their main requirements of n–6 LCPUFAs for membrane enrichment and eicosanoid synthesis via endogenous bioconversion from LA [Kornsteiner et al., 2008].

Table 2 demonstrates that an adequate intake for AA is also difficult to establish for different populations, because the intake differs widely between population groups. For instance, the AA intake varies between 0.03 g/day (Austrian vegetarians) and 0.23 g/day (German male omnivores) [Linseisen et al., 2003; Kornsteiner et al., 2008].

#### *FAO/WHO Dietary Recommendations for AA Intake*

AA is not essential for a healthy person, who gets enough LA (>2.5%E) from their normal diet.

### **Dietary Recommendations for n-3 Fatty Acid Intake**

#### *Dietary Recommendations for ALA Intake*

##### *Prevention of Deficiency*

Holman et al. [1982] published the first case of ALA deficiency in a 6-year-old girl, who was fed parenterally with an almost ALA-free diet, because of an abdominal gunshot wound. The girl had paresthesia, blurred vision, and difficulties in walking, which were reversed after shifting to a diet rich in ALA. It was estimated that 0.5–0.6%E per day prevents deficiency symptoms [Holman et al., 1982; Bjerve et al., 1987b].

Bjerve et al. [1989] compared the clinical and biochemical effects of ALA and n-3 LCPUFAs in humans. The dietary intake of n-3 LCPUFAs to maintain normal biochemical n-3 fatty acid status in plasma and erythrocyte lipids was estimated to be 0.35–0.40 g/day (0.4%E). The minimal dietary requirement of ALA was approximated to be 0.2–0.3%E or 0.3–0.4 g/day in adults [Bjerve et al., 1987a, b]. Skin abnormalities could be normalized when ALA intake was >115 mg/day or 0.16%E. A level of 0.50–0.55 g/day (0.4–0.6%E) reversed skin changes [Bjerve et al., 1989].

The D-A-CH reference intake values estimate a minimum requirement of 0.5%E from n-3 fatty acids [D-A-CH, 2000]. The Dietary Reference Intakes defined an AMDR for ALA (0.6–1.2%E) and recommend an AI of 1.6 g ALA/day for men and 1.1 g ALA/day for women. The AI is based on median intakes in the USA, where a deficiency (e.g. scaly dermatitis) is not known in healthy individuals [IOM, 2002].

Table 2 demonstrates that an AI for ALA is also difficult to establish for different populations, because the intake varies in a wide range between population groups. For instance, the ALA intake ranges between 0.5 g/day (French women) and 2.6 g/day (Austrian vegans).

#### *Plasma Lipids and CVD*

A number of studies have suggested that ALA is similar to LA with regard to its impact on CVD risk. It reduces TC and LDL-cholesterol levels. The reduction in TGs has only been observed with extreme high dosages (e.g. 60 ml linseed oil), which does not demonstrate physiologically relevant concentrations [Harris, 1997]. Cardioprotective effects of ALA may also reflect the impact of n-3 LCPUFAs biosynthesis on cardiac arrhythmia, inflammation, and thrombosis. Although it has to be pointed out that it has not been proven whether any of the cardioprotective effects of ALA reflect conversion to EPA and DHA especially, or are independent of n-3 LCPUFAs effects [Wijendran and Hayes, 2004].

Several epidemiologic studies have demonstrated a beneficial association of a higher ALA intake and reduced risk of CVD, including the Health Professional Follow-Up Study, the Nurses' Health Study and the National Heart, Lung, and Blood Institute Family Heart Study [Ascherio et al., 1996; Hu et al., 1999b; Djousse et al., 2001; Mozaffarian et al., 2005]. In the Nurses' Health Study, a higher intake of ALA was associated with a reduced risk of fatal ischemic heart disease after multivariate adjustment. The mean ALA intakes (g/day) from the lowest to the highest quintiles were 0.71, 0.86, 0.98, 1.12, and 1.36, and the relative risks for fatal CHD were 1.0, 0.99, 0.90, 0.67, and 0.55, respectively (p for trend = 0.01) [Hu et al., 1999b]. Conversely, there was a non-significant inverse association between ALA intake and risk of fatal ischemic heart disease among women in the  $\alpha$ -Tocopherol,  $\beta$ -Carotene Cancer Prevention Study [Pietinen et al., 1997]. The Zutphen Elderly Study did not observe a beneficial effect of ALA intake on CHD risk, but mentioned that the investigation of this topic was difficult due to the association between ALA and *trans* fatty acid intake [Oomen et al., 2001a].

