Lignan exposure: A worldwide perspective.

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Abbreviations: 24-HDR, 24-h dietary recall; END, enterodiol; ENL, enterolactone; EPIC, European Prospective Investigation into Cancer and Nutrition; FFQ, food frequency questionnaire; LARI, lariciresinol; MATA, matairesinol; MEDI, medioresinol; PINO, pinoresinol; SECO, secoisolariciresinol; SYRI, syringaresinol.

ABSTRACT:

Dietary lignans are phytoestrogens that are mostly found in plant-based foods, especially whole grains, seeds, nuts, legumes and vegetables. An accurate assessment of lignan exposure is crucial to evaluate their potential health benefits and to establish future recommendations and dietary guidelines. This narrative review aimed to: (i) summarize the pros and the cons of the current main assessment methods for lignan exposure ─*i.e.*, dietary questionnaires, food composition tables and biomarkers─, (ii) describe the individual lignans more consumed from a worldwide perspective, as well as their main food sources, (iii) determine the lignans concentrations in both urine and blood, and explore their heterogeneity among countries, and finally (iv) discuss the main determinants of lignan exposure.

INTRODUCTION

Chemistry and bioavailability

Lignans are secondary plant metabolites widely distributed in many plant-derived foods, such as whole grains, seeds, nuts, legumes, vegetables, and drinks (*e.g.*, tea, coffee, or wine) [1]. Lignans are bioactive compounds well-known by their ability to mimic or modulate the action of endogenous estrogens [2]. Thus, they have been suggested to play a role in the prevention of several chronic and hormone-related diseases such as cardiovascular disease [1, 3], breast cancer [4, 5], osteoporosis [6], and menopausal symptoms [7, 8]. Lignans are chemically polyphenolic compounds derived from two β-β'-linked phenylpropane (C6-C3) units. Based on the way in which oxygen is incorporated into the skeleton and cyclization patterns, they can be classified into 8 subgroups: furans, furofurans, dibenzylbutanes, dibenzylbutyrolactones, dibenzocyclooctadienes, dibenzylbutyrolactols, aryltetralins, and arylnaphthalenes. The most common lignans consumed and for which the evidence has shown the most compelling benefits for health are secoisolariciresinol (SECO), lariciresinol (LARI), pinoresinol (PINO), matairesinol (MATA); although other lignans are also frequently consumed [*e.g.*, sesamolin, sesamin, syringaresinol (SYRI) and medioresinol (MEDI)] [9].

In nature, lignans are generally linked to other molecules, mainly as glycosylated derivatives [10]. Lignan glycosides are absorbed in the gastrointestinal tract after being metabolized by gut mucosa and/or colonic microbiota into lignan aglycones and further converted into enterolignans [*i.e.*, enterolactone (ENL) and enterodiol (END)] [1, 11]. The efficacy of this conversion depends on several factors, especially on the microbiota

composition and function, and differs considerably among individuals. In an *in vitro* fecal microbiota metabolism system, 100% of LARI, 72% of SECO and 55% of PINO were converted to END; while approximately half of END and 62% of MATA were transformed to ENL [12]. Enterolignans, also called mammalian lignans, are efficiently absorbed and conjugated to glucuronide and/or sulfates by enterocytes. Finally, enterolignans are detected in blood (8-10h half-life) and excreted 30% through urine (residence time approximately 24h) and 50% via enterohepatic circulation and feces [11]. Only small amounts of LARI, MATA, PINO, SECO, and SYRI have been found in blood and urine [13] (Figure 1).

In plant-derived foods, the richest sources of lignans are sesame seed oil (1,294 mg/100g), flaxseed meal (867 mg/100g), and sesame seed meal (776 mg/100g), followed to a lesser extent by whole grains and virgin olive oil (< 5mg/100g). The lignan content of other or plant-derived foods is generally minimal with concentrations lower than 1 mg/100g [14]. Similarly, only negligible amounts of enterolignans have been detected in specific animal foods (*i.e.*, milk, eggs, and derived products), which are produced by the intestinal bacterial metabolism in the animals' guts after eating a diet rich in lignans [15]. A list of the top 25 richest foods of the main 6 individual lignans is shown in the Supplementary table 1.

Exposure assessment

In nutritional studies, lignan exposure has been assessed using either dietary questionnaires or nutritional biomarkers. Both methodologies have advantages and disadvantages. On one hand, dietary questionnaires [*e.g.*, food frequency questionnaires (FFQ), 24-h dietary recalls (24-HDR), and food diaries] are inexpensive, easy to administer and can estimate a

lot of dietary data simultaneously, including dietary patterns, foods, nutrients and non-nutrients [16]. On the other hand, dietary questionnaires are susceptible to random and systematic reporting errors since they are based on subjects' memory and their ability to estimate food portion sizes. Moreover, a food composition database is needed to convert food consumption into lignan intake. Phenol-Explorer [17] is the most comprehensive database on polyphenols that include all individual lignans (n~30) present in habitual foods. Other studies have used other food composition databases from Canada [18], the Netherlands [19], UK [20-22] and Finland [23]; although these only usually include the four main individual lignans. The main limitations of using these databases are the large amount of unknown values, the limited quantity of food items included, and the absence of composition data on cooked foods. Thus, the estimation of lignan intake may be inaccurate and tends to be underestimated. To improve accuracy of self-reported dietary estimates, researchers are using new technologies, which are practical, have lower costs and burden for both researchers and participants (*e.g.*, mobile phone applications) [24]. Moreover, they are using databases that are regularly updated, allowing to increase the number of available foods and individual lignans.

Nutritional biomarkers have become an alternative or complementary method for estimating dietary intake. An ideal dietary biomarker would accurately reflect its dietary intake and be specific, sensitive, and applicable to many populations. Their main advantage is that they are objective, take into account bioavailability, and offer more accurate assessment since they do not rely on subject's memory. In contrast, their disadvantages include the requirement of biological samples, the complexity of the analytical methodology, and the elevated cost [25]. During the last two decades, lignans and

especially enterolignans have been measured in blood and urine samples as potential biomarkers of dietary lignans. Currently, the analytical method generally used is liquid chromatography coupled to a tandem mass spectrometer (LC-MS/MS); although gas chromatography GC-MS and time-resolved fluorescence immunoassay have also been successfully used. These analytical methodologies allow us to have limits of detections below 0.1 mg/L [26].

Concentrations of enterolignans in plasma and urine have been extensively investigated as potential biomarkers of dietary lignan intakes. In a pooled analysis, urinary ENL levels have been highly correlated with MATA and SECO intake (r=0.78), but not urinary END (r=-0.14) [27]. However, in individual studies, correlations between lignan intake (sum of MATA and SECO) and urinary enterolignans (sum of ENL and END) were moderate (r=0.40-0.46) in 26 Canadian women [28] and low (r=0.16-0.25) in 195 adults from the California Teachers Study [29]. Weak associations between lignan intake and plasma END (r=0.09) and ENL (r=0.18) were observed in a Dutch study [30]. Similarly, correlations between lignan intake and sum of plasma/serum enterolignans were low (r=0.1-0.22) [31]. These low correlations could be due to the constrains to accurately assess dietary lignan intake (such as the aforementioned limitations of dietary questionnaires and food composition databases) or to difficulties to analyze the lignan content in foods, particularly in the extraction since they are usually bounded to dietary fiber [32]. It is also probable that a low correlation may exist due to the high inter- and intra-individuality in the absorption, metabolism and excretion of lignans or in the average lifetime of enterolignans in biospecimens (plasma and urine) [11]. Despite of these results, concentrations of

enterolignans, especially in urine, are considered suitable and reliable alternative measurements of lignan exposure.

WORLDWIDE DIETARY LIGNAN INTAKE

Geographical differences in the intake of lignans and their food sources

Due to differences in dietary patterns worldwide, lignan intakes vary considerably by geographical region, with mean intakes mostly ranging from 0.2 to 6.4 mg/d in adults (Table 1, Figure 2) [9, 33]. It is important to highlight that comparing results and estimates across studies presents several challenges due to differences in the amount of individual lignans included, and both the composition database and the dietary assessment method used. However, some studies used similar methodologies that allow us to compare results more easily.

