Status of women with respect to selected nutrients – A nationwide cross-sectional study

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Abstract

Background and aim: Vitamins, trace elements and certain polyunsaturated fatty acids are important in the maintenance of physical functions and prevention of diet-related diseases. Several factors influence the nutrient status, especially in women. Additionally, the nutritional requirement of women is increased in specific life stages, for example during pregnancy. Therefore, the aim of this thesis was to evaluate the status of vitamin D, long-chain (LC) omega-3 (n-3) polyunsaturated fatty acids (PUFAs) and iron in women who are in certain stages of life.

Methods: The nutrient status was examined within the scope of the cross-sectional nationwide "Vitamin and mineral status among German women" study, which analyzed the status of specific nutrients in 2367 women (18 - 66 years). The recruitment took place in cooperation with 125 general practitioners and gynecologists between April 2013 and March 2015. The vitamin D status of pregnant (n = 429) and breastfeeding women (n = 124) was assessed compared to non-pregnant and non-breastfeeding (NPNB) women of the same age, region and season of recruiting. Serum 25-hydroxyvitamin D (25(OH)D) – indicator of the vitamin D status – was determined by chemiluminescence immunoassay. The LC n-3 PUFA status was investigated in pregnant women in the third trimester (n = 213), breastfeeding women (n = 127) and middle-aged women (40 to 60 years) (n = 446). The evaluation was conducted by the omega-3 index, which is the relative eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) of the total fatty acids in the erythrocyte membranes. The iron status was estimated in women of reproductive age (n = 178) by the concentration of hemoglobin (Hb), ferritin, soluble transferrin receptor (sTfR) and the sTfR-ferritin index.

Results: Pregnant and breastfeeding women had a 3.7 and 4.0, respectively, times higher risk of vitamin D deficiency (25(OH)D concentrations < 25.0 nmol/L) compared to NPNB women who also showed a high prevalence of an inadequate vitamin D status. The omega-3 index was higher in pregnant women than in breastfeeding women (6.40 ± 1.31% vs. 5.50 ± 1.34%). However, the status is probably insufficient in 87.1% of these pregnant and breastfeeding women. A total of 97.3% of the middle-aged women (40 - 60 years) showed an omega-3 index less than 8%, which is associated with an increased risk of cardiovascular death. An inadequate iron status (ferritin < 20 µg/L and/or Hb < 12 g/dL) was prevalent in 16.3% of women of reproductive age.

Conclusion: The vitamin D status of pregnant and breastfeeding women as well as of NPNB women of the same age needs to be improved. The determination of the vitamin D status with the highest health advantage is necessary. Middle-aged women and possibly also pregnant and breastfeeding women have to increase their LC n-3 PUFA status. In further studies, the optimal LC n-3 PUFA status during pregnancy and breastfeeding period should be investigated. For the enhancement of the vitamin D and LC n-3 PUFAs status exist numerous opportunities, which suitability requires further investigations. Women of reproductive age should ensure an adequate iron intake to maintain their iron status. Therefore, educational work is necessary to inform about the different iron sources and their individual bioavailability.

Trial registration: German Clinical Trial Register DRKS00004789

Keywords: nutrient status, women, Germany

Zusammenfassung

Hintergrund und Ziel: Vitamine, Spurenelemente und bestimmte mehrfach ungesättigte Fettsäuren spielen eine wichtige Rolle in der Aufrechterhaltung von Körperfunktionen und in der Prävention von ernährungsassoziierten Erkrankungen. Insbesondere bei Frauen wird der Nährstoffstatus durch zahlreiche Faktoren beeinflusst und ist zudem in bestimmten Lebensphasen, wie der Schwangerschaft, erhöht. Das Ziel dieser Arbeit war daher den Status von Vitamin D, langkettigen Omega-3 Fettsäuren und Eisen bei Frauen in ausgewählten Lebensperioden zu untersuchen.

