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Gender Differences in the Long-Chain Polyunsaturated Fatty Acid Status: Systematic Review of 51 Publications

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Key Words
Arachidonic acid · Docosahexaenoic acid · Gender differences · Long-chain polyunsaturated fatty acids · Sex hormones

Abstract
Background/Aims: Sex hormones may influence the activity of enzymes which are involved in the synthesis of long-chain polyunsaturated fatty acids. The objective of this review was to assess the role of gender in determining the fatty acid composition of human samples, like plasma and erythrocyte membrane lipids, and adipose tissue. ***Methods:*** The method included a structured search strategy on MEDLINE, Scopus and the Cochrane databases, with formal inclusion/exclusion criteria, data extraction procedure and meta-analysis. ***Results:*** We evaluated 51 publications, dated from 1975 to 2011. Meta-analysis showed significantly lower values of both arachidonic acid (AA) and docosahexaenoic acid (DHA) in total plasma lipids (32 and 33 studies) and in plasma phospholipids (PL; 21 and 23 studies) in men than in women. Primary analysis of the phospholipid fraction showed the mean difference in AA to be 0.42% weight/weight (95% CI: 0.18–0.65, n = 7,769) and in DHA 0.37% weight/weight (95% CI: 0.24–0.51, n = 8,541), while there was no gender difference in the values of linoleic acid and α-linolenic acid. ***Conclusions:*** This systematic review based on 51 publications showed significantly lower contribution of AA and DHA to plasma total lipids and plasma PL in men than in women. Gender distribution should be regarded as a significant potential confounding factor in every study assessing data on fatty acid composition.

Introduction

Long-chain-polyunsaturated fatty acids (LCPUFA) have important functions in cell membranes as indispensable building stones for human development and optimal health. Docosahexaenoic acid (DHA) and arachidonic acid (AA) are considered to be the most important functional LCPUFA. They can be provided directly from the diet or can be synthetized from their essential fatty acid precursors α-linolenic acid (ALA) and linoleic acid (LA). Among other enzymes, Δ^6- and Δ^5-desaturases are required for the formation of the longer-chain metabolites of both n–3 and n–6 series. The competitive desaturation of the n–3 and n–6 series of fatty acids by Δ^6-desaturase is of major significance, because this step is considered to be the rate-limiting step of the pathway. The activity of this enzyme is modulated by hormones and by interactions of substrates and metabolic products [1, 2].

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The role of diet in influencing the proportion of fatty acids in plasma, blood cells and adipose tissue has been described in detail previously [3]. However, there are only narrative overviews [4], but no systematic review on the role of the most basic non-dietary determinant, gender, in influencing the fatty acid composition of different tissues. In order to investigate whether LCPUFA metabolism can be eventually influenced by sexual hormones, we decided to systematically review the gender-specific differences between women and men in the contribution of LCPUFA to the fatty acid composition of different biological samples.

Plasma phospholipids (PL), plasma cholesteryl esters (CE), plasma triacylglycerols (TG), total plasma lipids, erythrocyte and platelet lipids as well as subcutaneous adipose tissue from the abdomen or buttock are the lipid pools most often reported in the literature for the characterization of fatty acid status. Therefore, we decided to review data on gender differences in the fatty acid composition of these biomarkers.

Methods

Aim

The aim of this systematic literature review was to compare LCPUFA status on the basis of the fatty acid composition of different biomarkers in healthy males and females.

Inclusion Criteria

To be included into the review, a study needed to meet all of the following characteristics: (1) a study carried out in humans; (2) at least 14 participants included; (3) n–3 or n–6 LCPUFA status is reported in both males and females; (4) healthy individuals with normal weight were included, or population-based surveys were carried out in that the majority of participants were considered healthy; (5) omnivorous participants were included; (6) there was no dietary intervention (especially no lipid-modified diet) or drug therapy before sample collection, and (7) investigators measured at least 12 fatty acids by gas liquid chromatography, so the percentage distribution data contained the principal fatty acids of the fatty acid spectrum and presumably reflected a realistic proportion of fatty acids in the given lipid fraction.

Search Strategy

Electronic Searches

Ovid MEDLINE (www.ovid.com), Scopus (www.scopus.elsevier.com) and the Cochrane Library central database (www.thecochranelibrary.org) were searched from inception to February 2011 for studies containing LCPUFA values of both men and women (boys and girls) using text terms with appropriate truncation and relevant indexing terms. The search was in the form [n–3 LCPUFA terms] or [n–6 LCPUFA terms] and [biomarker terms] and [gender terms] and [differ*] and [human studies]. The results obtained by the full Ovid MEDLINE search strategy are shown in online supplementary table 1 (for all online suppl. material, see www.karger.com/doi/10.1159345599). The searches of the two other databases were also based on this strategy. We did not apply any language restriction.

Data Extraction

Titles and abstracts found by the electronic and bibliographic searches were screened for inclusion by a single reviewer (S.L.). Due to the large number of papers which were present in more than one database, duplications were filtered out to compile the final list of titles and abstracts to be screened. Thereafter, it was checked which of the titles and abstracts met the predetermined eligibility criteria. If articles seemed to meet the inclusion criteria, or the title and the abstract left room for doubt, the full text of the article was evaluated by two independent reviewers (S.L. and K.F.). If the two reviewers disagreed about the eligibility, the study was discussed in detail to reach a consensus decision.

Data for each study included were extracted by a single reviewer (S.L.) into a Microsoft Office Excel 2007 database file. To provide a standardized format, units of measurement were recalculated to percentage contribution of LCPUFA to total fatty acid composition of the relevant tissue (% weight/weight) from the original data in the publication. If it was not possible to convert data, we tried to contact the authors. If the authors could not be contacted (in most of the cases because of the long time elapsed since the publication of the papers), or the data were not available in the original form any more, those studies were excluded. The original forms in which fatty acid data in the included studies were expressed are shown in table 1. In some studies, the investigators measured the fatty acid composition in plasma, in other studies in serum. Because we feel that there is no major difference in the percent fatty acid composition of plasma and serum, for the uniformity of discussion, we used the term 'plasma' throughout the paper.

Statistical Analyses

Statistical analyses were performed using the Review Manager 5.1 software (Cochrane Collaboration, Oxford, UK). Mean differences (MD) were used for the analysis of continuous data. The confidence interval (CI) was established at 95%. Values of $p < 0.05$ were considered to indicate statistical significance. Statistical heterogeneity was assessed using I^2 statistics (I^2 of 50% or more indicating presence of heterogeneity).