In addition, Skeaff and Miller demonstrated that the intake of ALA (0.7–2.5 g) was not associated with changed risk of CHD death and events [Skeaff and Miller, 2009].

#### *Dietary Recommendations for EPA and DHA Intake*

##### *Plasma Lipids and CVD*

The principal n-3 LCPUFAs are EPA (C20:5n-3) and DHA (C22:6n-3). n-3 LCPUFAs reduced TG levels by 25% in healthy subjects and by 34% in hypertriglycerolemic subjects. LDL-cholesterol levels increased slightly (4.5%) in normal subjects, but rather markedly in hypertriglycerolemic persons (10.8%). HDL-cholesterol

levels increased insignificantly in both groups [Harris, 1997].

Epidemiological studies indicate that ingestion of n-3 fatty acids protects individuals from CHD [Dyerberg et al., 1975; Hu et al., 1997]. In the last century, the first population studies of Greenland Eskimos demonstrated that coronary atherosclerosis was less common among Eskimos in Greenland than among populations in industrialized countries [Dyerberg et al., 1975].

A cardioprotective effect was also found in one of the Seven Countries Study articles: the mortality from CHD was reduced by about 50% among subjects who ate at least 30 g fish per day, as opposed to subjects without fish intake [Kromhout et al., 1985]. Oomen et al. [2000] demonstrated that especially fatty fish is cardioprotective in Finland, Italy, and the Netherlands.

The Nurses' Health Study is a longitudinal study in which 84,688 healthy women aged 34–59 years were enrolled. Food frequency questionnaires were used to assess dietary intake of fish and n-3 fatty acids. Fish consumption was grouped as <1 time per month, 1–3 times per month, 1 time per week, 2–4 times per week, and 5 times per week. Adjustments for age, smoking, and other cardiovascular risk factors were carried out. The multivariable relative risks for all CHD across quintiles (from lowest to highest) were 1.0, 0.79, 0.71, 0.69, and 0.66 (p for trend = 0.001). Women with higher ingestion of n-3 LCPUFAs had a lower risk of CHD. Median intakes of n-3 LCPUFAs (g/day) of 0.03, 0.05, 0.08, 0.14 and 0.24 were associated with multivariable relative risks of 1.0, 0.93, 0.78, 0.68, and 0.67 (p for trend = 0.001) [Hu et al., 2002]. Mozaffarian et al. [2003] demonstrated that cardioprotective effects might depend on the quality of fish intake. Modest intake of tuna, boiled, or baked fish was associated with reduced risk of ischemic heart diseases, especially arrhythmic ischemic heart deaths, whereas fried fish and fish sandwiches did not demonstrate these effects.

In the DART I (Diet and Reinfarction Trial) study, subjects who had recovered from myocardial infarction were randomized to fish or fish oil consumption. After 2 years, persons told to eat fatty fish had a 29% reduction in all-cause mortality in comparison with the control group (no diet advice). The investigators concluded that the intake of 2 or 3 portions per week of fatty fish may contribute to a reduced mortality rate in men who have recovered from myocardial infarction [Burr et al., 1989].