Methodik: Der Nährstoffstatus wurde im Rahmen der bundesweiten Querschnittsstudie „Vitamin- und Mineralstoffversorgung bei Frauen in Deutschland“ erfasst. Die Studie analysierte den Status an ausgewählten Nährstoffen bei 2367 Frauen (18 - 66 Jahre). Die Rekrutierung erfolgte in Zusammenarbeit mit 125 Allgemeinmedizinern und Gynäkologen zwischen April 2013 und März 2015. Der Vitamin D Status von Schwangeren (n = 429) und Stillenden (n = 124) wurde im Vergleich zu Nichtschwangeren und Nichtstillenden desselben Alters sowie der gleichen Rekrutierungsregion und -jahreszeit beurteilt. Die Messung der Serum 25-Hydroxyvitamin D Konzentration (25(OH)D) – Indikator für den Vitamin D Status – erfolgte mittels Chemilumineszenz-Immunoassay. Der Omega-3 Status wurde bei Schwangeren im dritten Trimester (n = 213), Stillenden (n = 127) und Frauen im mittleren Alter (40 - 60 Jahren) (n = 446) anhand des Omega-3 Index analysiert – relative Eicosapentaensäure (EPA) und Docosahexaensäure (DHA) Konzentration der Gesamtfettsäuren in der erythrozytären Membran. Der Eisenstatus von Frauen im gebärfähigen Alter (n = 178) wurde mittels Hämoglobin- (Hb), Ferritin-, löslichem Transferrinrezeptor-Konzentration (sTfR) und dem sTfR-Ferritin Index bestimmt.

Ergebnisse: Das Risiko eines Vitamin D Defizits (25(OH)D < 25.0 nmol/l) war bei Schwangeren 3,7x und bei Stillenden 4,0x höher als bei Nichtschwangeren und Nichtstillenden, bei denen die Vitamin D Versorgung allerdings ebenfalls überwiegend unzureichend war. Der Omega-3 Index war bei Schwangeren höher als bei Stillenden (6,40 ± 1,31% vs. 5,50 ± 1,34%). Möglicherweise wiesen 87,1% der Schwangeren und Stillenden eine unzureichende Omega-3 Versorgung auf. Der Omega 3 Index lag bei 97,3% der Frauen zwischen 40 und 60 Jahren unterhalb von 8%, womit ein erhöhtes Risiko für kardiovaskulär bedingte Todesfälle vorliegt. Einen inadäquaten Eisenstatus (Ferritin < 20 µg/l und/oder Hb < 12 g/dl) hatten 16,3% der Frauen im gebärfähigen Alter.

Schlussfolgerung: Der Vitamin D Status sollte bei Schwangeren, Stillenden, aber auch bei nichtschwangeren und bei nichtstillenden Frauen derselben Altersklasse, verbessert werden. Zudem ist die Festlegung des Vitamin D Status mit dem höchsten gesundheitlichen Nutzen erforderlich. Eine ausreichende Omega-3 Versorgung muss bei Frauen im mittleren Alter und möglicherweise auch bei Schwangeren und Stillenden sichergestellt werden. Weitere Studien sind notwendig, die den optimalen Omega-3 Status während der Schwangerschaft und Stillzeit ermitteln. Für die Verbesserung der Versorgung von Vitamin D und den langkettigen Omega-3 Fettsäuren stehen verschiedene Möglichkeiten zur Verfügung, dessen Eignung in weiteren Studien untersucht werden muss. Frauen im gebärfähigen Alter sollten eine ausreichende Eisenaufnahme sicherstellen, um den Eisenstatus aufrechtzuerhalten. Die Aufklärung über die verschiedenen Eisenquellen und deren Verfügbarkeit sind hierfür obligatorisch.

Studienregistrierung: Deutsches Register Klinischer Studien DRKS00004789

Stichwörter: Nährstoffstatus, Frauen, Deutschland

List of scientific publications

This thesis is based on the following papers:

Original papers in peer-reviewed process

Paper I: Gellert S, Ströhle A, Hahn A (2017). Higher prevalence of vitamin D deficiency in German pregnant women compared with non-pregnant women. Arch Gynecol Obstet, 296 (1): 43-51.

Paper II: Gellert S, Ströhle A, Hahn A (2017). Breastfeeding woman are at higher risk of vitamin D deficiency than non-breastfeeding women - Insights from the German VitaMinFemin study. Int Breastfeed J, 12 (19).

Paper III: Gellert S, Schuchardt JP, Hahn A (2016). Higher omega-3 index and DHA status in pregnant women compared to lactating women – Results from a German nation-wide cross-sectional study. Prostaglandins Leukot Essent Fatty Acids, 109 (6): 22-28.

Paper IV: Gellert S, Schuchardt JP, Hahn A (2017). Low long chain omega-3 fatty acid status in middle-aged women. Prostaglandins Leukot Essent Fatty Acids, 117 (2): 54-59.

Paper V: Gellert S, Hahn A (2017). Iron status in relation to oral contraceptive use in women of reproductive age. Austin J Womens Health, 4 (1): 1025.

Conference contributions

Posters

Gellert S, Schuchardt JP, Hahn A (2015). MON-PP006: Omega-3 status of German women - A cross-sectional study. Clin Nutr, 34 (1): 129.