Results

Study Inclusion

The flow diagram of the literature search for this review is shown in figure 1. Altogether 7,925 titles and abstracts were identified via the electronic search or were found in the reference lists of the review articles. Three hundred and fifty-six of them appeared to be potentially relevant, so we attempted to collect them as full text articles. Thirteen full text articles (3.6%) could not be collected even after repeated attempts by the help of professional librarians, but 343 full text articles were available

Table 1. Basic characteristics of the studies included

First author publication year	Characteristics of the participants					Biomarkers reported	Fatty acids reported	Original expression of data
	Country	male subjects included n	female subjects included n	age of males years	age of females years			
Ando [5], 1990	Japan	31 29 37	68 45 22	54.3 ± 7.4 59.8 ± 4.9 64.9 ± 7.3	57.0 ± 8.6 59.0 ± 6.0 68.3 ± 8.8	plasma total lipids	LA, DHGLA, AA, EPA, DHA	mg/dl mean ± SD
Antonini [6], 1970	Italy	11	11	29 ± 6.6	27.4 ± 6.2	adipose tissue	LA	w/w% mean ± SD
Araki [7], 1990	Japan	27 57	110 121	20 – 49 50 – 79	20 – 49 50 – 79	plasma total lipids	LA, AA, EPA, DHA	w/w% mean ± SD
Bakewell [8], 2006	UK	13	23	26 ± 5	23 ± 4	plasma: total lipids, TG, FFA, PC, CE	LA, GLA, DHGLA, AA, ALA, EPA, DPA, DHA	w/w % mean ± SD
Bolton-Smith [9], 1997	UK (Scotland)	2,308	2,049	40 – 59	40 – 59	adipose tissue	LA, GLA, DHGLA, AA	w/w% mean ± SD
Brouwer [10], 1997	The Netherlands (Curacao)	51	26	56 ± 8	58 ± 5	plasma CE	LA, GLA, DHGLA, AA, ALA, EPA, DHA	mol% mean ± SD
Cheng [11], 2003	ROC (Taiwan)							
	urban rural	10 10	10 10	10 – 11 10 – 11	10 – 11 10 – 11	plasma TG	LA	w/w% mean ± SEM
Christensen [12], 1999	Denmark	35	25	38 ± 10	38 ± 11	granulocytes, platelets	LA, AA, ALA, EPA, DPA, DHA	w/w% mean ± SD
di Giuseppe [13], 2009	Italy, Belgium, UK	50	224	47 ± 1.1	44 ± 0.5	plasma total lipids, erythrocyte membrane	ALA, EPA, DPA, DHA	w/w% geometric mean SEM or 95% CI
Elizondo-Montemayor [14], 2010	Mexico	49	51	6 – 12	6 – 12	plasma PL	LA, GLA, DHGLA, AA, ALA, EPA, DPA, DHA	w/w% mean ± SD
Fernandez-Real [15], 2001	Spain	38	40	40.1 ± 13.3	38.1 ± 9.3	plasma total lipids	LA, DHGLA, AA, EPA, DHA	w/w% mean ± SD
Geppert [16], 2010	UK	40	34	32.6 ± 8.0	32.7 ± 7.3	platelet PC, platelet PEA	LA, GLA, DHGLA, AA, ALA, EPA, DPA, DHA	w/w% mean ± SD
Giltay [17], 2004	The Netherlands	72	71	29.6 ± 12.9	27.4 ± 10.2	plasma CE	LA, GLA, DHGLA, AA, ALA, EPA, DHA	w/w%, mean, 95% CI
Glew [18], 2010	Nigeria	22	29	55.5 ± 13.5	47.6 ± 8.3	plasma PL	LA, GLA, DHGLA, AA, ALA, EPA, DPA, DHA	w/w% mean ± SD
Glew [19], 2002	Nigeria	37	36	14	13	plasma PL	LA, GLA, DHGLA, AA, ALA, EPA, DPA, DHA	w/w% mean ± SD
Hagenfeldt [20], 1975	Sweden	6	8	26 – 35	23 – 31	plasma FFA	LA	w/w% mean ± SEM
Hirai [21], 2005	Japan	76	76	68.6 ± 10.6	67.8 ± 11.2	plasma total lipids	LA, GLA, DHGLA, AA, ALA, EPA, DPA, DHA	μg/ml mean ± SD
Hirai [22], 2000	Japan, The Netherlands	33 20	29 19	university students	university students	plasma total lipids	LA, AA, ALA, EPA, DHA	mg/100 ml mean ± SD
Hodge [23], 2007	Australia, UK, Italy, Greece	2,048	2,391	55 ± 8.8	54.4 ± 8.5	plasma PL	LA, AA, ALA, EPA, DHA	w/w% mean ± SD
Innis [24], 1988	Canada (Inuit) Vancouver group	11 9 41 14 12	17 12 59 13 12	11 – 15 16 – 20 21 – 50 >50 21 – 50	11 – 82 16 – 20 21 – 50 >50 21 – 50	erythrocyte PC, erythrocyte PEA	LA, GLA, DHGLA, AA, ALA, EPA, DPA, DHA	w/w% mean ± SEM
Iwamoto [25], 2002	Japan	20	20	adults	adults	plasma CE	LA, AA, EPA, DHA	mol% mean ± SEM

Table 1 (continued)

First author publication year	Characteristics of the participants					Biomarkers reported	Fatty acids reported	Original expression of data
	Country	male subjects included n	female subjects included n	age of males years	age of females years			
Jagannathan [26], 1969	India	27	15	22 – 50	26 – 45	adipose tissue	LA	w/w% mean ± SEM
Kale [27], 2008	India	25	21	33.6 ± 9.7	35.1 ± 8.0	erythrocyte membrane	LA, GLA, AA, ALA, EPA, DPA, DHA	w/w% mean ± SD
Karlsson [28], 2006	Sweden	6	9	11.3 – 15.4	11.7 – 14.5	plasma PL	LA, GLA, DHGLA, AA, ALA, EPA, DHA	mol% mean ± SD
Kieu [29], 2002	South Vietnam					plasma total lipids	LA, GLA, DHGLA, AA, ALA, EPA, DPA, DHA	w/w% mean ± SD
	rural	32	68	47.5 ± 5.5	47.5 ± 5.2			
	suburban	40	58	46.6 ± 5.0	47.6 ± 6.4			
	urban	39	59	46.4 ± 4.7	47.2 ± 5.9			
Kuriki [30], 2003	Japan	15	79	45.3 ± 10.6	47.2 ± 8.1	plasma total lipids	LA, AA, ALA, EPA, DPA, DHA	w/w% mean ± SD
Lee [31], 2000	Hong Kong	81	113	43.4 ± 11.2	43.8 ± 11.6	plasma total lipids	LA, GLA, AA, ALA, EPA, DHA	w/w% mean ± SD
Lemaitre [32], 2008	Israel	112	118	<45	<45	erythrocyte membrane	LA, DHGLA, AA, EPA, DHA	w/w% mean ± SD
		49	42	45 – 60	45 – 60			
		44	52	≥60	≥60			
Lucas [33], 2009	Canada	127	170	18 – 74	18 – 74	plasma PL	LA, AA, ALA, EPA, DPA, DHA	w/w% mean ± SD
Mamalakis [34], 2006	Greece	59	71	37.7 ± 7.9	36.2 ± 6.7	adipose tissue	LA, GLA, DHGLA, AA, ALA, EPA, DPA, DHA	w/w% mean ± SD
Mamalakis [35], 1998	Greece	85	59	23 – 69	23 – 69	adipose tissue	LA, DHGLA, AA, ALA, EPA, DPA, DHA	w/w% mean ± SD
McNamara [36], 2010	USA	10	10	35.9 ± 8.8	36.1 ± 9.3	erythrocyte membrane	LA, DHGLA, AA, EPA, DPA, DHA	w/w% mean ± SEM
Melchert [37], 1987	Germany	38	70	21 – 77	18 – 85	plasma total lipids, HDL	LA, GLA, DHGLA, AA, ALA, DHA	w/w% mean ± SD
						plasma CE	LA, GLA, DHGLA, AA, ALA, EPA, DHA	
						plasma TG	LA, GLA, AA, ALA, DHA	
						plasma FFA	LA, DHGLA, AA, ALA, DHA	
Metherel [38], 2009	Canada	9	7	22.4 ± 1.2	22.1 ± 1.8	whole blood, plasma total lipids, erythrocyte membrane, fingertip prick blood	LA, GLA, DHGLA, AA, ALA, EPA, DPA, DHA	w/w% mean ± SD
Mitchell [39], 1983	New Zealand	9	9	10 – 13	10 – 13	erythrocyte membrane	LA, DHGLA, AA, ALA, EPA, DPA, DHA	w/w% mean ± SD
Nakamura [40], 1995	Japan	18	13	30 – 39	30 – 69	plasma total lipids	LA, AA, EPA, DHA	w/w% mean ± SD
		13	13	40 – 49	40 – 49			
		12	15	50 – 59	50 – 59			
		12	14	60 – 69	60 – 69			
Nikkari [41], 1995	Finland	41	41	43 ± 4.3	40 ± 4.3	plasma PL	LA, GLA, DHGLA, AA, EPA, DHA	w/w% mean ± SD
						plasma CE	LA, GLA, DHGLA, AA, ALA, EPA, DHA	
						plasma TG	LA, AA, ALA, DHA	