The GISSI-Prevenzione Trial (Gruppo Italiano per lo Studio della Sopravvivenza nell' Infarto Miocardico Prevenzione Trial) was a prospective randomized clinical

trial of 11,324 patients after myocardial infarction. Subjects were randomly assigned to 4 equal groups to test a daily dose of 850 mg EPA and DHA from fish oil, 300 mg tocopherol or n-3 LCPUFAs fish oil plus tocopherol, and a control group (received neither). The primary combined efficacy endpoint was death, non-fatal myocardial infarction, and stroke. Treatment with n-3 LCPUFAs, but not tocopherol, significantly reduced the risk of the primary endpoint. Health benefits were attributable to a reduction in the risk of death in particular cardiovascular death [GISSI-Prevenzione Investigators, 1999].

The JELIS (Japan EPA Lipid Intervention Study) demonstrated that high doses of purified EPA (1.8 g/day) and statin reduce the frequency of major coronary events (relative reduction 19%) in hypercholesterolaemic Japanese patients compared to the control group (statin only), although this population has already high intakes of n-3 LCPUFAs [Yokoyama et al., 2007].

On the one hand, 3 well-designed trials (DART I, GISSI and JELIS) demonstrated significant benefits for n-3 LCPUFAs in patients with established CHD; on the other hand, other studies have not reported positive outcomes [Lee et al., 2008]. For instance, investigations by Ness et al. [2002] and Burr et al. [2003] seemed to have higher rates of sudden cardiac deaths in the trial than in the control groups. These trials were suboptimally conducted, and thus the results are controversial [Lee et al., 2008].

The data from the secondary and primary prevention studies support the theory that the intake of n-3 LCPUFAs reduces all-cause mortality, cardiac and sudden death, and stroke [Wang et al., 2006]. n-3 LCPUFAs appear to confer cardiovascular health benefits mainly through EPA and DHA enrichment of membrane phospholipids. This enrichment can lower abnormal ventricular arrhythmias and blood pressure, improve arterial and endothelial function, lower platelet aggregations and positively influence autonomic tone [Lee et al., 2008].

Skeaff and Miller [2009] came to the conclusion that the observational evidence that a strong inverse relationship is present between n-3 LCPUFAs or fish intake and risk of CHD is convincing. The evidence from 2 well-designed randomized controlled trials (GISSI and DART I) support these findings.

In addition, fish intake probably decreases colorectal cancer risk, and limited data are suggestive of a causal relationship between n-3 LCPUFAs intake and colorectal cancer risk reduction [Gerber, 2009].

The evidence implies that there are more consistent benefits with the dosage of EPA and/or fish oil at 1,000–2,000 mg per day. The strength of the evidence is consid-

ered as probable for depression. In cases of cognitive decline, aggression, hostility, anti-social behavior and age-related maculopathy, the strength of evidence is regarded as possible, whereas the evidence is insufficient to date for Alzheimer's disease, schizophrenia, and Huntington's disease [Crawford and Sinclair, 2009].

Epidemiological evidence suggests that n-3 LCPUFAs may modify the risk for certain neuropsychiatric disorders and reduced n-3 LCPUFAs status in blood (e.g. plasma, erythrocytes). Supplementation with fish oil indicates reduced symptoms associated with these neurological diseases [Young and Conquer, 2005].

In summary, the benefits of n-3 LCPUFAs on neurological functions are recognized, although much more research is needed to get a clear picture of the potential mechanisms and risk reduction of neurological diseases [Young and Conquer, 2005].

The Eurodiet project recognizes that there is a need to raise the intake of n-3 fatty acid content (2 g ALA + 200 mg n-3 LCPUFAs/day), especially marine oils, due to the European consensus on coronary prevention [Eurodiet, 2000]. Gebauer et al. [2006] have made similar recommendations. The n-3 fatty acid recommendation to reach essential n-3 fatty acid adequacy, defined as the amount necessary to avoid deficiency symptoms, is 0.6–1.2%E for ALA; up to 10% of this can be provided by n-3 LCPUFAs [Gebauer et al., 2006].