Gellert S, Ströhle A, Willers J, Hahn, A (2015). SUN-PP247: Sunshine duration and vitamin D status – Results from the „VitaMinFemin Study“. Clin Nutr, 34 (1): 115.

Gellert S, Ströhle A, Hahn A (2016). Einfluss der regionalen Sonnenscheindauer auf die Vitamin-D-Versorgung von Frauen in Deutschland. Proc Germ Nutr Soc, 21: 39.

Gellert S, Ströhle A, Hahn A (2016). Vitamin-D-Status von Frauen mit Kinderwunsch - Eine bundesweite Querschnittsstudie. Geburtshilfe Frauenheilkd, 76 (10): 180

Gellert S, Hahn A (2016). Einfluss von oralen Kontrazeptiva auf die Eisenversorgung, Geburtshilfe Frauenheilkd, 76 (10): 164.

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List of abbreviations

-	Negative influence
+	Positive influence
(+)	Probably positive influence
1,25$(OH)_2$D	1,25-dihydroxyvitamin D, calcitriol
1α(OH)ase	1α-hydroxylase
17 HDHA	17-hydroxydosahexaenoic acid
24(OH)ase	24-hydroxylase
25(OH)D	25-hydroxyvitamin D, calcidiol
7-DHC	7-dehydrocholesterol, provitamin D_3
AA	Arachidonic acid, C20:4n-6
ALA	α-linoleinic acid, C18:3n-3
ApoE	Apolipoprotein E
ß	Standardized coefficient
BMI	Body mass index
C	Carbon
CD36	Cluster of differentiation 36
CH_2	Methylene group
CH_3	Methyl group
CI	Confidence interval
COOH	Carboxyl group
D-A-CH	Deutschland, Österreich, Schweiz
DGE	Deutsche Gesellschaft für Ernährung, German Nutrition Society
DHA	Docosahexaenoic acid, C22:6n-3
DMT1	Divalent metal transporter 1
DCYTB	Duodenal cytochrome B
Elovl2 or 5	Elongation of very long-chain fatty acids 2 or 5
EPA	Eicosapentaenoic acid, C20:5n-3
Fads1 or 2	Fatty acid desaturase 1 or 2
FA	Fatty acids
Fe^{2+}	Bivalent iron, ferrous
Fe^{3+}	Trivalent iron, ferric
FGF-23	Fibroblast growth factor-23
FPN1	Ferroportin 1
H^+	Hydrogen ion
Hb	Hemoglobin
HCP1	Heme carrier protein 1

HEPH	Hephaestin
HIF-2	Hypoxia inducible factor-2
HNF1ß	Hepatocyte nuclear factor 1 beta
HNF6	Hepatocyte nuclear factor 6
HO-1	Heme oxygenase-1
HPO_4^{2-}	Hydrogenphosphat
HR	Hazard ratio
HRT	Hormonal replacement therapy
ID	Iron deficiency non-anemic
IDA	Iron-deficiency anemia
IDE	Iron-deficient erythropoiesis
IRP	Iron regulatory protein
IUD	Intrauterine device
K^+	Potassium ion
LA	Linoleic acid
LC	Long-chain
LNG	Levonorgestrel intrauterine systems
N-3	Omega-3
N-6	Omega-6
Na^+	Sodium ion
NB	Non-breastfeeding
NHE	Sodium-hydrogen exchanger
NP	Non-pregnant
OC	Oral contraceptive
OH	Hydroxide ion
Omega-3 index	Relative eicosapentaenoic acid and docosahexaenoic acid concentration in relation to total fatty acids in erythrocyte membranes
OR	Odds ratio
P	Probability
PPARα	Peroxisome proliferator-activated receptor alpha;
PSD95	Postsynaptic density protein 95
PTH	Parathyroid hormone
PUFAs	Polyunsaturated fatty acids
RAR	Retinoic acid receptor
RES	Reticuloendothelial system
RR	Relative risk
RXR	Retinoid X receptor

S-phase	Synthesis phase
STfR	Soluble transferrin receptor
STfR-F index	Soluble transferrin receptor-ferritin index
TfR	Transferrin receptor
TG	Triacylglyceride
UL	Tolerable upper intake level
UVB	Ultraviolet B
VDBP	Vitamin D binding protein
VDR	Vitamin D receptor
VitaMinFemin	Vitamin and mineral status among German women
WMD	Weighted mean difference

1. General introduction

1.1. Nutritional requirements and aim of this dissertation thesis

As early as over 500 years before Christ, Hippocrates knew that “food be thy medicine and the medicine your food”. Nutrition not only ensures the energy supply but is also essential to maintaining physical, psychological and metabolic functions and to preventing diet-related illnesses. Micronutrients, vitamins and also certain fatty acids (FA) have a special relevance to these functions (WHO 1985). Therefore, reference values for the dietary intake are recommended to ensure the required supply of nutrients for the majority of healthy people. In Germany, the recommendations are established by the German Nutrition Society (Deutsche Gesellschaft für Ernährung, DGE) in cooperation with the Austrian Nutrition Society (Österreichische Gesellschaft für Ernährung) and the Swiss Society for Nutrition (Schweizerische Gesellschaft für Ernährung) (D-A-CH) (D-A-CH 2015).