Table 1 (continued)

First author publication year	Characteristics of the participants					Biomarkers reported	Fatty acids reported	Original expression of data
	Country	male subjects included n	female subjects included n	age of males years	age of females years			
Saadatian-Elahi [42], 2009	GR (Athens) ES (Granada) ES (Murcia) North Spain IT (Ragusa/Nap.) IT (Florence) IT (Turin) DE (Heidelberg) DE (Potsdam) The Netherlands UK (Cambridge) Denmark SE (Malmö) SE (Umeå)	91 93 96 94 90 94 96 95 96 95 95 96 100 94	100 100 100 100 99 99 100 96 99 100 100 100 95 99	45 – 64	45 – 64	plasma PL	LA, GLA, DHGLA, AA, ALA, EPA, DPA, DHA	w/w% mean ± SD
Sfar [43], 2010	Tunisia	96	104	55.7 ± 13.1	53.1 ± 13.7	plasma total lipids	LA, AA, ALA, EPA, DHA	w/w% mean ± SD
Smit [44], 2003	The Netherlands	29	34	22 – 49	22 – 47	erythrocyte membrane	LA, GLA, DHGLA, AA, ALA, EPA, DPA, DHA	mol% mean ± SD
Sutherland [45], 1995	Fiji (urban) Fiji (rural)	39 37	44 34	39 ± 16 38 ± 14	36 ± 15 43 ± 18	erythrocyte membrane	LA, GLA, DHGLA, AA, ALA, EPA, DPA, DHA	w/w% mean ± SD
Takita [46], 1996	Japan	28 87 81 20 17	15 58 48 30 10	20 – 29 30 – 39 40 – 49 50 – 59 60 – 69	20 – 29 30 – 39 40 – 49 50 – 59 60 – 69	plasma total lipids	LA, AA, EPA, DHA	w/w% mean ± SD
Tavendale [47], 1992	UK (Scotland)	529 508 593 555	518 469 479 463	40 – 44 45 – 49 50 – 54 55 – 59	40 – 44 45 – 49 50 – 54 55 – 59	adipose tissue	LA, GLA, DHGLA, AA, DPA, DHA	w/w% mean ± SD
Tjønneland [48], 1993	Denmark	23	63	42 – 63	40 – 63	adipose tissue	LA, GLA, DHGLA, AA, ALA, EPA, DHA	w/w% mean ± SD
Umemura [49], 2005	Japan	175	246	19.4 ± 1	19.2 ± 0.5	plasma total lipids	LA, GLA, DHGLA, AA, ALA, EPA, DPA, DHA	w/w% mean ± SD
Vallés [50], 1988	Spain	49	49	16 – 75	16 – 75	plasma: PL, TG, FFA, CE, platelet PL, TG, FFA	LA, EPA	w/w% mean ± SD
Warensjö [51], 2006	Sweden	554	295	40.6 ± 9.1	40.6 ± 9.9	plasma CE	LA, GLA, DHGLA, AA, ALA, EPA, DHA	w/w% mean ± SD
Wennberg [52], 2011	Sweden	308	248	53 ± 7.7	58 ± 7.2	plasma PL	ALA, EPA, DPA, DHA	w/w% mean, range
Wennberg [53], 2007	Sweden	288	207	55.2 ± 7.5	55.4 ± 7.6	plasma PL, erythrocyte membrane	ALA, EPA, DPA, DHA	w/w% median, SD
Yamada [54], 2000	Japan	107[a] 78[b]	154 124	30 – 89	30 – 89	plasma total lipids	LA, AA, ALA, EPA, DPA, DHA	w/w% mean ± SEM
Yeh [55], 1996	Nigeria	110[c] 126[d]	65 96	42.4 ± 8.9 39.7 ± 10.3	41.4 ± 8.1 35.4 ± 9.1	plasma total lipids	LA, GLA, DHGLA, AA, ALA, EPA, DHA	mol% mean ± SD

Means ± SD and ranges. FFA = Free fatty acids. Groups were classified by cluster analysis [5], age [7, 24 (only Inuits), 32, 40, 46, 47] and geographic area [42].

[a] Fishing group; [b] farming group; [c] senior staff group; [d] junior staff group.

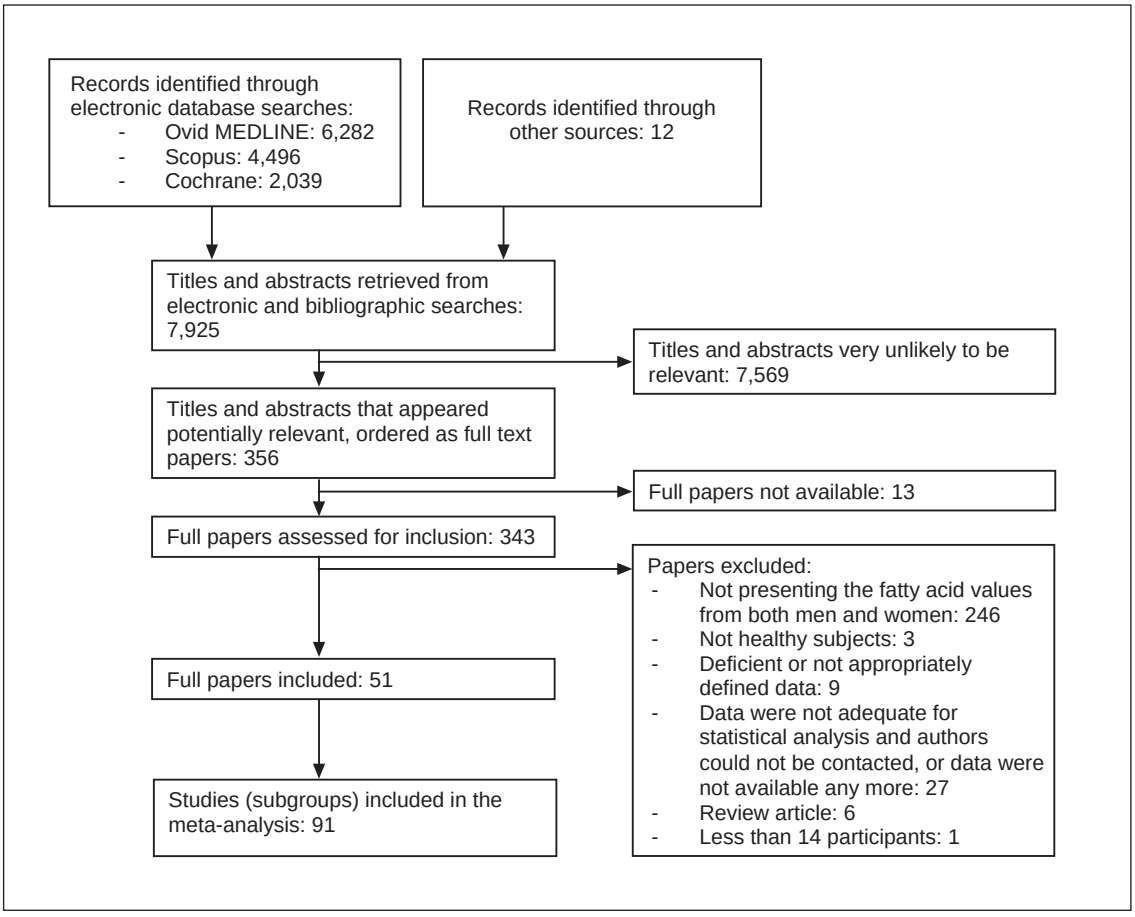

Fig. 1. Flow diagram of the systematic literature search.