Europe

Europe is the continent with more studies estimating the intake of lignans (Table 1). In adults, the mean intake ranged from 0.2 mg/d to 5.2 in France [34] and Latvia [35], respectively. Unsurprisingly, the highest intake of lignans (9.1 mg/d) was reached in a vegetarian/vegan UK population, since lignan is almost exclusively found in plant-based foods [9]. Despite the differences between studies, the existence of large multi-center studies such as the European Prospective Investigation into Cancer and Nutrition (EPIC) and the Healthy Lifestyle in Europe by Nutrition in Adolescents (HELENA) allows to compare lignan intakes across Europe using the same methodology [9, 36, 37]. Data from the EPIC study, that used Phenol-Explorer database, indicates that Mediterranean countries

144 have a higher intake than the non-Mediterranean ones [9, 36]. However, the HELENA
145 study, which used the Dutch database, showed a small decreasing north-to-south gradient
146 [37].

147 Data from studies using different methodology and databases indicates that the highest
148 lignan intake in Europe usually occurs in northern countries, including Scandinavian and
149 Baltic countries (Table 1). Considering the assessment of at least 6 individual lignans
150 (LARI, MATA, PINO, SECO, SYRI, and MEDI), the average of overall lignan intake
151 ranged between 2.3 mg/d and 5.2 mg/d. Intake estimates were lower (0.9-1.8 mg/d) if only
152 LARI, MATA, PINO, and SECO were considered. LARI, PINO and SECO were usually
153 the individual lignans more consumed, although SYRI was also common. The main food
154 sources of lignans in this region were whole grain cereals (especially rye, oat, and wheat),
155 bread, flaxseeds, and berries.

156 The mean intake of lignans in Central European countries, such as UK, Poland, Germany,
157 and the Netherlands, ranged between 0.6 [38] and 2.3 mg/d [9]. Most of the studies in this
158 region only assessed LARI, MATA, PINO, and SECO, and therefore, the intakes may be
159 slightly underestimated. In a Polish study [39] the mean intake of lignans was extremely
160 high (12.1 mg/day) due to a Phenol-Explorer error in the lignans content of some specific
161 vegetables [17] that were the main food sources in this Polish study (such as cucumber). In
162 Central European countries, LARI, PINO and SECO were the main individual lignans
163 consumed. Bread, seeds, and vegetables were the most common food sources of lignans in
164 this region.

Lastly, southern European countries, also referred as Mediterranean countries, had a highly variable intake, ranging from 0.2 mg/day in France [36] to 4.3 mg/day in Greece [9]. France and Spain had relatively low intakes (0.2-2.1 mg/d), while Italy and Greece generally had a high consumption (0.7-4.3 mg/d) [9, 36]. In an Italian study [40] the mean intake was extremely high (80 mg/d). Although the authors did not provide any rationale for such results, it is possible that this could be due to a processing error in the Eurofir-eBASIS food composition database [41]. LARI, PINO and SECO were also the most consumed individual lignans in this region; although depending on the study, the proportions largely vary. These countries typically follow a Mediterranean dietary pattern, where the main food sources of lignans are derived from olive oil, vegetables, fruits (mostly citrus fruit), wine (predominantly red wine) and in a minor percentage bread and cereal products.

Americas

In the US, there is also a great quantity of studies describing the lignan intake (Table 1). Most of these studies used the Canadian database [18] which only contains data on the four traditional individual lignans: LARI, MATA, PINO, and SECO. The mean intake of total lignans ranged between 0.1 and 6.4 mg/d [42, 43] although in the majority of these studies, their intake was <1mg/d. In this region the main food sources were tea and coffee, probably due to a lower consumption of fruits, vegetables and whole grains compared to Europe. In the US, SECO was clearly the most consumed individual lignan, followed by far by LARI and PINO. In two Canadian studies, the intake of total lignans was slightly lower than in the US, ranging from 0.2 to 0.4 mg/d [44, 45] and the main food sources were legumes,

187 seeds, cereals and grains, and berries. To date, only SECO and MATA were assessed in
188 Canada, which clearly underestimate total lignan intake.

189 To our knowledge, the existing data in Latin-American countries is limited to Mexico [33,
190 46] and Brazil [47-49]. The mean intake of total lignans was similar in both countries,
191 varying from 0.1 to 2.3 mg/d. A Brazilian study [47] was not included in the current
192 review, since its mean intake was exceptionally high 13.6 mg/d, possibly due to an error in
193 data calculation. As in Europe, SECO, LARI and PINO were the main contributors to total
194 lignans in this region. Main food sources were generally vegetables, fruits, nuts, seeds and
195 vegetable oils. However, there is a potential underestimation of lignan intakes in Latin
196 American countries due to the limited food composition data on some tropical foods [33],
197 such as mamey, zapote, papaya, sweet potato, nopal, guava, jicama, and prickly pears.
198 Those are frequently consumed in this region, but their lignan content is not available in
199 any food composition database yet.

200 *Other continents*

201 In Australia, two studies estimated the intake of total lignans in women only [50, 51]. Their
202 mean intake ranged from 0.7 to 2.7 mg/d. SECO was the major individual lignan consumed
203 and the main food sources were soy and linseed [51].

204 In Asian countries, lignan intake was estimated only in two Iranian-based [52, 53] and one
205 Korean-based [54] studies. In Iran, the mean intake of total lignans, including all individual
206 lignans, varied between 0.2 mg/d and 2.4 mg/d; whereas in Korea, including only MAT and
207 SECO, the mean intake was 1.5-1.8 mg/d. Data on main food sources was not available in
208 this region.

Determinants of lignan intake

Lignans were positively correlated to total energy intake [55]; therefore, participants consuming more energy were more likely to be those with a higher intake of total lignans. Although a Latvian study [35] showed a greater consumption of total lignans in men compared to women; data from EPIC showed that women had a higher intake of lignans after adjusting for total energy consumption (3.6 mg/d in women vs. 2.5 mg/d in men) [9]. Interestingly, one Korean study [54] observed slight differences between menopausal statuses in women (1.8 mg/d in postmenopausal women vs. 1.5 mg/d in premenopausal women). In the EPIC study [9], results indicated that lignan intake also increased with age. For instance, young adults (35-44 years) had a lower intake of total lignans (2.8 mg/d) than older adults (65-74 years; 3.5mg/d) [9]. In children and adolescents, the two available European studies [36, 56] found that the mean intake was higher in adolescents (15-18 years) than in children (2-15 years), 0.98 - 1.10 mg/d vs. 0.61 - 1.00 mg/d, respectively.

The results by lifestyle factors and other sociodemographic variables are controversial. For example, some studies showed that subjects with obesity had a higher intake of lignans [9, 36, 45, 57, 58-60] than individuals with normal weight; whereas in other studies occurred the opposite [9, 35, 61-63]. Discrepancies were also observed comparing lignan intake by educational level, smoking status, physical activity, and alcohol consumption.

WORLDWIDE ENTEROLIGNANS CONCENTRATIONS

Geographical differences in total enterolignans concentrations

229 Concentrations of lignan metabolites (END and ENL) in biospecimens, as potential
230 biomarkers of lignan intake, are useful indicators of lignan exposures across populations. In
231 order to straightforwardly compare concentrations of enterolignans, all estimates have been
232 converted into the same units (nmol/L) in Tables 2 and 3. These summarize the most
233 representative studies assessing urinary and blood (*i.e.*, serum or plasma) enterolignan
234 concentrations, respectively. Levels of urinary entrolignans were usually 100-fold higher
235 than those found in blood (serum or plasma). The mean urinary END concentrations
236 worldwide ranged from 38 [64] to 763 nmol/L [65] and for ENL from 148 [66] to 3,651
237 nmol/L [67] (Table 2, Figure 3). In the case of plasma and serum, END concentrations
238 varied between 0.2 nmol/L [68] and 7.0 nmol/L [69] while ENL levels ranged from 4.9
239 nmol/L [68] to 39.2 nmol/L [69]. Levels of enterolignans in plasma and serum were similar
240 (Table 3, Figure 3). Mean concentrations of END were between 2 to 13 times lower than
241 ENL in both urine and blood.

242 *Europe*

243 Few studies (n=8) have measured urinary enterolignans in Europe (Table 2). Northern
244 European countries tend to have the highest levels of enterolignans (ENL=768-3,267
245 nmol/L) [65, 70] followed by Central European countries (END= 204-288 and ENL=
246 2,414-3,333 nmol/L nmol/L) [71-75]. Data for Mediterranean countries were limited. There
247 is only one study from Italy, that reported a high urinary concentration (END=763 and
248 ENL=1,577 nmol/L) (76).