For the assessment of the nutrient supply, the dietary intake of food is usually evaluated by validated questionnaires such as food frequency questionnaires or food records. Based on these data, the nutrient intake is calculated using food composition tables. The resulting intake is compared with the dietary intake recommendations of professional societies. However, the calculated nutrient intake allows only estimations about the nutrient status because of several influencing factors (Elmadfa & Leitzmann 2015). For example, the nutrient content in foods are subject to fluctuations (Souci et al. 2015). Moreover, the bioavailability of micronutrient is affected by food processing (Platel & Srinivasan 2016) as well as absorption-promoting and absorption-inhibiting factors, which is especially relevant to the micronutrient iron (Collings et al. 2013). In contrast, the nutrient intake of vitamin D contributes only insignificantly to the vitamin D status because the human body can synthesize the vitamin D requirement endogenously via ultraviolet B (UVB) radiation (Seckmeyer et al. 2013). In addition, the nutrient requirements of women are partially dependent on the physiological status (D-A-CH 2015). For example, the maternal nutrient status of specific nutrients, such as long-chain (LC) omega-3 (n-3) polyunsaturated fatty acids (PUFAs), also provides the fetal and infantile nutrient supply with these nutrients (Gil-Sanchez et al. 2010; Meldrum et al. 2012). In addition, the status of certain nutrients is influenced by the menstruation (Napolitano et al. 2014) and possibly even by hormones (Magnusardottir et al. 2009; Pilz et al. 2017). These factors are partly considered in the dietary intake recommendations (D-A-CH 2015). Nevertheless, biochemical parameters should be analyzed instead of dietary intake to reflect the current nutrient status. The biochemical parameters have a high accuracy when assessing the actual nutrient status and detect nutrient deficiencies at an early stage. In this respect, the measured biochemical

values are compared with the scientific biochemical reference values (Elmadfa & Leitzmann 2015).

For Germany, biochemical data on various vitamins and minerals were collected by as early as the 1980s as part of the "Nutrition Survey and risk factors analysis" study on 2,000 subjects (Heseker et al. 1994; Kohlmeier et al. 1995). Newer nationwide data on the nutrient supply are available for certain nutrients and partly only for specific population groups, such as for LC n-3 PUFAs (Geppert et al. 2005; Kröger et al. 2011) or vitamin D (Hintzpeter et al. 2008; Weisse et al. 2013; Wuertz et al. 2013; Richter et al. 2014; Jungert & Neuhauser-Berthold 2015; Rabenberg et al. 2015). Surveys of the nutrient status of women in specific stages of life are limited or nonexistent, although this aspect should be assessed due to the changing requirements during the lifetime of women.

Study objectives

To gain knowledge about the nutrient supply situation of women, the status of vitamin D, LC n-3 PUFAs and iron was investigated in women with an increased requirement or in certain phases of life for which the supply situation is most likely critical. The following issues are the basis of this dissertation thesis and are described in the scientific publications (chapter 2):

1. How does the risk of an inadequate vitamin D status in pregnant women compared to non-pregnant women of the same age, region and season of recruiting? (*Paper I*, chapter 2.1.1)
2. Do breastfeeding women have a higher risk of an inadequate vitamin D status than non-pregnant and non-breastfeeding women of the same age, region and season of recruiting? (*Paper II*, chapter 2.1.2)
3. How is the status of LC n-3 PUFAs in pregnant and lactating women? (*Paper III*, chapter 2.2.1)
4. Are middle-aged women adequately supplied with LC n-3 PUFAs? (*Paper IV*, chapter 2.2.2)
5. Do women of reproductive age show an adequate iron status, and how do oral contraceptives affect the iron status depending on several other influencing factors? (*Paper V*, chapter 2.3)

1.2. Vitamin D

1.2.1. Structure, metabolism and endogenous synthesis

Structure and metabolism

The fat-soluble vitamin D derivatives have a secosteroid structure with different substituents among the various compounds. One of the important derivatives is vitamin D_2 (ergocalciferol), which is produced by provitamin D_2 (ergosterol) in plants. The second is vitamin D_3, which is formed by provitamin D_3 (7-dehydrocholesterol, 7-DHC) in the skin (Bikle 2014) (**Figure 1**).