for detailed assessment for inclusion. Reasons for excluding studies are presented in figure 1. In articles where the investigators analyzed the fatty acid composition of more than one biomarker (for example, plasma and erythrocyte membrane lipids), data were analyzed as originating from 2 separate studies. In some studies, the investigators divided the study population into subgroups in parallel (for example, according to age or geographical location). These subgroups were also included into our review as separate studies. Finally, 91 comparisons reported in 51 publications fulfilled the inclusion criteria.

Methods Used in the Studies Reviewed

Among the studies reviewed, there were some methodological differences in the analytical methods used for the determination of fatty acid composition of the different biomarkers. The blood samples collected were stored in a deep-frozen state, but the storage temperature was different (–20, –30, –40, –70 or –80°C). Lipid extraction was carried out by chloroform and methanol in most, but not all the studies. The separation of different lipid fractions was performed by thin layer chromatography. Fatty acid analysis was carried out by gas liquid chromatography in all studies. In some studies, a packed column was used instead of capillary columns (capillary column: 34 papers; packed column: 10 papers, and column type not reported: 7 papers).

Biomarkers Identified

We found 11 publications analyzing plasma PL, whereas 8 analyzed plasma CE, 5 plasma TG, 18 total plasma lipids, 9 total erythrocyte membrane lipids, 1 platelets and 7 adipose tissue fatty acid composition. A description of biomarkers identified in 3 or more studies, including also the number of studies, subgroups and participants from both genders, and the results of the

Table 2. Primary analysis of biomarkers identified in 3 or more studies

	Individual studies, n	Participants, n		MD [95% CI]	Heterogeneity (I^2), %
		men	women		
Total plasma lipids					
LA	32	1,594	2,012	−1.55 [−1.96, −1.14][a]	40
GLA	11	738	881	−0.33 [−0.07, 0.00]	78
DHGLA	14	792	943	−0.05 [−0.17, 0.06]	92
AA	32	1,594	2,012	−0.22 [−0.37, −0.07][a]	60
ALA	18	1,137	1,614	−0.03 [−0.06, 0.00]	60
EPA	32	1,607	2,166	0.02 [−0.07, 0.11]	69
DPA	11	634	1,118	0.06 [0.03, 0.09][b]	55
DHA	33	1,644	2,236	−0.12 [−0.22, −0.03][a]	46
Plasma PL					
LA	22	3,704	4,163	−0.19 [−0.43, 0.05]	50
GLA	19	1,480	1,553	0.00 [−0.00, 0.01]	36
DHGLA	19	1,480	1,553	−0.07 [−0.15, 0.01]	56
AA	21	3,655	4,114	−0.42 [−0.65, −0.18][a]	83
ALA	22	4,052	4,403	−0.00 [−0.01, 0.00]	72
EPA	24	4,146	4,493	−0.03 [−0.08, 0.02]	54
DPA	20	2,002	2,003	0.01 [−0.01, 0.04]	77
DHA	23	4,097	4,444	−0.37 [−0.51, −0.24][a]	80
Plasma CE					
LA	8	805	530	−1.03 [−1.84, −0.21][a]	45
GLA	6	736	461	0.08 [0.03, 0.14][b]	32
DHGLA	6	736	461	0.06 [0.02, 0.09][b]	49
AA	7	756	481	0.21 [−0.24, 0.66]	79
ALA	6	736	461	−0.01 [−0.03, 0.00]	0
EPA	8	805	530	0.01 [−0.07, 0.10]	55
DHA	7	756	481	0.02 [−0.08, 0.04]	68
Plasma TG					
LA	6	128	138	0.35 [−0.81, 1.53]	57
AA	3	59	69	0.07 [−0.13, 0.28]	76
ALA	3	59	69	−0.03 [−0.20, 0.13]	0
DHA	3	59	69	−0.12 [−0.57, 0.32]	68
Erythrocyte membrane lipids					
LA	10	363	371	0.05 [−0.19, 0.30]	0
GLA	5	139	140	−0.00 [−0.01, 0.01]	8
DHGLA	9	338	350	−0.02 [−0.12, 0.08]	18
AA	10	363	371	−0.41 [−0.86, 0.05]	64
ALA	8	480	577	0.01 [−0.02, 0.04]	69
EPA	12	701	802	0.03 [−0.00, 0.07]	27
DPA	9	495	590	0.14 [−0.05, 0.33]	79
DHA	12	698	802	−0.19 [−0.31, −0.06][a]	3
Erythrocyte PC					
LA	5	87	113	−0.11 [−2.61, 2.38]	39
GLA	5	87	113	0.09 [−0.23, 0.41]	43
DHGLA	5	87	113	−0.18 [−0.40, 0.04]	0
AA	4	46	54	−1.88 [−4.05, 0.29]	0
ALA	3	61	88	−0.01 [−0.42, 0.40]	0
EPA	5	87	113	−0.41 [−0.74, −0.08][a]	0
DPA	5	87	113	0.32 [−0.05, 0.69]	0
DHA	5	87	113	−0.25 [−1.30, 0.80]	62
Erythrocyte PEA					
LA	5	87	113	0.26 [−0.58, 1.09]	0
GLA	4	78	101	0.02 [−0.13, 0.18]	0
DHGLA	5	87	113	−0.12 [−0.37, 0.13]	25
AA	5	87	113	0.12 [−2.08, 1.85]	38
ALA	5	87	113	0.08 [−0.15, 0.32]	0
EPA	5	87	113	0.01 [−1.10, 1.13]	30
DPA	5	87	113	0.25 [−0.38, 0.88]	6
DHA	5	87	113	0.21 [−1.16, 1.57]	0
Adipose tissue					
LA	10	4,698	4,197	−0.49 [−0.60, −0.38][a]	0
GLA	7	4,575	4,112	0.03 [0.01, 0.04][b]	92
DHGLA	8	4,660	4,171	−0.04 [−0.05, −0.03][a]	93
AA	8	4,660	4,171	0.03 [0.02, 0.05][b]	74
ALA	3	167	193	0.01 [−0.02, 0.03]	0
EPA	3	167	193	0.01 [0.01, 0.02][b]	0
DPA	6	2,329	2,059	−0.01 [−0.04, 0.02]	97
DHA	7	2,352	2,122	−0.01 [−0.04, 0.01]	96

Significantly higher fatty acid values ([a] $p < 0.05$) in women than in men and significantly higher fatty acid values ([b] $p < 0.05$) in men than in women are indicated.

primary analysis (MD, I^2) are presented in table 2. We discuss in detail only these biomarkers. Descriptive data of biomarkers detected in less than 3 studies are presented in table 1.