249 Most of the studies measuring enterolignan concentrations in blood specimens, of which 20
250 were conducted in plasma and 10 in serum, were performed in Central and Northern

European countries (Table 3). The lowest concentrations of END and ENL were 0.2 nmol/L and 4.9 nmol/L, respectively, in a UK-based study [68]; while the highest levels were derived from a Dutch population: 7.0 nmol/L for END and 39.2 nmol/L for ENL [69]. Comparing studies that used the same analytical methodology, in general, concentrations in Central European countries (*e.g.*, the Netherlands, Germany, UK) were slightly lower than in Scandinavian countries [68, 77]. However, when all studies were considered independently of lignan assessments, levels of enterolignans in central European countries were very heterogeneous [68, 69]. The lowest mean enterolignan concentrations were found in Mediterranean countries: 0.3 nmol/L for END and 6.7-7.8 nmol/L for ENL [77]. Italy was the Mediterranean country with the highest END (1.3 nmol/L) and ENL (9.1 nmol/L) concentrations in plasma [77], which is similar to intake estimations.

Americas

To our knowledge, only US data was available from both North and South American continents, with the exception of a Jamaican study. In the US, several studies assessed enterolignan concentrations in urine (n=15) (Table 2), plasma (n=2), and serum (n=2) (Table 3). Both urinary END and ENL excretions varied considerably among US studies from 38 [64] to 609 nmol/L [67] for END, and from 285 [64] to 3,651 nmol/L [67] for ENL. Indeed, US populations included the worldwide minimum mean of END levels (285 nmol/L) and the worldwide maximum mean of ENL excretions (609 nmol/L). In the Jamaican study, the mean intake of END was in the upper side of the interval of the US studies (2,671 nmol/L) [78].

Similarly, a high variability in blood END levels was observed among US studies, ranging between 1.5 nmol/L [79] and 6.0 nmol/L [80] while the range of mean levels for ENL was narrower from 11.5 nmol/L [81] to 22.5 nmol/L [79].

Asia

To date, urinary concentrations of enterolignans in Asia were measured in Singapore [82], Japan [66, 83], Vietnam [83], Cambodia [83] and India [83]. The mean of urinary END concentrations varied from 60 nmol/L in Cambodia [83] to 245 nmol/L [83] in Vietnam. For ENL, the highest mean value was found in Vietnam (1,678 nmol/L) [83] while the lowest excretion was identified in a Japanese study (148 nmol/L) [66].

Several studies in East Asia (such as Japan, China, Korea and Vietnam) assessed enterolignans in plasma and showed a relatively low variation in their mean concentrations (~3-fold variation). Thus, END concentration means ranged from 2.0 nmol/L [84] to 5.6 [85] in the two Chinese studies. Mean ENL concentrations in blood samples were between 10.2 nmol/L [86] and 32.7 nmol/L [87] in Vietnam and Japan, respectively. In the study of Liu et al. [84] median plasma concentrations of ENL (2.0 nmol/L) and END (16.4 nmol/L) seem to be exchanged. Mean ENL concentrations in Korea were extremely high (177.8 nmol/L in women and 249.3 nmol/L in men), around 10-fold higher than values found in any other study from other continents.

Determinants of the total enterolignans concentrations

Data from studies that analysed separately men and women showed that urinary concentrations of enterolignans were slightly higher in women than in men [67, 70, 83],

with one exception [64]. Urinary ENL and END excretions were the highest in adults (20-60 years), followed by the elderly (>60 years) and, finally, by adolescents (12-19 years) [67]. This pattern according to age and sex is consistent with findings from dietary lignans adjusted for energy intake. A Danish study suggested that smoking and higher BMI were associated with lower concentrations of ENL [88]. No other information was found for concentrations of entrolignans (in both urine and blood) and other determinants, such as educational level and physical activity.

STRENGHTS & LIMITATIONS

Dietary data

The main limitation of this review was that each study used a different methodology to estimate the lignan intake. Firstly, differences in both the type of dietary questionnaire (FFQ, 24h dietary recall, history of diet) and the amount of food items included in the questionnaire could complicate comparisons in the habitual estimation of individual foods, particularly lignan-rich products. Although, the vast majority of studies used validated FFQs; very few of these questionnaires were specifically validated for lignans. Secondly, available food composition tables/databases were not complete. They have missing data on several foods and, especially, on some individual lignans. Only Phenol-Explorer [17] contains data on all commonly consumed lignans; while others only have data on two (MATA and SECO) or four individual lignans (MATA, SECO, LARI, and PINO). These four lignans are the most abundant ones accounting for at least 50% of total lignan intake in Europe [9]. Thirdly, most of the presented studies were not representative of the entire population, so the results may not be totally generalizable. However, the inclusion of

several medium-to-large size studies from the same geographical area enhances generalizability. Fourth, studies evaluating reliability of enterolignans as biomarkers of lignan intake are limited; especially those investigating all individual lignans, and correlations were moderate for urinary concentrations [27-29] and low for plasma/serum concentrations [31]. Therefore, inconsistent results have been observed comparing results using dietary conventional dietary questionnaires and biomarkers. For example, a recent meta-analysis showed no associations between dietary lignan intake and cancer outcomes; while a higher concentration of serum/plasma ENL was inversely associated with overall cancer survival [89].

Biomarker data

Variability in results due to differences in procedures and methods in the analysis of concentrations of enterolignans in blood and urine were relatively minor, since all analytical methodologies were validated. The main limitation was that the studies only analyzed one sample per subject. It is well-known that enterolignans are relatively short-term nutritional biomarkers [11] and therefore multiple measurements would be recommended to estimate habitual exposure at individual level. However, the mean of a single punctual measure in a large quantity of subjects was a suitable way to reflect the habitual mean of lignan concentrations at population level. Another limitation was the relatively small size of all studies and therefore the limited generalizability of the results.

CONCLUSIONS

Overall, common mean intakes of total lignans worldwide ranged from 1 to 5 mg/d, with a higher intake in vegetarian populations (9.1 mg/d). There was a large heterogeneity in the

337 estimations of lignan intake across studies partially due to real differences among
338 geographical areas and populations and to differences between dietary assessment methods
339 used. Food sources also varied across regions, although the most typical ones were whole
340 grain cereal products, seeds, vegetables, and fruits.

341 As expected, similar trends and differences between regions were observed using dietary
342 and biomarker data. END concentrations were usually 10-fold lower than ENL levels in
343 both urine and blood. Results of enterolignans in plasma and serum were equivalent. END
344 and ENL concentrations in urine were approximately 100 times higher than in blood.

345 More food composition data is warranted in order to update current databases on lignans
346 and improve dietary intake estimations. Data from some regions, particularly in low- and
347 middle-income countries (Africa, Latin America, and some areas in Asia), was scarce or
348 null; therefore, further studies combining both dietary and biomarker data in these regions
349 are requested to improve data coverage globally.

350 Finally, an accurate estimation of lignan exposure is essential to better understand
351 associations between lignan intake and the risk of chronic diseases. In our opinion,
352 although, current estimations of dietary lignan intake are getting more precise, they are
353 often underestimated. Thus, concentrations of enterolignans in blood and urine are still
354 preferable to estimate lignan exposure in epidemiological studies. This data will be crucial
355 for setting and improving current dietary recommendations for populations.

356 **CONFLICT OF INTEREST**

357 The authors are not aware of any conflicts of interest.

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FIGURE CAPTIONS

Figure 1. Scheme of human bioavailability of dietary lignans.

Figure 2. Mean of means/medians of total dietary lignan intake (mg/d) by country.

Figure 3. Mean of means/medians of urinary and blood enterolignan concentrations (nmol/L) by country; A: urinary enterolactone, B: urinary enterodiol, C: blood enterolactone, D: blood enterodiol.