Vitamin D_2 and vitamin D_3 are metabolized by the same pathway within the fat absorption and metabolism. The absorption rate of vitamin D_3 is approximately 78.6% (Thompson et al. 1966) and increases with the intake of fat during a meal (Dawson-Hughes et al. 2015). Vitamin D is released in the liver by the degradation of chylomicrons. Precholecalciferol is hydroxylated to calcidiol (25-hydroxyvitamin D = 25(OH)D), which is transported to the kidney via vitamin D binding protein (VDBP). The active form of vitamin D – calcitriol (1,25-dihydroxyvitamin D = $1,25(OH)_2D$) – is converted by 1α-hydroxylase (1α(OH)ase, CYP27B1). For constant concentrations, 25(OH)D and $1,25(OH)_2D$ can be cleaved by 24-hydroxylase (24(OH)ase) to calcitroic acid (Bikle 2014). Vitamin D is mainly stored in the fatty tissue (Mawer et al. 1972) with a half-life of about two months (Preece et al. 1975; Dlugos et al. 1995; Vieth 1999).

Endogenous synthesis

Vitamin D has a special position within the vitamins because vitamin D_3 can be synthesized endogenously via UVB radiation (290 - 315 nm) (MacLaughlin et al. 1982) (**Figure 1**). In this way, 7-DHC in the skin is cleaved by sunlight to form precholecalciferol, which is metabolized. Inactive vitamin D isomers are formed by strong UVB radiation to avoid vitamin D intoxication (hypervitaminosis) (Holick 2007).

The vitamin D requirement can be achieved by endogenous vitamin D synthesis (Seckmeyer et al. 2013). However, several conditions influence the conversion rate and therefore the vitamin D status. On the one hand, the endogenous synthesis depends on the UVB radiation (Bogh et al. 2011) and therefore **geo-climate conditions** are determinative for the synthesis:

- **Latitude**: The availability of UVB radiation declines with higher latitude (O'Neill et al. 2016).
- **Season**: It is feasible to synthesize vitamin D in Central Europe during the whole year (Seckmeyer et al. 2013). However, in northern latitudes such as Germany, the synthesis is limited between October and March (Engelsen et al. 2005) because the UVB radiation for the production of vitamin D is considerably lower in the winter months than in the summer months (Serrano et al. 2017). For example, three days in December are necessary to synthesize adequate vitamin D amount (25 µg [≙1000 international units; conversion factor:

40]) in Central Europe, whereas only 18 minutes are required in June (Seckmeyer et al. 2013).

- **Time of day**: The effective solar UVB radiation to produce vitamin D is the highest around noon (Serrano et al. 2017).
- **Thick ozone**, **clouds** (Engelsen et al. 2005) and **shade** reduce the synthesis capacity (Turnbull et al. 2005).