The American Heart Association distinguishes between people without disease (500 mg EPA and DHA per day), with documented coronary artery diseases (1 g per day), and hypertriglyceridemic patients, who benefit from a high dosage with 3–4 g per day of EPA and DHA from fish oil. This dosage reduces TG levels by 20–40%. This is the first time that the American Heart Association has endorsed both fish oil supplements and/or dietary-based intake of n-3 LCPUFAs. This recommendation is based on a convincing and further growing body of evidence, which supports the cardiovascular health benefits and TG-lowering effects of fish oil [Kris-Etherton et al., 2003].

While the IOM recognizes that high intakes of n-3 LCPUFAs may impair immune response and result in prolonged bleeding times, there is not enough data to establish a MAL for EPA and DHA based on infection responsiveness. The reason for this is that studies on immune function were done in vitro, and it is not known how these artificial conditions simulate human immune cell response in vivo. In addition, data on n-3 LCPUFAs intakes and bleeding times are mixed, and a clear dose-response effect was not demonstrated. The observed prolonged bleeding times in Eskimos, whose diets are rich in

EPA and DHA from fish intake, are lacking information if EPA and DHA were the sole basis for these observations. Therefore the IOM did not establish a MAL for EPA and DHA, although highly concentrated fish oil supplements should be taken with caution, due to possible adverse effects [IOM, 2002].

#### *FAO/WHO Dietary Recommendations for n-3 Fatty Acid Intake*

It was estimated that 0.5–0.6%E ALA per day prevents deficiency symptoms. The n-3 fatty acid intake can range between 0.5 and 2%E. The minimum dietary requirement of ALA for adults to avoid deficiency symptoms is  $\geq 0.5\%E$ , whereas the higher value 2%E (ALA) plus n-3 LCPUFAs, EPA, and DHA (AMDR 250–2,000 mg) can be part of a healthy heart diet probably preventing CHD and possibly some cancers and degenerative diseases of aging. The MAL for n-3 LCPUFA is by 3 g/day, because high supplement intakes of n-3 LCPUFAs have been demonstrated to reduce cytokine production and increase lipid peroxidation. High supplement intakes of n-3 LCPUFAs (>3 g/day) have been demonstrated to reduce cytokine production [Meydani, 2000; Vedin et al., 2008; Sanders, 2009], whereas the requirement for antioxidants (i.e., tocopherol) is increased [Elmadfa and Schwalbe, 1989].

#### **Dietary Recommendations for *Trans* Fatty Acid Intake**

##### *Plasma Lipids and CVD*

*Trans* fatty acids are characterized by a double bond in the *trans* configuration. They are formed during the hydrogenation of essential PUFAs (e.g. LA and ALA) either in the rumen of the ruminants or in oil-hardening in the food industry. *Trans* fatty acids have effects on serum lipid profile markedly different from those of their natural *cis* isomer [Zock and Katan, 1992; Katan et al., 1994].

*Trans* fatty acids can increase the risk of CHD through several mechanisms. The *trans* configuration impacts physical properties, including closer packing or aligning of acyl chains, and decreases membrane fluidity when compared to fatty acids with *cis* configuration. They raise TC and LDL-cholesterol, while reducing HDL-cholesterol levels relative to *cis* unsaturated fatty acids, resulting in an increased ratio of TC to HDL-cholesterol. In addition, *trans* fatty acids raise TGs and lipoprotein(a), which are positively associated with a risk of CHD. Moreover, they adversely influence LA and ALA metabolism and prosta-

glandin balance by inhibiting the enzyme  $\Delta 6$ -desaturase [Zock and Katan, 1992; Katan et al., 1994; Kris-Etherton and Yu, 1997; Hu et al., 2001; Mensink et al., 2003].

Prospective cohort studies, including the Seven Countries Study, the Nurses' Health Study, the  $\alpha$ -Tocopherol,  $\beta$ -Carotene Study, and the Zutphen Elderly Study demonstrated the positive relationship between *trans* fatty acid intake and the risk of CHD [Kromhout et al., 1985; Willett et al., 1993; Hu et al., 1997; Pietinen et al., 1997; Oomen et al., 2001b; Oh et al., 2005].