892 Figure 1.

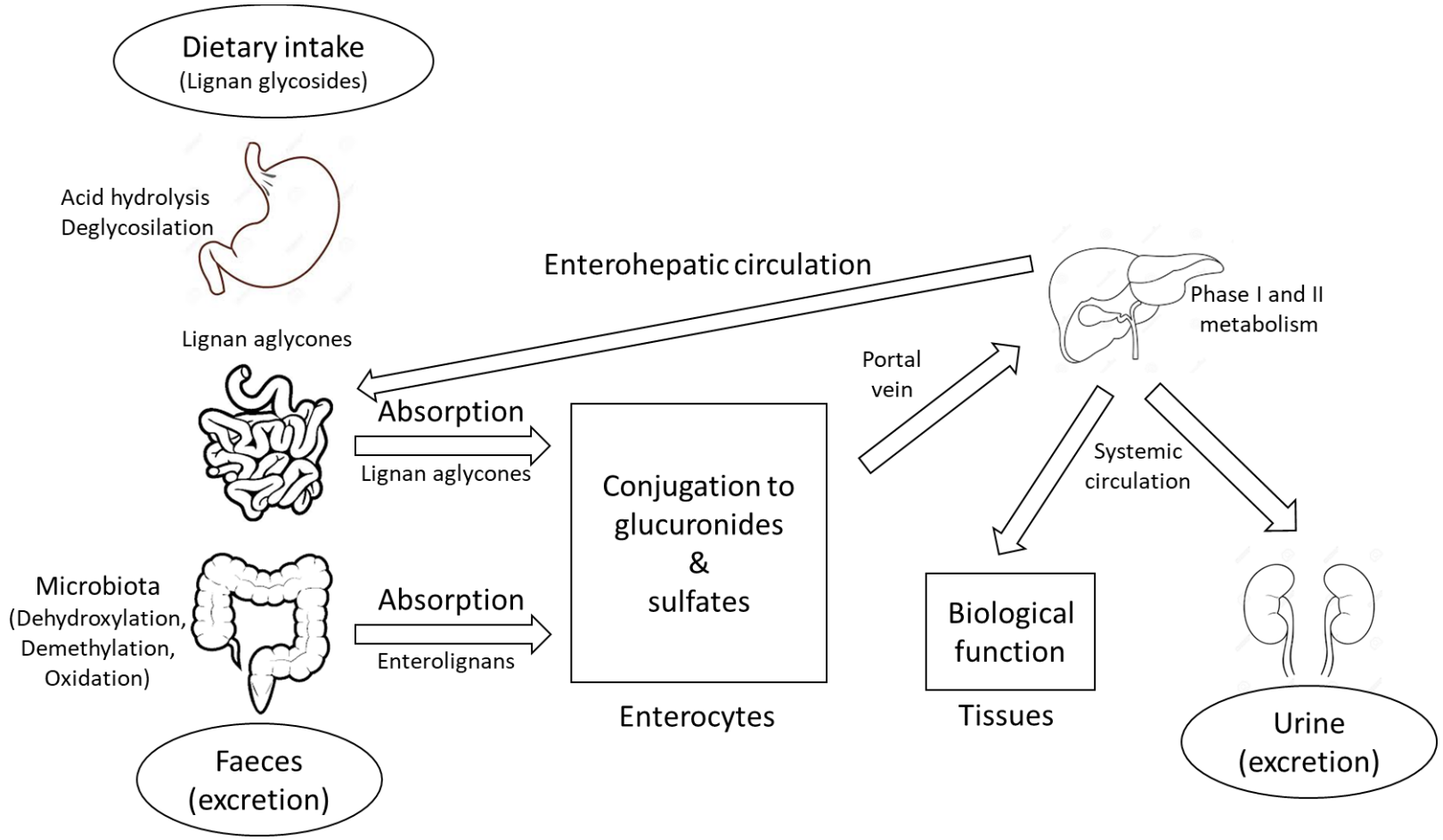

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Figure 2.

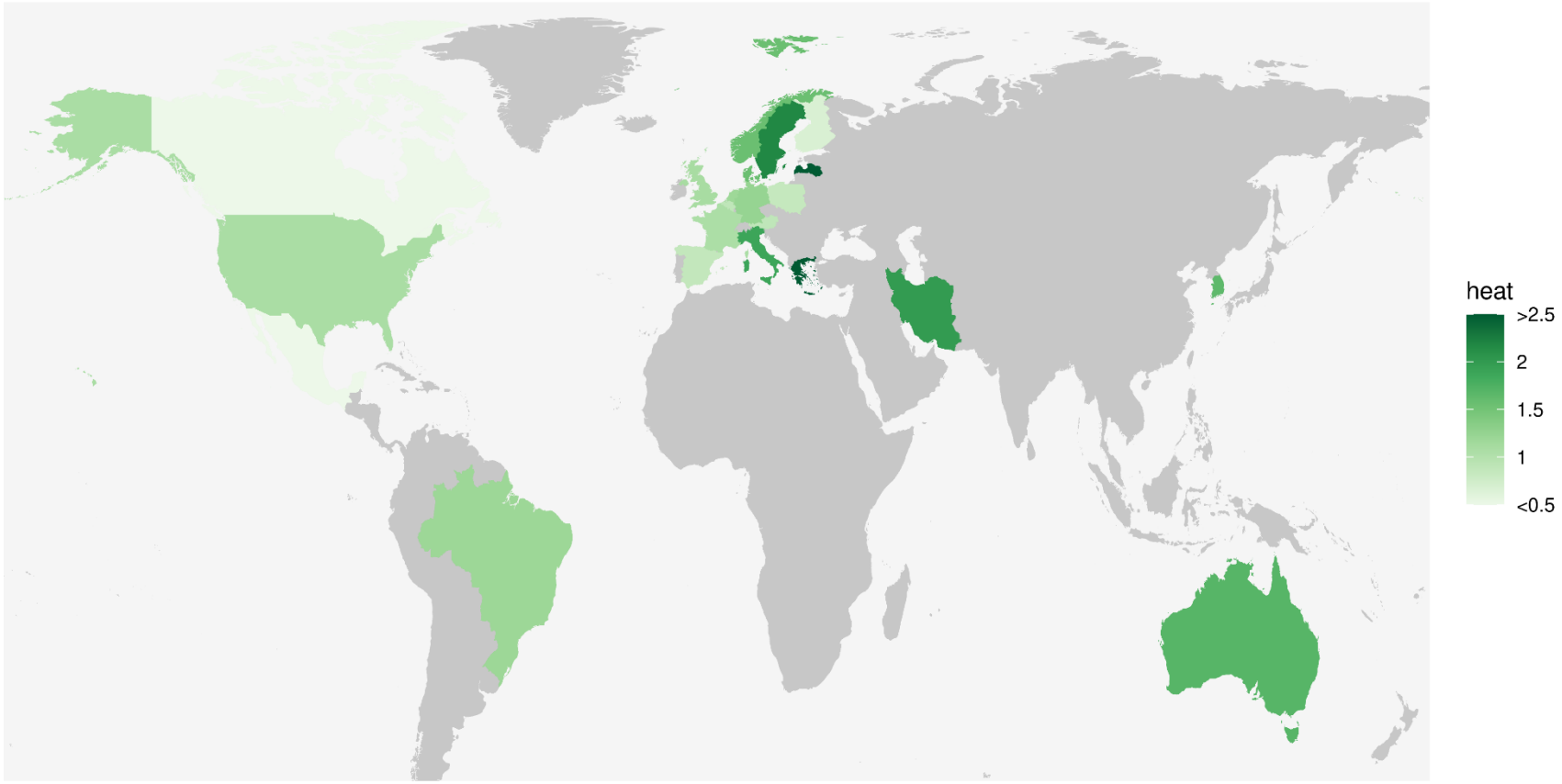
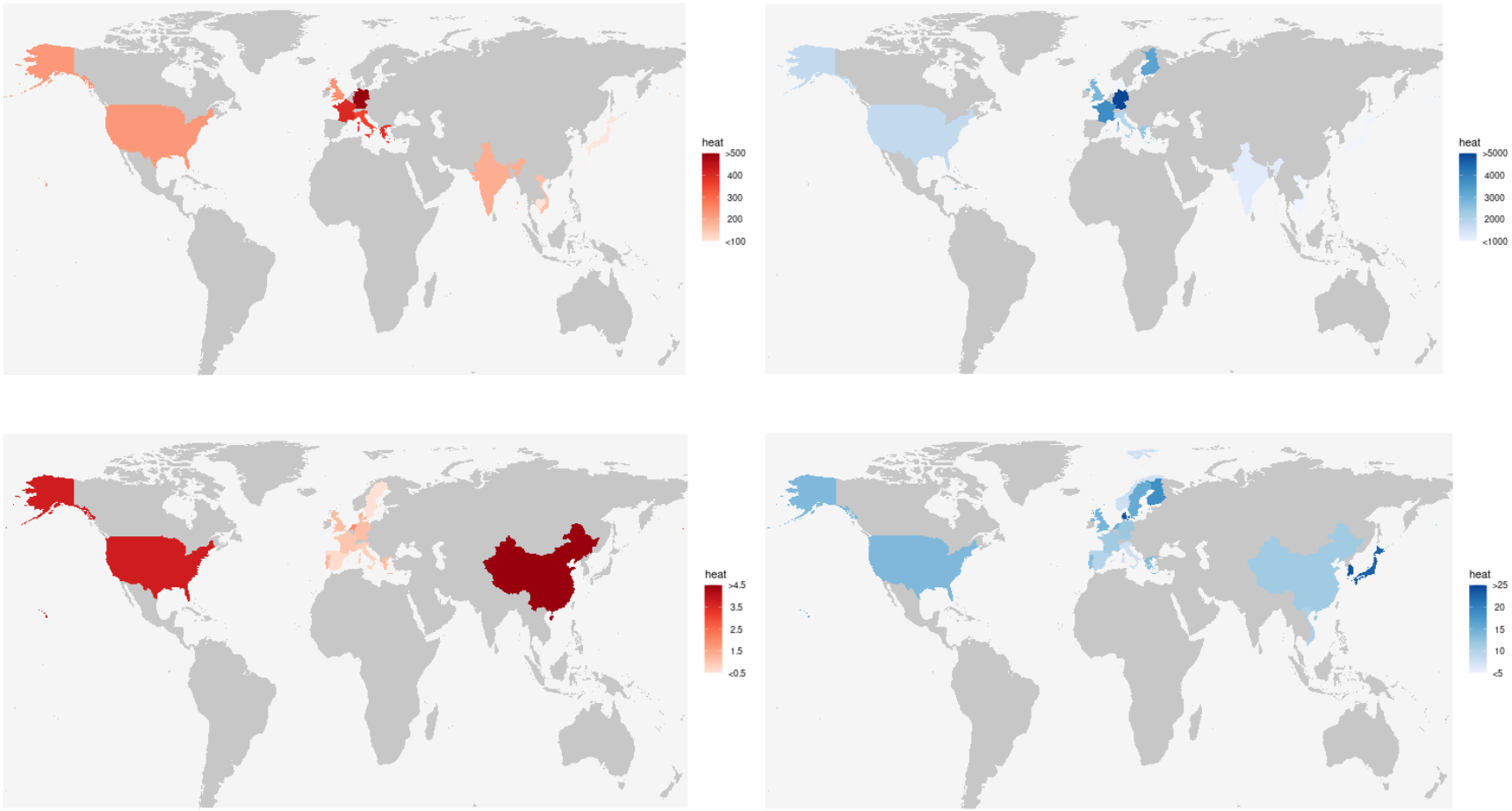