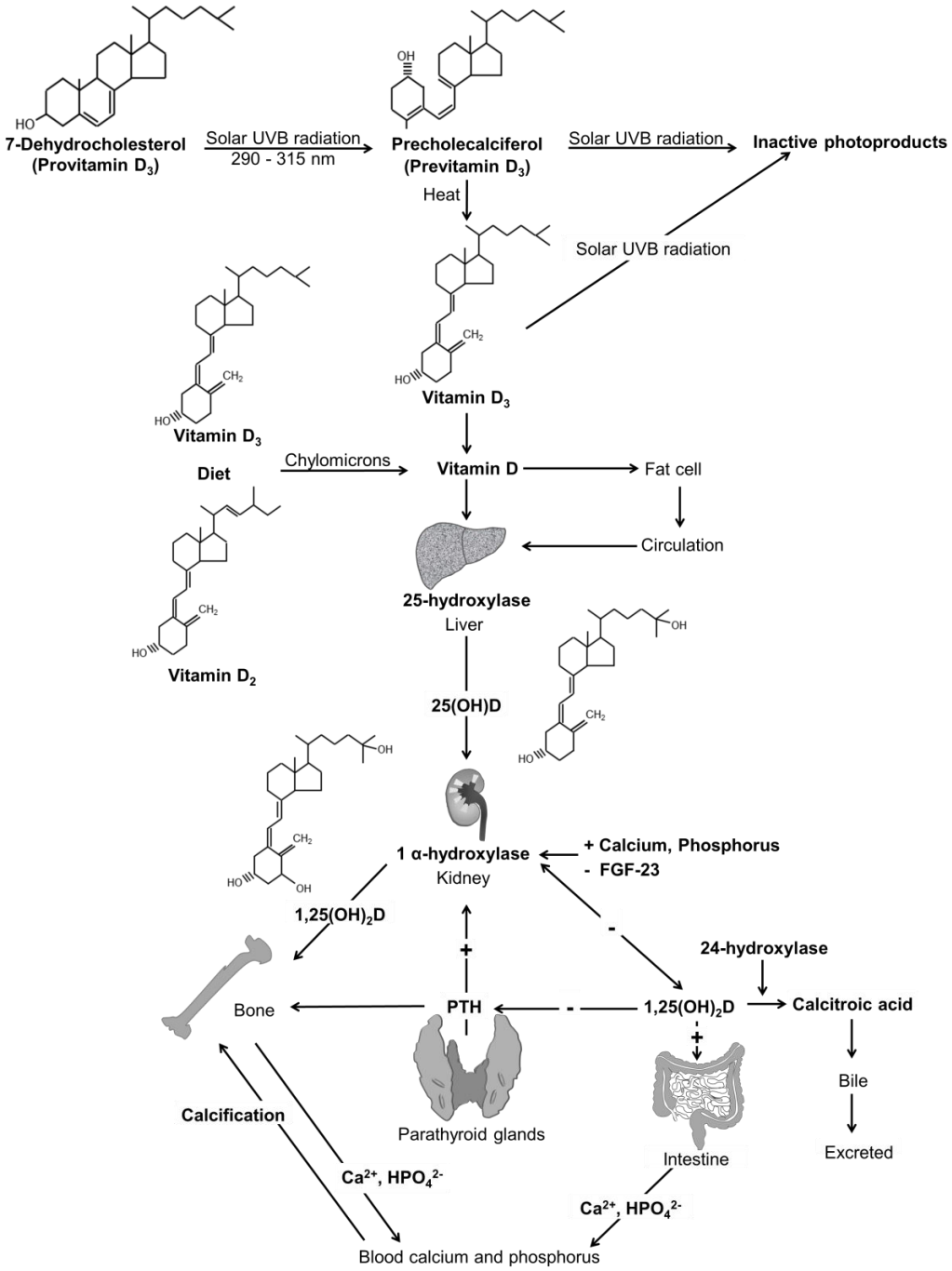

Figure 1 Vitamin D metabolism.

Figure was modified according to Holick 2007 and with addition of Deluca 2011 and Bikle 2014. Structural formula of 25(OH)D and $1,25(OH)_2D$ relate to $25(OH)D_3$ and $1,25(OH)_2D_3$.
Abbreviations: -, negative influence; +, positive influence; $1,25(OH)_2D$, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; CH_2, methylene group; CH_3, methyl group; FGF-23, fibroblast growth factor-23; HPO_4^{2-}, hydrogenphosphat; OH, hydroxide ion; PTH, parathyroid hormone; UVB, ultraviolet B.

Moreover, vitamin D synthesis capacity is **negatively** affected by **personal factors**:

- **Non-modifiable factors:** increasing skin pigmentation (Webb & Engelsen 2006; Libon et al. 2013; Xiang et al. 2015), increasing age (MacLaughlin & Holick 1985; Need et al. 1993) and burns (Schumann et al. 2012)
- **Modifiable factors:** lower skin area (Osmancevic et al. 2015) and therefore wearing clothing (Seckmeyer et al. 2013) with increasing darkness (Matsuoka et al. 1992), vertical body posture (Seckmeyer et al. 2013) and the use of sunscreens (Matsuoka et al. 1987)

1.2.2. Function

The effects of vitamin D are mediated non-genomic and genomic by binding on the vitamin D receptor (VDR). Non-genomically, 1,25$(OH)_2$D is bound on the VDR in the caveolae of the plasma membrane (Haussler et al. 2011). Genomically, 1,25$(OH)_2$D cooperates with the VDR and forms a heterodimer with the retinoid X receptor (RXR). This VDR/RXR complex binds to a specific deoxyribonucleic acid region of the genes – the vitamin D response element – which leads to the activation or suppression of the transcription (Christakos et al. 2016).