Skeaff and Miller demonstrated that high (1.6–6.4%E) compared with low (0.8–2.4%E) *trans* fatty acid consumption was related with a significantly raised risk of relative risk of CHD death and events [Skeaff and Miller, 2009].

However, the EURAMIC [Aro et al., 1995] study did not find a significant association between *trans* fatty acid biomarkers in the adipose tissue and the risk of myocardial infarction. This result was also demonstrated after exclusion of Spain, which was uniformly very low due to high olive oil intake [Aro et al., 1995].

#### *Dietary Recommendations for Trans Fatty Acid Intake*

The Food and Drug Administration estimated the average adult's daily ruminant *trans* fatty acid intake in the USA, which is about 1.5 g for men and 0.9 g for women. The average intake of both men and women is about 1.2 g, which correspond to 0.5%E ([www.cfsan.fda.gov/~acrobat/fr03711a.pdf](http://www.cfsan.fda.gov/~acrobat/fr03711a.pdf)).

If similar average intake values from industrially hydrogenated fat could be anticipated, then the *trans* fatty acid intake from all sources should be limited to 1%E.

#### **Food-Based Dietary Guidelines**

Fats and oils belong in a nutritious diet. However, the amount and type of fat consumed influence health.

Moderate dietary fat intake can increase the risk of heart diseases in a population with a low fat intake (<20%E) [Suh et al., 2001]. Therefore, promoting an acceptable macronutrient range of dietary fat between 20 and 35%E may not be advisable for all population groups and should be done with caution, especially when no signs of deficiency are obvious. Therefore, the minimum fat intake should be greater than 15%E, while paying attention to an adequate intake of essential fatty acids. The absorption of fat-soluble vitamins can also be achieved with very low amounts of fat (e.g. 12%E for carotenoids) [Ribaya-Mercado et al., 2007].

The total fat intake can range between 20 and 35%E with focus on the energy balance and diet quality. Higher fat intakes are associated with raised saturated fat, cholesterol, and total energy intake. The intake of SFA should be below 10%E, whereas *trans* fatty acids should be <1%E to balance cholesterol levels in a normal range [Department of Health and Human Services, 2005; Deutsche Gesellschaft für Ernährung, 2006].

Therefore, lean cuts of meat and poultry should be preferred in comparison to sausages rich in fat (e.g. salami), crumbed and fried fish, and meats. These animal products can provide significant amounts of SFA. They can be part of a balanced diet, but only in small amounts. The intake of lean meat and the removal of visible fat can help to limit total fat intake as well as SFA and cholesterol intake [National Health and Medical Research Council, 2003].

Conversely, fatty fishes, which are rich in the longer chain derivatives of n-3 fatty acids, are recommended, especially for people who are at risk of CHD. Fish, but especially fatty fish like sardines, salmon, tuna, herring, and mackerel, are part of a healthy diet and are recommended in least 2 meals per week [National Health and Medical Research Council, 2003].

The majority of the fat should come from plant oils, which are excellent sources of PUFAs and MUFAs. Good sources of the essential n-6 PUFAs (LA) are vegetable oils, including soybean oil, corn oil, sesame oil, sunflower oil, groundnut oil, rice bran oil, cottonseed oil and safflower oil, whereas soybean oil, rapeseed oil, mustard oil, walnut oil, and flaxseed oil are rich in the n-3 PUFAs (ALA). n-3 LCPUFAs (EPA and DHA) are available from fish. Vegetable oils that are rich in MUFAs include canola, olive, sunflower (product of new breeding techniques or by blending PUFA-rich oils with MUFA-rich ones to end up with high oleic oil), and nuts oils [Kornsteiner et al., 2006; Boskou and Elmadfa, 2009, in press; Farhoosh et al., 2009].

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