Fatty Acids Reported

In this study, we focused on the following 8 PUFAs: LA, γ-linolenic acid (GLA), dihomo-GLA (DHGLA) and AA from the n–6 series and ALA, eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA) and DHA from the n–3 series. In table 1, we list the fatty acids from these 8 if the authors included the values into the publication.

Fatty Acid Composition of Total Plasma Lipids

Primary analysis showed significantly higher contribution of the n–6 essential fatty acid, LA, and the n–6 long-chain metabolite, AA, to plasma total lipids of women compared to men (fig. 2; table 2). As to n–3 fatty acids, the values of the principal LCPUFA, DHA, were significantly higher (fig. 3), while the values of its precursor, DPA, were significantly lower in women compared to men (table 2). However, with the exception of LA and

Study or subgroup	Men			Women			Weight %	MD IV, random (95% CI)	MD IV, random, 95% CI
	mean	SD	total	mean	SD	total			
Total plasma lipids – AA									
Ando [5], 1990 (group I)	6.6	2.06	31	6.77	2.12	68	2.0	–0.17 (–1.05, 0.71)	
Ando [5], 1990 (group II)	6.76	2.3	29	6.88	2.06	45	1.6	–0.12 (–1.15, 0.91)	
Ando [5], 1990 (group III)	6.1	1.86	37	6.43	2.26	22	1.4	–0.33 (–1.45, 0.79)	
Araki [7], 1990 (20–49 y)	5.8	1	27	5.9	0.9	110	4.2	–0.10 (–0.51, 0.31)	
Araki [7], 1990 (50–79 y)	5.2	1	57	5.6	1	121	4.8	–0.40 (–0.71, –0.09)	
Bakewell [8], 2006	4.8	0.8	13	5.1	0.2	23	4.0	–0.30 (–0.74, 0.14)	
Fernandez-Real [15], 2001	7.3	1.4	38	7.2	1.1	40	3.3	0.10 (–0.46, 0.66)	
Hirai [22], 2000 (Dutch)	6.81	2.1	20	7.03	2.14	19	1.0	–0.22 (–1.55, 1.11)	
Hirai [22], 2000 (Japanese)	4.9	1.56	33	5.17	1.05	29	2.8	–0.27 (–0.93, 0.39)	
Hirai [21], 2005	3.95	1	76	4.12	0.99	76	4.8	–0.17 (–0.49, 0.15)	
Kieu [29], 2002 (rural)	6.5	1.4	39	6.8	1.5	59	3.2	–0.30 (–0.88, 0.28)	
Kieu [29], 2002 (suburban)	5.9	1.3	40	6.2	1.4	58	3.4	–0.30 (–0.84, 0.24)	
Kieu [29], 2002 (urban)	6.2	1.6	32	6.4	1.4	68	2.9	–0.20 (–0.85, 0.45)	
Kuriki [30], 2003	5.77	1.16	15	6.24	1.09	79	2.9	–0.47 (–1.10, 0.16)	
Lee [31], 2000	5.8	1.7	81	6	1.8	113	3.7	–0.20 (–0.70, 0.30)	
Melchert [37], 1987	6.35	1.28	37	6.35	1.36	70	3.5	0.00 (–0.52, 0.52)	
Metherel [38], 2009	6.17	1.06	9	5.5	0.92	7	1.7	0.67 (–0.30, 1.64)	
Nakamura [40], 1995 (30s)	5.3	1.4	18	7.5	1.8	13	1.3	–2.20 (–3.37, –1.03)	
Nakamura [40], 1995 (40s)	5.4	1.1	13	6.2	0.9	13	2.3	–0.80 (–1.57, –0.03)	
Nakamura [40], 1995 (50s)	5.7	1.4	12	5.8	2	15	1.1	–0.10 (–1.39, 1.19)	
Nakamura [40], 1995 (60s)	4.5	1.5	12	5.2	1.1	14	1.6	–0.70 (–1.73, 0.33)	
Sfar [43], 2010	6.85	1.56	96	7.02	1.52	104	4.1	–0.17 (–0.60, 0.26)	
Takita [46], 1996 (20–29 y)	4.4	1.3	28	4.1	0.9	15	2.8	0.30 (–0.36, 0.96)	
Takita [46], 1996 (30–39 y)	4.5	1.2	87	4.7	1	58	4.5	–0.20 (–0.56, 0.16)	
Takita [46], 1996 (40–49 y)	4.4	1.1	81	4.4	1.2	48	4.2	0.00 (–0.42, 0.42)	
Takita [46], 1996 (50–59 y)	4.4	1.3	20	4.9	1.2	30	2.6	–0.50 (–1.21, 0.21)	
Takita [46], 1996 (60–69 y)	4.8	1.8	17	4.3	0.6	10	1.8	0.50 (–0.43, 1.43)	
Umemura [49], 2005	7.1	1.3	175	6.6	1.1	246	5.3	0.50 (0.26, 0.74)	
Yamada [54], 2000 (farming)	5.1	1.77	78	5.5	1.11	124	4.0	–0.40 (–0.84, 0.04)	
Yamada [54], 2000 (fishing)	5.9	1.03	107	6	1.24	154	5.1	–0.10 (–0.38, 0.18)	
Yeh [55], 1996 (junior staff)	4.56	1.22	126	5.41	1.42	96	4.6	–0.85 (–1.21, –0.49)	
Yeh [55], 1996 (senior staff)	5.27	1.4	110	5.91	1.94	65	3.4	–0.64 (–1.18, –0.10)	
Subtotal (95% CI)			**1,594**			**2,012**	**100.0**	**–0.22 (–0.37, –0.07)**	
Heterogeneity: $t^2 = 0.09$; $\chi^2 = 77.70$, d.f. = 31 ($p < 0.00001$); $I^2 = 60\%$									
Test for overall effect: Z = 2.90 (p = 0.004)									

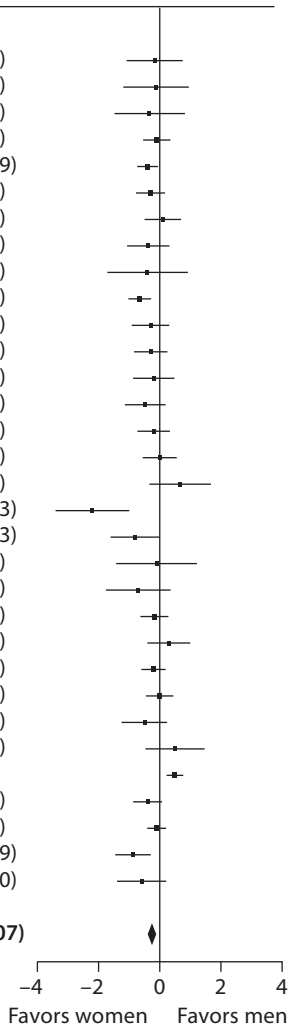

Fig. 2. MD in the percent contribution of AA to total plasma lipids of healthy male and female subjects. Groups I–III [5] were classified by cluster analysis. y = Years.

DHA, considerable heterogeneity was seen among the results of the individual studies.

To filter out the potential effect of age, we tried to classify the individual studies into three age categories: 0–12 (a), 13–50 (b) and ≥51 years (c). In the case of plasma total lipids, classification according to age categories yielded sufficient numbers of studies to evaluate the effect of gender in the two adult groups only. Among the long-chain metabolites, in the group aged 13–50 years only the values of DHA (MD: –0.16; 95% CI: –0.26, –0.06; 2,418 participants; $I^2 = 45\%$) were significantly higher in women, while the values of DPA were significantly lower in women compared to men (MD: 0.07; 95% CI: 0.03, 0.01; 1,130 participants; $I^2 = 67\%$). In the group aged ≥51 years (containing postmenopausal women), the values of the n–6 LCPUFA, DHGLA (MD: –0.14; 95% CI: –0.24, –0.04; 137 participants; $I^2 = 19\%$) and AA (MD: –0.25; 95% CI: –0.43, –0.08; 892 participants; $I^2 = 0\%$) were significantly higher in women compared to men, whereas DHA values did not differ between the two genders.