Skeletal effects

1,25$(OH)_2$D regulates the **calcium and phosphate homeostasis** by influencing the intestinal calcium absorption (Pansu et al. 1983; Aloia et al. 2014), the intestinal phosphate absorption (Rizzoli et al. 1977) and the renal calcium reabsorption (Yamamoto et al. 1984). In the bone, 1,25$(OH)_2$D affects the bone mineralization as well as the bone resorption and thus effects on the calcium and phosphate level. The stimulation of osteoblasts by 1,25$(OH)_2$D results in a bone mineralization (Matsumoto et al. 1991). However, 1,25$(OH)_2$D also promotes the osteoclastic bone resorption via stimulation of a soluble factor by osteoblasts (McSheehy & Chambers 1987). The regulation of the serum calcium levels is also indirectly affected by 1,25$(OH)_2$D because it suppresses the parathyroid hormone (PTH) (Silver et al. 1986). PTH is responsible for the release of bone mineral by osteoclasts (Weisbrode et al. 1978).
As a result, an inadequate vitamin D status could cause rickets in children (Shaw 2016), osteomalacia in adulthood (Bhan et al. 2012) as well as fractures (Brincat et al. 2015; Fu et al. 2015), falls (Rothenbacher et al. 2014; Brincat et al. 2015) and secondary hyperparathyroidism (Lips 2001).

Extra skeletal effects

VDR and 1α(OH)ase are also expressed in tissues such as the cardiovascular system (Chen et al. 2008), brain (Eyles et al. 2005), colon (Matusiak et al. 2005) and breast (McCarthy et al. 2009). Therefore, a probably association of vitamin D with many diseases is conceivable:

- Cardiovascular diseases (Anderson et al. 2010; Ford et al. 2014)
- Diabetes mellitus type 2 (Mitri et al. 2011) and diabetic nephropathy (Derakhshanian et al. 2015)
- Inflammatory diseases (Duan et al. 2014; Lin et al. 2016; Sadeghian et al. 2016)
- Cancer such as colon (Ma et al. 2011; Ying et al. 2015) and breast cancer (Chen et al. 2010; Kim & Je 2014)
- All-cause mortality (Garland et al. 2014; Pilz et al. 2016)

However, the data situation is inconsistent for some of these diseases (James et al. 2013; Sperati et al. 2013; Seida et al. 2014; Lugg et al. 2015; Jacobs et al. 2016) and partially intervention studies are missing.

Effects during pregnancy and breastfeeding period

During pregnancy, the maternal vitamin D status is not only important for the mother's health, but also for the health of the fetus and infant (**Table 1**). The fetal and infant vitamin D status depends on the maternal vitamin D supply (Wagner et al. 2012). This arrangement is shown by having a high correlation of the maternal 25(OH)D concentration – biochemical parameter of vitamin D status – with the 25(OH)D concentration of the cord blood (Dror et al. 2011; Wuertz et al. 2013; Pena et al. 2015) and breastmilk (við Streym et al. 2016). Moreover, VDR is present in the placenta (Pospechova et al. 2009) and even in fetal tissues (Betts et al. 2015). The maternal vitamin D status also influences the protein expression of 1α(OH)ase in the placenta (O'Brien et al. 2014) and the 25(OH)D concentration in the breast milk upon delivery (Mohamed et al. 2014).

During **pregnancy**, the vitamin D metabolism changes with a two-three times higher $1,25(OH)_2D$ concentration than in non-pregnant women (Papapetrou 2010; Hollis et al. 2011). This increase is independent of the rise of VDBP (Bikle et al. 1984). Calcitonin is probably responsible for the higher $1,25(OH)_2D$ concentration (Hollis et al. 2011) because it controls the 1α(OH)ase activity (Zhong et al. 2009) and is enhanced during pregnancy (Silva et al. 1981). It is suggested that at this time the $1,25(OH)_2D$ concentration is disengaged from the calcium, phosphorus and PTH metabolism (Hollis et al. 2011). Therefore, the enhanced $1,25(OH)_2D$ concentration does not result in a hypercalcemia and hypercalciuria (Hollis et al. 2011). A 25(OH)D concentration of at least 100.0 nmol/L (≙ 40 ng/ml, conversion factor: 2.496) is needed to ensure an optimal production of $1,25(OH)_2D$ during pregnancy (Hollis et al. 2011).

Table 1 Influence of vitamin D on the course of pregnancy, development and health of the fetus and infant and the mother's health.