Figure 3.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902 Table 1. Characteristics of the studies included in the review of dietary lignan intake.

Author (Reference)	Year	Country	Population			Dietary survey	FCDB	TOTAL LIGNANS		
			N	Sex	Age (y)			Individual lignans	Intake (mg/d)	Food sources
Wisnuwarda-ni [36]	2006-2007	MED countries	915	F (53%)	12–18	2 x 24-HDR	Phenol Explorer	All[4]	1.2 (0.0)[1]	Breads (71%), fruit (8%), vegetables (7%)
		non-MED countries	1,513						0.9 (0.0)[1]	Breads (58%), fruit (12%), vegetables (7%)
Zamora-Ros [9]	1995-2000	MED countries	11,285	F (64%)	35-74	24-HDR	Phenol Explorer	All[4]: SECO (18%), LARI (14%), Sesamolin (12%), Sesamin (12%)	3.6 (0.1)[1]	Vegetable oils (26%), cakes & biscuits (20%), breads (12%)
		non-MED countries	24,443						2.3 (0.1)[1]	Breads (22%), spices (16%), seeds (16%), vegetable oils (11%)
		UK healthy	309						9.1 (0.9)[1]	Seeds (48%), vegetable oils (10%), vegetables (9%)
Tetens [37]	2000-2002	Denmark	2,463	F (53%)	25-64	7-DR	Dutch DB	LARI (43%), PINO (32%), SECO (22%), MATA (3%)	1.5[2]	Cereals (27-30%), fruit & berries (18-25%), coffee & tea (21%), vegetables (19-20%)
	2002	Finland	2,007	F (55%)	25-64	48-HDR		LARI (43%), PINO (37%), SECO (17%), MATA (2%)	1.1[2]	Cereals (27-36%), fruit & berries (22-31%), vegetables (16-20%), coffee & tea (17%)
	1994-1996	Italy	1,268	F (54%)	25-64	7-DR		LARI (45%), PINO (42%), SECO (13%), MATA (1%)	1.1[2]	Fruit & berries (42-46%), vegetables (26-28%), cereals (17%)
	1987-1990	Sweden	83,760	F (45%)	45-79	FFQ		PINO (44%), LARI (41%), SECO (13%), MATA (2%)	1.8[2]	Cereals (26-42%), vegetables (18-30%), fruit & berries (15-23%), coffee & tea (18-19%)
	2000-2001	UK	1,724	F (56%)	19-64	7-DR		LARI (43%), PINO (39%), SECO (16%), MATA (2%)	1.2[2]	Coffee & tea (30-32%), vegetables (23-25%), fruit & berries (15-20%),

										cereals (15-17%)
Kilkkinen [57]	1997	Finland	1,359	M	25-63	24-HDR	Finish DB	MATA (73%), SECO (27%)	0.2[2]	Cereals (49%), fruits (25%), vegetables (12%)
			1,493	F	25-64			MATA (80%), SECO (20%)	0.2[2]	Fruits (39%), cereals (35%), vegetables (13%)
Nurmi [90]	1995	Finland	100	M	58(6)[1]	4-DR	Dutch DB	LARI (40%), PINO (38%), SECO (14%), MATA (7%)	1.2 (0.5)[3]	Rye products, berries, coffee, tea, vegetable roots
Hedelin [63]	1991-1992	Sweden	48,268	F	30-49	FFQ	Finish DB II	LARI, MATA, PINO, SECO, SYRI, MEDI	2.3 (1.8-2.8)[3]	Rye bread (57%), wheat bread (27%), cereals (8%)
Hedelin [62]	1991-1992	Sweden	46,977	F	30-49	FFQ	Finish DB II	LARI, MATA, PINO, SECO, SYRI, MEDI	2.3 (1.0–4.0)[3]	Rye bread, wheat bread, cereals, berries
Suzuki [55]	1987-1990	Sweden	51,823	F	40-76	FFQ	Own DB	LARI, MATA, PINO, SECO	0.9 (0.7-1.0)[3]	–
Hedelin [91]	2001-2002	Sweden	1,130	M	35-79	FFQ	Finish DB II	SECO (38%), SYRI (30%), PINO (15%), LARI (13%), MEDI (12%), MATA (1%)	4.9[2]	Flaxseed (36%), Rye bread (39%), wheat bread (15%)
Meija [35]	2009-2011	Latvia	172	M	40-75	FFQ	Canadian DB	SECO (58%), SYRI (22%), PINO (11%), LARI (6%), MATA (1%), MEDI (1%)	5.2 (6.4)[1]	Seed & rye bread (86%), flaxseed (7%);
			97	F					3.3 (4.4)[1]	Seed & rye bread (57%), flaxseed (35%)
Bhakta [92]	1995-1999	UK	108	F	25-75	≥9 x 24HDR	Finish DB II	SECO (93%), MATA (7%)	0.1 (0.1)[1]	Breads (75%), vegetables (9%), fruit & fruit juices (7%)
Bhakta [93]	1995-1999	UK (Asian)	221	F	<75	≥4 x 24HDR	Own DB	SECO (93%), MATA (7%)	0.1 (0.1)[1]	Breads (70%), vegetables (12%)
		UK (British)	49					SECO (93%), MATA (7%)	0.2 (0.1)[1]	Breads (60%), fruit & fruit juices (21%)
Mulligan [94]	1993-1997	UK	9,680	M	40-75	7d DR	Own DB	MATA, SECO, Shonanin	0.3 (0.2)[1]	Tea & coffee (33%), beer (12%), vegetables (9%)
			10,757	F					0.3 (0.1)[1]	Tea & coffee (37 %), vegetables