Study or subgroup	Men			Women			Weight %	MD IV, random (95% CI)	MD IV, random, 95% CI
	mean	SD	total	mean	SD	total			
Total plasma lipids – DHA									
Ando [5], 1990 (group I)	4.76	2.06	31	4.99	1.86	68	1.1	–0.23 (–1.08, 0.62)	
Ando [5], 1990 (group II)	4.46	2.16	29	4.54	1.76	45	0.9	–0.08 (–1.02, 0.86)	
Ando [5], 1990 (group III)	4.52	2.4	37	5.17	2.16	22	0.6	–0.65 (–1.84, 0.54)	
Araki [7], 1990 (20–49 y)	5.2	1.2	27	5.1	1.1	110	2.5	0.10 (–0.40, 0.60)	
Araki [7], 1990 (50–79 y)	5.8	1	57	5.6	0.9	121	4.5	0.20 (–0.11, 0.51)	
Bakewell [8], 2006	1.2	0.3	13	1.7	0.7	23	4.2	–0.50 (–0.83, –0.17)	
di Giuseppe [13], 2009	1.89	0.47	50	2.08	0.51	224	7.2	–0.19 (–0.34, –0.04)	
Fernandez-Real [15], 2001	2.03	0.4	38	1.95	0.7	40	5.3	0.08 (–0.17, 0.33)	
Hirai [22], 2000 (Dutch)	1.26	0.81	20	1.36	0.68	19	2.7	–0.10 (–0.57, 0.37)	
Hirai [22], 2000 (Japanese)	2.2	1.22	33	2.22	0.95	29	2.2	–0.02 (–0.56, 0.52)	
Hirai [21], 2005	3.69	1.43	76	3.38	1	76	3.4	0.31 (–0.08, 0.70)	
Kieu [29], 2002 (rural)	3	0.5	39	3.2	0.6	59	5.9	–0.20 (–0.42, 0.02)	
Kieu [29], 2002 (suburban)	2.5	0.5	40	2.7	0.6	58	5.9	–0.20 (–0.42, 0.02)	
Kieu [29], 2002 (urban)	2.2	0.4	32	2.5	0.5	68	6.5	–0.30 (–0.48, –0.12)	
Kuriki [30], 2003	4.05	0.99	15	4.6	0.83	79	2.3	–0.55 (–1.08, –0.02)	
Lee [31], 2000	3.2	2.1	81	3.4	2.2	113	1.8	–0.20 (–0.81, 0.41)	
Melchert [37], 1987	2.15	0.53	37	2.36	0.59	70	5.9	–0.21 (–0.43, 0.01)	
Metherel [38], 2009	1.07	0.26	9	1.34	0.24	7	5.4	–0.27 (–0.52, –0.02)	
Nakamura [40], 1995 (30s)	7.3	2.7	18	7.1	2.3	13	0.3	0.20 (–1.57, 1.97)	
Nakamura [40], 1995 (40s)	7.2	3.2	13	7.4	2	13	0.2	–0.20 (–2.25, 1.85)	
Nakamura [40], 1995 (50s)	8	2.8	12	7.2	1.3	15	0.3	0.80 (–0.92, 2.52)	
Nakamura [40], 1995 (60s)	7.7	2	12	7.9	2.6	14	0.3	–0.20 (–1.97, 1.57)	
Sfar [43], 2010	2.88	0.95	96	3.31	0.81	104	5.4	–0.43 (–0.68, –0.18)	
Takita [46], 1996 (20–29 y)	2.5	1	28	2.4	0.6	15	2.6	0.10 (–0.38, 0.58)	
Takita [46], 1996 (30–39 y)	3.3	1.3	87	3.2	1.3	58	3.0	0.10 (–0.33, 0.53)	
Takita [46], 1996 (40–49 y)	3.6	1.3	81	3.9	1.2	48	2.9	–0.30 (–0.74, 0.14)	
Takita [46], 1996 (50–59 y)	4	1.6	20	4.1	0.9	30	1.3	–0.10 (–0.87, 0.67)	
Takita [46], 1996 (60–69 y)	4.3	1.6	17	3.7	1.2	10	0.7	0.60 (–0.46, 1.66)	
Umemura [49], 2005	3.4	0.9	175	3.2	1	246	6.5	0.20 (0.02, 0.38)	
Yamada [54], 2000 (farming)	8.2	3.53	78	7.4	2.23	124	1.0	0.80 (–0.08, 1.68)	
Yamada [54], 2000 (fishing)	8.6	3.1	107	8.3	2.49	154	1.5	0.30 (–0.41, 1.01)	
Yeh [55], 1996 (junior staff)	4.11	1.5	126	4.52	1.44	96	3.5	–0.41 (–0.80, –0.02)	
Yeh [55], 1996 (senior staff)	4.2	1.5	110	4.51	1.83	65	2.3	–0.31 (–0.84, 0.22)	
Subtotal (95% CI)			**1,644**			**2,236**	**100.0**	**–0.12 (–0.22, –0.03)**	
Heterogeneity: $t^2 = 0.03$; $\chi^2 = 59.61$, d.f. = 32 (p = 0.002); $I^2 = 46\%$									
Test for overall effect: Z = 2.56 (p = 0.01)									

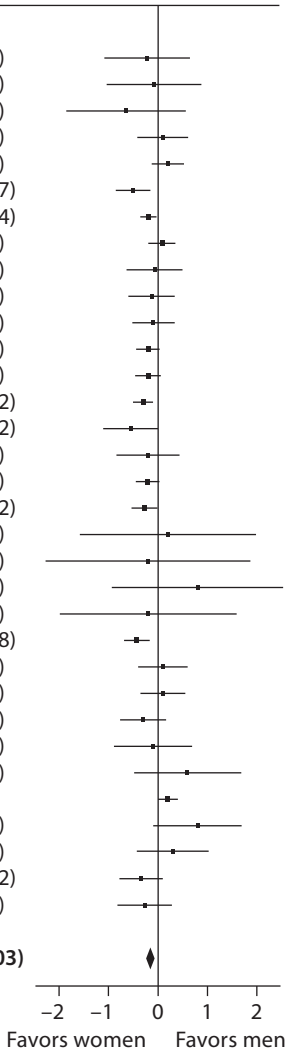

Fig. 3. MD in the percent contribution of docosahexaenoic acid to total plasma lipids of healthy male and female subjects. Groups I–3 [5] were classified by cluster analysis. y = Years.

To consider the potential effect of diet, we classified the studies based on the results of Meyer [56] according to fish eating habits, assigning the Inuit of Nunavik and the Japanese as high n–3 LCPUFA intake group and all other people as low n–3 LCPUFA intake group. In the high fish (n–3 LCPUFA) intake group, values of AA were significantly higher in women compared to men (MD: –0.23; 95% CI: –0.44, –0.02; 2,291 participants; $I^2 = 68\%$), while there was no significant difference in the DHA levels between the two groups (MD: –0.00; 95% CI: –0.12, 0.12; 2,291 participants; $I^2 = 17\%$). In the low fish intake group, both AA (MD: –0.24; 95% CI: –0.41, –0.07; 1,383 participants; $I^2 = 8\%$) and DHA (MD: –0.24; 95% CI: –0.31, –0.16; 1,598 participants; $I^2 = 11\%$) were significantly higher in women.

Fatty Acid Composition of Plasma PL

Plasma PL compositional data were reported for the largest number of men (n = 4,097) and women (n = 4,444).

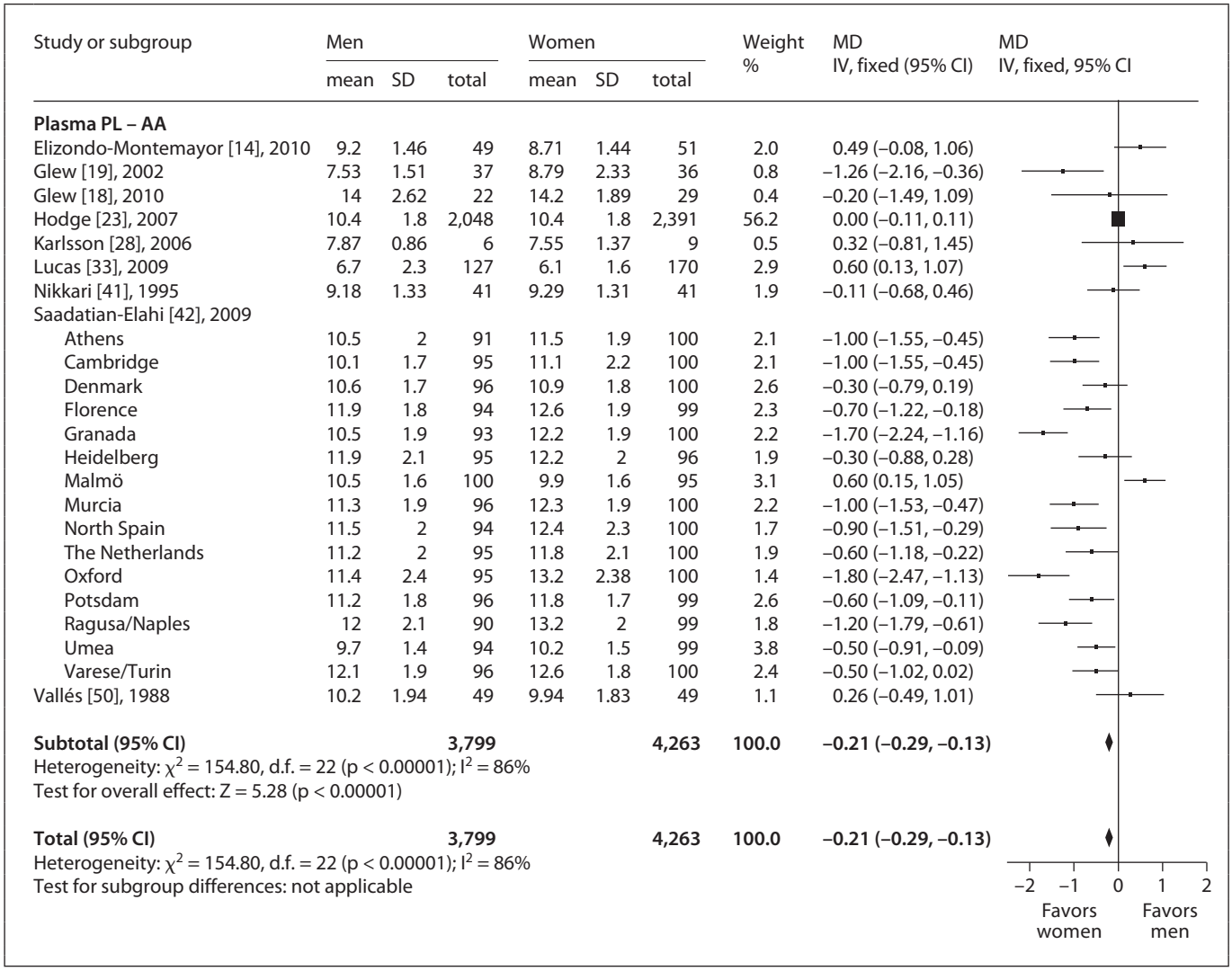

Fig. 4. MD in the percent contribution of AA to plasma PL of healthy male and female subjects.

There was 1 cross-sectional study among the articles [42] included that contained 16 subgroups stratified according to geographic areas; we were able to include 14 subgroups (in one area only women were recruited, whereas another subgroup had to be excluded, because there were also vegans among the participants). Primary analysis revealed significantly higher contribution of both AA (MD: –0.42; 95% CI: –0.65, –0.18; 7,769 participants; I^2 = 81%) and DHA (MD: –0.37; 95% CI: –0.51, –0.24; 8,541 participants; I^2 = 79%) to the fatty acid composition of plasma PL in women (fig. 4, 5), while in LA and ALA there was no gender difference. There were not enough studies to carry out subgroup analysis either by age or fish eating habits.

Fatty Acid Composition of Plasma CE

Plasma CE fatty acids were reported in 8 publications. There was no gender difference in AA and DHA values (table 2), but GLA and DHGLA were found significantly higher in men as compared to women.

Fatty Acid Composition of Plasma TG

Five publications reported fatty acid composition of plasma TG in both men and women. The primary analysis showed no difference between both sexes in any of the fatty acids discussed (table 2).