										(12%), fruits (9%)
Grosso [38]	1993-1997	Poland	10,477	F (50%)	45-69	FFQ	Phenol Explorer	All[4]	0.6 (12)[1]	Seeds (51%) tea (27%), dark bread (8%)
Witkowska [95]	2003-2014	Poland	1,683	F	>20	24-HDR	Dutch DB	SECO (45%), LARI (26%), PINO (26%), MATA (3%)	1.1 (4.4)[1]	Vegetables (38%), flaxseed (22%), tea (12%)
Witkowska [39]	2003-2005	Poland	6,661	F (53%)	20-74	24-HDR	Phenol Explorer	All[4]	12.1[2]	Cucumber (41%), red cabbage (22%)
Linseisen [96]	1992-1995	Germany	666	F	43(6)[1]	FFQ	Own DB	SECO (94%), MATA (6%)	0.6 (0.3–1.3)[3]	Nuts & seeds (75%), vegetables (7%), coffee (6%)
Boker [97]	1993-1997	Netherlands	17,140	F	50-69	FFQ	Dutch DB	SECO (93%), MATA (7%)	1.0[2]	Breads (41%), coffee & tea (23%), fruits (14%)
Milder [61]	1997-1998	Netherlands	4,661	F (55%)	≥19	2-DR	Dutch DB	LARI (43%), PINO (32%), SECO(24%), MATA(0.6%)	1.2 (2.1)[1]	Tea & coffee (37%), nuts & seeds (14%),
Milder [30]	1997-2002	Netherlands	306	F (56%)	19-75	FFQ	Dutch DB	LARI (47%), PINO (35%), SECO (18%), MATA (1%)	1.1 (0.4)[1]	Vegetables & black tea (>20%), whole-grain bread, fruits, wine.
Milder [98]	1985-1995	Netherlands	570	M	64-84	DH	Dutch DB	LARI (48%), PINO (36%), SECO (15%), MATA (1%)	1.0 (0.8-1.0)[3]	Tea (28%), vegetables (27%), bread (14%)
Pérez-Jiménez [99]	1994-2001	France	4,942	F (47%)	35–60	6 x 24-HDR	Phenol Explorer	All[4]	0.4 (0.2)[1]	Coffee (21%), refined wheat products (18%), whole-grain wheat products (16%)
Lefèvre-Arbogast [100]	1999-2000	France	1,329	F (62%)	≥65	24-HDR	Phenol Explorer	All[4]	0.4 (0.3)[1]	Wine (65%), olive oil (12%), tea & infusion (9%), soy products (8%)
Adriouch [34]	1994-1996	France	3,903	F (47%)	35–60	≥6 x24-HDR	Phenol Explorer	All[4]	0.2 (0.1)[1]	Bread (30%), red wine (29%), olive oil (15%), tea (9%)
Pellegrini [101]	2002-2003	Italy	242	F (38%)	60(8)[1]	3D-WR	Dutch DB	SECO (52%), LARI (27%), PINO (17%), MATA (3%)	0.7 (0.3)[1]	Red wine, fruits & vegetables (80%)
Pounis [58]	2005-	Italy	14,029	F (50%)	35[2]	FFQ	Eurofir-	⊢	80 (60-106)[3]	Seasonal fruits (41%), grain & pod

	2010						eBASIS			vegetables (11%)
Godos [102]	2014–2015	Italy	1,947	F (33%)	>18	FFQ	Phenol Explorer	All[4]	2.8 (2.6)[1]	Citrus fruits (44%), red orange (32%), garlic (11%)
Godos [103]	2014-2015	Italy	1,936	F (28%)	>18	FFQ	Phenol Explorer	All[4]	1.4 (1.1-2.0)[1]	Citrus fruits, garlic, olive oil, bread
Russo [40]	2015-2016	Italy	340	M	>18	FFQ	Phenol Explorer	LARI (54%), PINO (34%), SECO (4%), MATA (1%)	3.1 (2.7)[1]	Cereals, fruits, vegetables, grains, nuts
González [104]	–	Spain	127	M	73(7)[1]	FFQ	Phenol Explorer	All[4]	0.5 (0.3)[1]	Olive oil, white bread, & red wine (93%)
			177	F	77(6)[1]				0.4 (0.2)[1]	
Peñalvo [56]	1998-2000	Spain	3,438	F (57%)	2–24	24-HDR	Alignia DB	PINO (42%), SECO (17%), LARI (13%), MATA (1%)	0.8 (0.5–1.3) [3]	Olive oil (27%), refined wheat bread (17%), whole-grain wheat bread (8%)
Zamora-Ros [105]	1996-1998	Spain	401	M	65 (12)[1]	FFQ	UK DB	SECO, MATA, LARI, PINO	0.7 (0.5–1.0)[3]	Fruit (32%), vegetables (31%), cereals products (10%)
Tresserra-Rimbau [106]	2003-2009	Spain	7,200	M&F	55-80	FFQ	Phenol Explorer	All[4]	0.9 (0.4)[1]	Olive oil (47%), virgin olive oil (25%), whole-grain wheat-flour bread (6%)
Mendonça [107]	1999-	Spain	17,065	F (61%)	20-89	FFQ	Phenol Explorer	All[4]	0.6 (0.4)[1]	Olive oil, dried fruits, gazpacho, bread
Petrick [108]	1997-2000	US	183	M&F	20-80	FFQ	Canadian DB	SECO, MATA	0.6 (0.1)[1]	Coffee (31), wine (12), & citrus juice (9%)
Petrick [109]	1993-1995	US	662	M&F	30-79	FFQ	Canadian DB	SECO, MATA	0.07 (0.03)[1]	Coffee (35%), citrus juice (13%), wine (10%)
Williams [110]	2003-2008	US	216	F	55 (13)[1]	FFQ	Canadian DB	SECO, MATA ,LARI, PINO	0.1(0.1-0.2)[3]	–
Carmichael [4	1997-2005	US	3,118	F	~18-40	FFQ	UK DB	SECO (87%), MATA (13%)	0.2 (0.05-0.3)[3]	Coffee & tea, alfalfa sprouts, flaxseed

2]										
Waetjen [111]	2008	US	1,459	F	42-52	FFQ	Own DB	SECO, MATA, LARI, PINO	0.2[2]	–
Bandera [112]	2004-2008	US	391	F	>21	FFQ	Own DB	SECO (89%), LARI (6%), PINO (4%), MATA (1%)	1.0[1]	–
Chang [113]	1995-2007	US	110,215	F	20-84	FFQ	Canadian DB	SECO, MAT, LARI, PINO	0.8 (0.3-1.3)[3]	Vegetables, fruits, whole grains
McCann [114]	1996-2001	US	1,122	F	35-79	FFQ	Canadian DB	SECO (50%), PINO (21%) MATA (3%), LARI (3%)	0.2 (0.1)[1]	Whole-grain bread, peaches , orange juice, coffee ,onions, string beans, tea
Fink [43]	1996-1997	US	1,500	F	<65	FFQ	Own DB	SECO, MATA	6.4 (4.7)[1]	Tea (99%), strawberries (0.5%), whole grain products(0.3%)
Horn-Ross [59]	1996-1999	US	470	F	35-79	FFQ	Own DB	SECO (77.9%), MATA (16.9%),	0.2 (0.1-0.2)[3]	–
Mervish [115]	2004-2014	US	1,044	F	6-8	24-HDR	Phenol Explorer	All[4]	0.4[2]	Orange juice (35%), strawberries (17%), broccoli (8%)
van der Schouw [116]	1994	US	468	M	47-83	FFQ	US DB	SECO (97%), MATA (3%)	0.7 (0.5-0.9)[3]	Tea & coffee (28%), alcoholic beverages (9%), cereals & grains (7%)
Horn-Ross [117]	1992-1998	US	558	F	20-74	FFQ	Own DB	SECO (71%), MATA (29%)	0.1 (0.1-0.2)[3]	–
McCann [118]	1986-1991	US	696	F	40-85	FFQ	US DB	SECO, MATA	0.5 (0.3)[1]	Coffee, carrots, cucumbers, strawberries
Schabath [61]	1995-2003	US	1,735	F (49%)	–	FFQ	US DB	SECO, MATA	5.3 (3.4-9.7)[3]	Coffee 52%, tea 30%, flaxseed (6%)
de Kleijn [119]	1991-1994	US	964	F	–	FFQ	US DB	SECO (97%), MATA (3%)	0.6 (0.4-0.8)[3]	Other fruits (13%), cereals and grains (11%), berries (8%)

Cotterchio [44]	2001	Canada	1,890	F (47%)	20-74	FFQ	Own DB	SECO, MATA	0.2 (0.1–0.3)[3]	Legumes, seeds, cereals/grains, berries, dried fruit, vegetables
Morisset [45]		Canada	115	F	≤70	FFQ	Canadian DB	SECO, MAT, LARI, PINO	0.4 (3.8)[1]	–
Chávez-Suárez [120]	2012-2017	Mexico	100	F	25-80	FFQ,	Own DB	SECO (73%), END (18%), ENL (7%), MATA (2%)	1.1 (1.6)[1]	–
						24-HDR		SECO (75%), END (16%), ENL (5%), MATA (4%)	0.4 (1.8)[1]	
Hernández-Ramírez [46]	2004-2005	Mexico	478	F (46%)	>20	FFQ	Own DB	LARI (54%), PINO (26%), SECO (20%), MATA (0.1%)	0.3 (0.2-0.5)[3]	Vegetables, fruits, legumes
Zamora-Ros [33]	2006-2011	Mexico	106,466	F	>20	FFQ	Phenol Explorer	All4: LARI (46%), PINO (21%), SECO (18%)	0.1 (0.03-0.2)[3]	Broccoli & cauliflower (11%), strawberries (9%), fruit-flavoured water (6%)
Nascimento-Souza [47]	2016	Brasil	620	F (70%)	60-98	24-HDR	Phenol Explorer	All4: LARI(50%)	13.6 (25.5)[1]	Orange (16%), broccoli (15%), flaxseed (15%)
Miranda [48]	2008 - 2009	Brasil	550	F (65%)	>12	24-HDR	Phenol Explorer	All[4]	0.1 (0.1-0.2)[3]	Sesame seed oil (71%), nuts (20%), sesame seeds (4%)
Miranda [49]	2008	Brasil	1,103	F (54%)	>20	24-HDR	Phenol Explorer	All[4]	2.3(0.7)[1]	Cereals oil (71%), nuts (26%), olive oil (2%)
Lahmann [50]	2002-2007	Australia	2,078	F	18-79	FFQ	Canadian & UK DB	SECO (68%), LARI (12%), MATA (10%), PINO (8%)	0.7 (0.3)[1]	–
Hanna [51]		Australia	511	F	40-80	FFQ	AusNut DB		2.7 (3.0)[1]	Soy, linseed
Sohrab [52]	2006-2008	Iran	2,618	F (56%)	19-84	FFQ	Phenol Explorer	All[4]	0.2 (0.1-0.3)[3]	Nuts, whole grains
Sohrab [53]	1999	Iran	1,265	F (56%)	19-74	FFQ	Phenol Explorer	All[4]	3.8 (2.4-5.7)[3]	–

Jang [54]	2004	Korea	48	F PreM	40-51	24-HDR	US DB	END (34%), ENL (33%), SECO (28%), MATA (5%)	1.5 (0.3)[1]	–
			53	F PostM	41-57			END (36%), ENL (32%), SECO (25%), MATA (7%)	1.8 (0.5)[1]	–

Abbreviations: 24-HDR (24-hour dietary recall), DB (Database), DH (Dietary History), DR (Dietary record), F (Female), FCDB (Food Composition DataBase), FFQ (Food Frequency Questionnaire), LARI (lariciresinol), M (Male), MATA (matairesinol), MED (Mediterranean), MEDI (medioresinol), PINO (pinoresinol), PostM (Post-menopausal), PreM (Pre-menopausal), SECO (secoisolariciresinol), SYRI (syringaresinol)

[1-3]Type of estimation: [1]mean (SD), [2]mean, [3]median (p25-p75)

[4]All lignans, including: 1-AcetoxyPINO, 7-HydroxyMATA, 7-HydroxySECO, 7-OxoMATA, Anhydro-SECO, Arctigenin, Conidendrin, CycloLARI, DimethylMATA, Episesamin, Episesaminol, IsohydroxyMATA, IsoLARI, LARI, LARI-sesquilignan, MATA, MEDI, Nortrachelogenin, PINO, SECO, SECO di-O-glucoside, SECO-sesquilignan, Sesamin, Sesaminol, Sesamol, Sesamolin, Sesamolinol, SYRI, Todolactol A, Trachelogenin

914 Table 2. Characteristics of the studies included in the review of urinary lignan excretions.

Author (Reference)	Data collection	Country	N	Sex	Age	Type of study	Urine	Analytical method	END (nmol/L)	ENL (nmol/L)
Zamora-Ros [71]	1995-1999	Europe[4]	475	F (58%)	33-77	Cohort	24h	LC-MS/MS	247[2]	2,080[2]
Uehar [65]	⊷	Finland	126	F	24-65	C-S	24h	TR-FIA	⊷	3,267[1]
Krogholm [70]	2002-2004	Denmark	84	M	38-63	Cohort	24h	LC-MS	⊷	768[1]
							Overnight		⊷	696[1]
			107	F			24h		⊷	1,050[1]
							Overnight		⊷	970[1]
Ward [72]	1993-1997	UK	828	M	45-75	NCC	⊷	GC-MS	204[2]	2,953[2]
			889	F (43%)					210[2]	3,333[2]
Low [73]	1993-1997	UK	125	F	45-76	Cohort	Spot	LC-MS	288[1]	2,561[1]
Grace [74]	1993-1997	UK	219	F	45-75	NCC	Spot	GC-MS	274[1]	2,792[1]
Low [75]	1993-1997	UK	267	M	45-75	Cohort	Spot	GC-MS	207[1]	2,414[1]
Durazzo [76]	⊷	Italy	13	F	48-58	CT	24h	LC-CEAD	763[1]	1,577[1]
									348[1]	1,092[1]
Park [121]	2001-2006	US	404	M	45-75	NCC	Spot	LC-MS/MS	⊷	1,313[2]
Hu [122]	1997-2010	US	1,111	F	25-55	Cohort	Spot	LC-MS	159[1]	2,938[1]
Reger [123]	1999-2010	US	6,009	F (52%)	>40	C-S	Spot	LC-MS/MS	248[1]	2,041[1]
Martínez Steele [124]	2009-2010	US	2,692	M/F	>6	C-S	Spot	LC–MS/MS	133[2]	728[2]
Adlercreutz [125]	⊷	US	10	F	58[1]	C-S	24h	GC-MS	267[3]	2,120[3]
			10						213[3]	1,533[3]
			7						140[3]	693[3]
Miles [126]	2006	US	80	F (50%)	18-45	CT	24h	GC-MS	533[1]	3,000[1]
									267[1]	1,933[1]
Rybak [64]	2003-2006	US	2,873	M	≥20	C-S	Spot	LC-MS/MS	41[1]	302[1]
				F					38[1]	285[1]
Reger [127]	1999-2004	US	5,179	F (52%)	>18	C-S	Spot	LC-MS	133[2]	1,178[2]
Eichholzer [128]	1999-2004	US	2,028	F (49%)	>18	C-S	Spot	LC-MS	147[2]	1,507[2]
	2005-2008		2,628	F (48%)				LC-MS/MS	164[2]	1,683[2]
Xu [67]	2001-2010	US	694	M	12-19	C-S	Spot	LC-MS	278[1]	2,246[1]
			600	F					463[1]	2,618[1]
			1,273	M	20-60				552[1]	2,950[1]
			1,226	F					609[1]	3,319[1]

			578	M	>60				533[1]	3,651[1]
			584	F					386[1]	2,907[1]
Valentín-Blasini [129]	1999-2000	US	334	F (52%)	6-11	C-S	Spot	LC-MS	89[3]	802[3]
			757		12-19				84[3]	852[3]
			1,496		≥20				93[3]	758[3]
Valentín-Blasini [80]	1988-1994	US	199	F (61%)	20-58	C-S	Spot	LC-MS/MS	209[1]	1,718[1]
Sun [130]	1995-2001	US	452	F	53-79	NCC	Spot	LC-MS	123[1]	2,506[1]
			655		32-52				77[1]	2,172[1]
Kunisue [83]	2005-2009	US	10	M	24-63	C-S	24h	LC-MS/MS	43[1]	738[1]
			6	F	23-48				129[1]	872[1]
Levine [131]	2005-2009	US	471	F	18-40	Cohort	Spot	LC-MS/MS	94[2]	754[2]
Simon [78]	⊢	Jamaica	171	F	20-75	CC	Spot	TR-FIA	⊢	2,671[2]
Liu [66]	2000-2001	Japan	500	F	20-70	C-S	Spot	GC-MS	95[3]	148[3]
Uehar [65]	⊢	Japan	111	F	24-65	C-S	24h	TR-FIA	⊢	ND
Kunisue [83]	2005	Japan	15	M	22-54				126[1]	1,376[1]
			11	F	21-35				80[1]	1,074[1]
	2002	Vietnam	31	M	20-78				133[1]	772[1]
			32	F	21-73				245[1]	1,678[1]
	2006	Vietnam	14	M	21-74				80[1]	503[1]
			14	F	33-74				182[1]	705[1]
	2000	Cambodia	13	M	21-48				60[1]	571[1]
			24	F	21-46				86[1]	671[1]
	2005	India	16	M	27-62				179[1]	1,141[1]
			23	F	20-70				119[1]	940[1]
	2006	India	18	M	26-55				255[1]	1,443[1]
			24	F	20-48				205[1]	1,342[1]
Talaei [82]	1999-2004	Singapore	564	F (58%)	45-74	NCC	Spot	LC-MS/MS	228[1]	1,140[1]

Abbreviations: CC (Case-Control), C-S (Cross-Sectional, CT (Clinical Trial), END (Enterodiol), ENL (Enterolactone), F (Female), HCC (Hospital-based Case-Control), GC-MS (Gas Chromatography–Mass Spectrometry), LC-CEAD (Liquid Chromatography-Coulometric Electrode Array Detector), LC-MS (Liquid Chromatography–Mass Spectrometry), M (Male), NCC (Nested Case-Control), ND (Non Detected), PCC (Population-based Case-Control), TR-FIA (Sensitive Time-Resolved Fluoroimmunoassay).