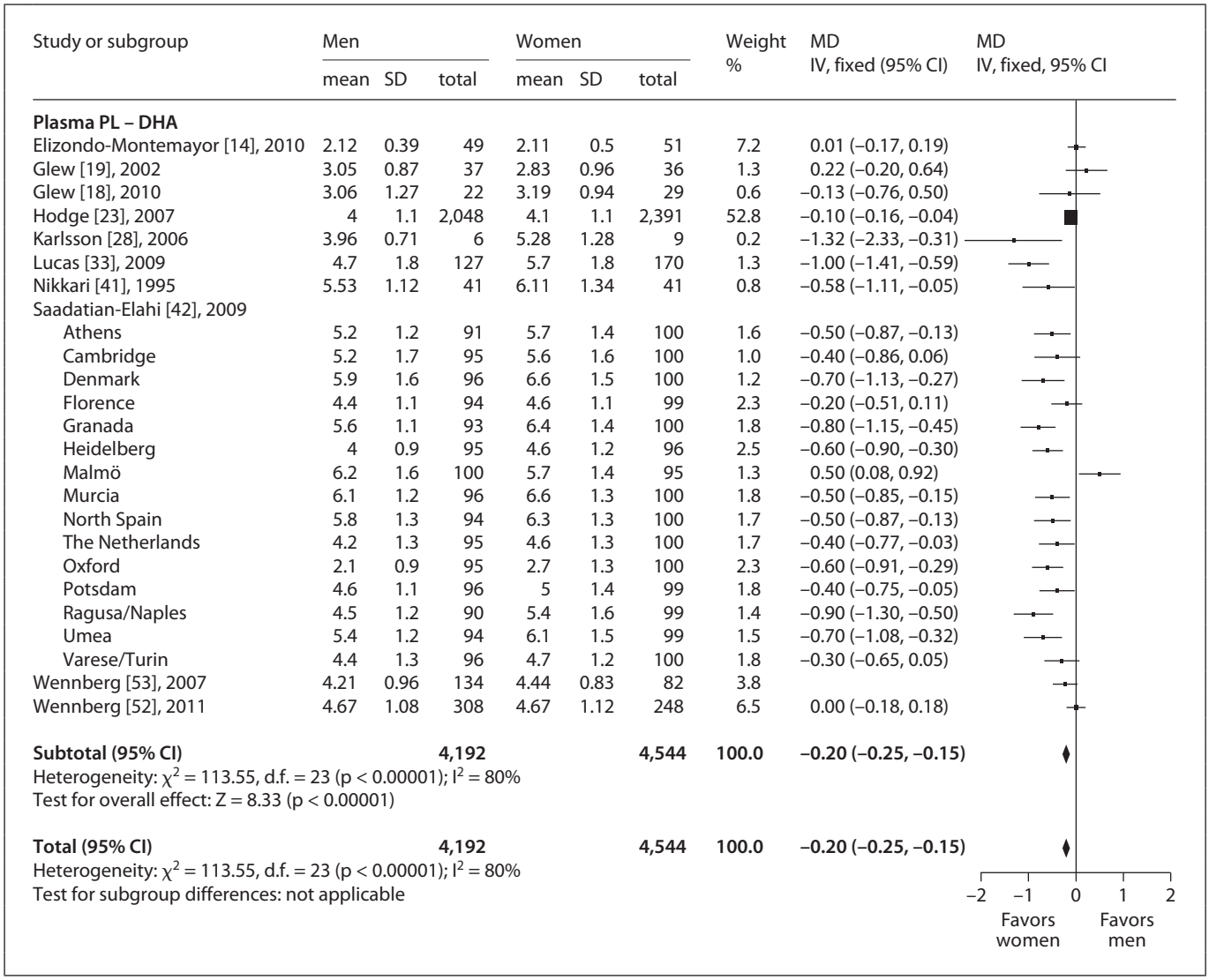

Fig. 5. MD in the percent contribution of DHA to plasma PL of healthy male and female subjects.

Fatty Acid Composition of Erythrocyte Membrane Total Lipids

There were 9 publications reporting fatty acid composition of the erythrocyte membrane total lipids in both sexes. The primary analysis showed significant differences only in DHA values, which were higher in women than in men (table 2). Because most of these studies were carried out in participants older than 50 years, in spite of the apparent abundance of data (12 studies with 1,224 participants), there was no possibility to carry out subgroup analysis either by age or fish eating habits.

Fatty Acid Composition of Erythrocyte Phosphatidylcholine and Phosphatidylethanolamine

There was 1 paper reporting erythrocyte phosphatidylcholine (PC) and phosphatidylethanolamine (PEA) fatty acid composition in 5 subgroups [24]. In erythrocyte PC the values of EPA were significantly higher in women than in men, whereas in erythrocyte PEA there was no difference between the two sexes in any of the fatty acids discussed (table 2).

Fatty Acid Composition of Adipose Tissue

In adipose tissue the values of LA and DHGLA were significantly higher in women than in men, while the values of GLA and AA, and from the n–3 series the values from EPA, were significantly higher in men than in women.

Discussion

Endogenous synthesis of AA and DHA from their essential fatty acid precursors, LA and ALA, requires the contribution of elongases and desaturases. Since the elongation steps are rapid, whereas the desaturation steps are slower, the latter are considered as the rate-limiting steps. In this systematic review, we found higher contributions of LCPUFA (AA and DHA) to both plasma total lipids and plasma PL in women than in men. We also found significantly higher values of DHA, but not of AA, in women than in men in erythrocyte lipids. It may be assumed with good reason that the higher AA and DHA values found in plasma PL of women may be due to the higher activity of desaturases, especially that of Δ^6-desaturase.

The effects of sex hormones on essential fatty acid metabolism in humans have already been reviewed in detail by Childs et al. [57]. In short, human studies demonstrated that males and females differ in their ability to synthesize n–3 LCPUFA from ALA, leading to the higher circulating concentrations of DHA in women than in men [57]. In the same review, a significant relationship between plasma and tissue fatty acid composition and circulating sex hormone concentrations was seen, suggesting that estrogen stimulates, whereas testosterone inhibits, the conversion of essential fatty acids into their longer-chain metabolites. This is consistent with findings from both animal studies [58] and human stable-isotope studies, which also showed that women have a higher capacity than men to synthesize DHA from ALA [1, 59].

We also tried to evaluate the influence of age on the gender differences in fatty acid composition of biological samples. Since previously several authors suggested that gender differences seen in fatty acid compositional data may be due to the higher estrogen levels in women, we decided to make subgroups according to the presumably changing estrogen levels of women in the course of their life cycle: 0–12 (a), 13–50 (b) and 50–75 years (c). In serum total lipids, the higher levels of LCPUFA in women than in men were also seen in the oldest age group, where mostly postmenopausal women were present. This finding on its own may indicate that not only the higher estrogen levels are responsible for the sex differences in LCPUFA values observed, e.g. in addition to the physiological and hormonal changes caused by aging, different age groups can have very different dietary habits, which may also influence the composition of serum lipids. Moreover, many postmenopausal women receive estrogen supplementation therapy, which in fact may further modify the picture. The data obtained in the present study indicate that gender differences in fatty acid status may be relevant also in the elderly.

Diet is considered as the major factor influencing fatty acid composition in tissues. Plasma PL fatty acid composition represents the dietary intake of fatty acids over periods of weeks or months before sample collection [60, 61], while the rate of changes in red blood cells is slower than that seen in plasma lipids [62, 63]. The adipose tissue fatty acid pattern represents the diet ingested in the previous 1–2.5 years [64, 65]. In the vast majority of the studies included into our review, the composition of diets was not investigated, so it is not possible to tell to what extent dietary fatty acids influence our results. However, there were enough studies to carry out a subgroup analysis in the total plasma lipid fraction by n–3 LCPUFA intake characteristic for the investigated populations. This analysis resulted in an appreciable decrease in the degree of heterogeneity, which confirms the important role of diet in determining LCPUFA status. In the high DHA intake group (including Japanese and Inuit subjects), no significant difference in DHA values was seen between men and women . This observation suggests that gender is a significant potential confounding variable mainly in populations with low dietary n–3 intake.

We think that our systematic review has some strongpoints. Firstly, we were able to identify a considerable number of studies investigating a relatively great number of women and men. Secondly, the studies included in the present review originated from a wide diversity of geographic locations; consequently, the results obtained may be applied without serious geographical restriction. Thirdly, the studies analyzed were carried out during more than 3 decades, so the phenomena observed do not seem to be changing over time. However, there are also some weaknesses of our study. Firstly, studies included were mostly observational studies and not randomized controlled trials, so the quality control potential of the studies included into the review was limited. Secondly, in case of plasma PL, 14 data sets (subgroups) originated

from the same cross-sectional study, so these data influenced the statistical results notably. However, these subgroups represented 14 different geographic areas, and so there are good arguments for handling them as different studies. Thirdly, the analytical methods used by the different research groups were not standardized. However, methods of fatty acid analysis are not yet as rigorously standardized as many other laboratory methods, so any systematic review of fatty acid data faces the same difficulty. It is also important to add that there are several factors which influence fatty acid metabolism and differ between genders (e.g. dietary fatty acid intake, alcohol ingestion, relative body fatness or level of physical activity). These factors may all contribute to the gender differences observed in fatty acid composition of different biological samples; however, the main objective of the present review was not to investigate the potential contribution of these factors, but to draw attention to the fact that gender-related differences exist.

In supplementation studies reporting fatty acid composition in serum PL, serum total lipids or erythrocyte membrane lipids, gender distribution should be regarded as significant potential confounding variable.

Acknowledgments

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Disclosure Statement

The authors confirm that there are no financial or other relationships which might lead to a conflict of interest in the publication of this work.

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