[1-3]Type of estimation: [1]mean, [2]median, [3]geometric mean

[4]France, Italy, Greece, and Germany

921 ENL and END concentrations have been converted into nmol/L from the original studies.

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924 Table 3. Characteristics of the studies included in the review of blood lignan concentrations.

Reference	Data collection	Country	N	Sex	Age	Type of study	Specimen	Methods	END (nmol/L)	ENL (nmol/L)
Travis [71]	1992-2000	Europe[4]	1,042	M/F	60.1[1]	NCC	Plasma	LC-MS/MS	1.0[2]	12.4[2]
Peeters [26]	1992-2012	Europe[4]	1,344	F (51%)	54-55	Cohort	Plasma	LC-MS	1.0[3]	8.7[3]
		UK healthy	70	F (49%)					3.6[3]	17.8[3]
Pérez-Cornago [68]	1992-2000	Europe[4]	1,042	M	59.6[1]	NCC	Plasma	LC-MS/MS	1.0[3]	11.2[3]
	1993-1997	UK	130	M	64.7[1]				0.2[3]	4.9[3]
	1981-1991	Finland, Norway, Sweden	2,209	M	46.5[1]			TR-FIA	⊢	5.8[3]
	⊢	Sweden	1,664	M	60.0[1]				⊢	9.6[3]
	1985-2017	Sweden	514	M	58.0[1]				⊢	14.6[3]
Uehara [65]	⊢	Finland	87	F	24-65	C-S	Plasma	TR-FIA	⊢	25.0[1]
Stumpf [132]	1983	Finland	85	M/F	35-49	CT	Plasma	TR-FIA	⊢	19.5[2]
Pietinen [133]	1990-1995	Finland	75	F PreM	25-75	PCC	Serum	TR-FIA	⊢	20.7[1]
			133	F PostM					⊢	28.9[1]
Vanharanta [134]	2005	Finland	167	M	42-60	NCC	Serum	TR-FIA	⊢	23.5[1]
Kilkkinen [135]	1986-1999	Finland	420	M	50-69	Case-Cohort	Serum	GC-MS	⊢	18.1[1]
Vanharanta [136]	1995	Finland	100	M	58,6[1]	CT	Serum	TR-FIA	⊢	16.6[1]
Kilkkinen [137]	1997	Finland	1,168	M	25-64	C-S	Serum	TR-FIA	⊢	13.8[2]
			1,212	F					⊢	16.6[2]
Vanharanta [138]	1998-2000	Finland	1,889	M	42-60	Cohort	Serum	TR-FIA	⊢	17.1[1]

Hedelin [91]	2002	Sweden	1,130	M	67.8[1]	PCC	Plasma	TR-FIA	⊢	24.0[1]
Sonestedt [139]	1991-1996	Sweden	728	F	56.3[1]	NCC	Plasma	TR-FIA	⊢	16.3[2]
Stattin [140]	2001	Sweden	525	M	59.9[1]	NCC	Plasma	TR-FIA	⊢	15.0[1]
Lin [141]	2003-2004	Sweden	135	F	55-75	Cohort	Serum	TR-FIA	⊢	23.2[1]
Hultén [142]	1986-1994	Sweden	308	F	51.2[1]	NCC	Plasma	TR-FIA	⊢	22.9[1]
	1995-2000		185		58.1[1]				⊢	20.4[1]
Aarestrup [143]	1993- 1997	Denmark	149	F	50-64	Case-Cohort	Plasma	TR-FIA	⊢	31.0[1]
Eriksen [144]	1993-1997	Denmark	850	F (40%)	50-64	Case-Cohort	Plasma	LC-MS/MS	⊢	10.9[2]
Johnsen [88]	1993-1997	Denmark	857	F	50-64	NCC	Plasma	TR-FIA	⊢	38,0[1]
Kuijsten [69]	⊢	Netherlands	3	F (25%)	28-53	C-S	Plasma	LC-MS	7.0[1]	39.2[1]
Milder [30]	1997-2002	Netherlands	637	F (55%)	19-75	PCC	Plasma	LC-MS/MS	1.4[1]	11.3[1]
Verheus [145]	1993-1997	Netherlands	87	F PreM	51.6[1]	NCC	Plasma	LC-MS	0.6[1]	8.9[1]
			296	F PostM	58.6[1]				0.6[1]	8.9[1]
Heald [146]	1998 2001	Scotland	483	M	50-74	PCC	Serum	GC-MS	⊢	16.2[2]
Bhakta [92]	1995-1999	UK	58	F	25-75	PCC	Plasma	TR-FIA	⊢	13.7[1]
Ward [72]	1993-1997	UK	815	M	45-75	NCC	Serum	LC-MS	0.7[2]	18.1[2]
			877	F (43%)					0.3[2]	17.4[2]
Morton [85]	⊢	UK	36	M	41–74	C-S	Plasma	GC-MS	⊢	13.1[1]
	⊢	Portugal	50		35–71				1.2[1]	13.1[1]
Low [73]	1993-1997	UK	109	F	45-76	NCC	Serum	GC-MS	1.3[1]	12.4[1]
Grace [74]	1993-1997	UK	187	F	45-75	NCC	Plasma	LC-MS	1.3[1]	12.8[1]
Low [75]	1993-1997	UK	267	M	45-75	Cohort	Plasma	LC-MS/MS	1.0[1]	12.8[1]
Xie [81]	1996-1999	US	802	F	25-42	NCC	Plasma	LC-MS	⊢	11.5[2]
Bhakta [93]	⊢	UK	40	F	25-75	PCC	Plasma	TR-FIA	⊢	28.5[1]
		UK (Asian)	100						⊢	13.9[1]

Piller [147]	1992-1995	Germany	237	F	≤50	PCC	Plasma	TR-FIA	⊢	9.7[1]
Zeleniuch-Jacquotte [79]	1985-1991	US	60	F	34-65	Cohort	Serum	CG-MS	1,5[2]	21,2[2]
Valentín-Blasini [80]	1988-1994	US	199	F (61%)	20-58	C-S	Serum	LC-MS	6.0[1]	11.9[1]
Horner [148]	⊢	US	78	M	20-40	C-S	Plasma	TR-FIA	⊢	11.0[3]
			115	F						13.3[3]
Uehar [65]	⊢	Japan	111	F	40–60	C-S	Plasma	TR-FIA	⊢	13.3[1]
Morton [87]	⊢	Japan	102	M	40-85	C-S	Plasma	GC-MS	⊢	32.7[1]
			125	F	40-89				⊢	22.8
Morton [85]	⊢	China	53	M	31–85	C-S	Plasma	GC-MS	5.6[1]	20.8[1]
Liu [84]	2010-2012	China	264	F (71%)	35-60	NCC	Plasma	LC-MS	16.4[2]	2.0[2]
Ko [149]	1993-2004	Korea	206	F	60.4[1]	HCC	Plasma	LC-MS	⊢	249.3[1]
			185	M					⊢	177.8[1]
	2003-2007	Vietnam	114	F	54.5[1]				⊢	10.2[1]
			92	M					⊢	10.4[1]

Abbreviations: C-S (Cross-Sectional), CT (Clinical Trial), END (enterodiol), ENL (enterolactone), HCC (Hospital-based Case-Control), GC-MS (Gas chromatography–mass spectrometry), LC-MS (Liquid Chromatography–Mass Spectrometry), NCC (Nested Case-Control), PCC (Population-based Case-Control), PostM (Post-menopausal), PreM (Pre-menopausal), TR-FIA (sensitive time-resolved fluoroimmunoassay)

[1-3]Type of estimation: [1]mean, [2]median, [3]geometric mean

[4]Europe: Denmark, France, Germany, Greece, Italy, Netherlands, Spain, Sweden, UK

ENL and END concentrations have been converted into nmol/L from the original studies.