Influence on the course of pregnancy	
Preterm birth	• Maternal 25(OH)D concentrations > 100.0 nmol/L compared with < 50.0 nmol/L are associated with a lower risk for preterm birth (< 37th week of gestation) (RR 0.41; 95% CI 0.20, 0.86) (Wagner et al. 2016).
Caesarean section	• Maternal 25(OH)D concentrations < 37.5 nmol/L versus ≥ 37.5 nmol/L are related with a higher risk (OR 3.84; 95% CI 1.71, 8.62) (Merewood et al. 2009). • The results are inconsistent (Aghajafari et al. 2013).
Small for gestational age infant	• Maternal 25(OH)D concentrations < 37.5 nmol/L versus ≥ 37.5 nmol/L are associated with a higher risk (OR 1.85; 95% CI 1.52, 2.26) (Aghajafari et al. 2013).
Influence on the development and health of fetus and infant	
Neuropsychological development	• Maternal 25(OH)D concentrations > 75.0 nmol/L compared with < 50.0 nmol/L result in a higher mental score (ß 2.60; 95% CI 0.63, 4.56) and psychomotor score (ß 2.32; 95% CI 0.36, 4.28) of their infants (11 - 23 months) (Morales et al. 2012a).
Bone health	• Per 10.0 nmol/L increase of the maternal 25(OH)D concentration, the bone mineral content (19.2 g; 95% CI 5.60, 32.70) and bone mineral density are higher (4.6 mg/cm^2; 95% CI 0.10, 0.90) (Zhu et al. 2014). • Lower maternal and infantile 25(OH)D concentrations in active rickets than in healed rickets (Elidrissy 2013).
Type 1 diabetes	• Vitamin D supplementation – regardless of amount – in infants during the first year of life is associated with a lower incidence and risk (RR 0.12; 95 % CI 0.03, 0.51) (Hyppönen et al. 2001)
Allergy	• Possible U-shaped relation (Rueter et al. 2014), but the results are inconsistent (Rueter et al. 2014; Papadopoulou et al. 2015).
Respiratory tract infections	• The highest quartile of maternal 25(OH)D concentration versus the lowest quartile is related with a lower risk (OR 0.67; 95% CI 0.50, 0.90) in the offspring of the first year (Morales et al. 2012b).
Influence on the maternal health	
Preeclampsia	• Maternal 25(OH)D concentrations < 30.0 nmol/L compared with ≥ 50.0 nmol/L are associated with a higher risk (OR 2.23; 95% CI 1.29, 3.83) (Achkar et al. 2015).
Postpartum depression	• Maternal 25(OH)D concentrations < 47.0 nmol/L versus > 70.0 nmol/L are related with a higher risk (OR 2.72; 95% CI 1.42, 5.22) (Robinson et al. 2014).
Gestation diabetes mellitus	• Maternal 25(OH)D concentrations < 50.0 nmol/L compared with ≥ 50.0 nmol/L are associated with a higher risk (OR 1.38; 95% CI 1.12, 1.70) (Wei et al. 2013).
Bacterial vaginosis	• Higher risk at a lower maternal 25(OH)D concentration (Aghajafari et al. 2013).

Abbreviations: ß, standardized coefficient; 25(OH)D, 25-hydroxyvitamin D; CI, confidence interval; OR, odds ratio; RR, relative risk.

During **breastfeeding period**, prolactin also stimulates 1α(OH)ase (Ajibade et al. 2010). Postpartum, the $1,25(OH)_2D$ concentration is higher in breastfeeding women than in bottle-feeding women, however, lies in a normal range comparable with non-pregnant (NP) and non-breastfeeding (NB) women (Carneiro et al. 2010). The vitamin D activity of milk varies and is only between 0.125 and 2.0 µg/L (Hollis et al. 1981; Specker et al. 1985; Ala-Houhala et al. 1988; Hollis & Wagner 2004; Wagner et al. 2006). Therefore, a daily vitamin D intake of 10 µg is recommended for infants up to the age of one year (D-A-CH 2015). This estimated value is recommended, regardless of the vitamin D intake via breastmilk or formula as well as the endogenous synthesis. Nevertheless, a maternal vitamin D supplementation (160 µg/day) during breastfeeding period is as effective as an infant supplementation (Hollis et al. 2015).

1.2.3. Nutritional requirements, recommendations and supply situation

Vitamin D intake

Only a few foods contain vitamin D in relevant amounts. Fatty fish such as smoked eel (smoked: 90.0 µg/100 g), herring (25.0 µg/100 g) or salmon (16.0 µg/100 g) contain the highest amounts (Souci et al. 2015).

Recommendation for vitamin D intake is challenging due to the endogenous vitamin D synthesis. The D-A-CH society recommends a vitamin D intake of 20 µg/day for adults (from 15 years up) as well as for pregnant and breastfeeding women (D-A-CH 2015). This estimated value is recommended in case of absent endogenous vitamin D synthesis (D-A-CH 2015) and based on the fact that 20.0 µg/day ensures a sufficient vitamin D status (25(OH)D concentration > 50.0 nmol/L) in 90.0 - 95.0% of the population (Cashman et al. 2008). Corresponding to the German nutrition report, an average vitamin D intake of 1.5 - 1.7 µg/day is only ingested by women (19 - 35 years) (DGE 2012). Therefore, an excess of the tolerable upper intake level (UL) of 100 µg/day (EFSA 2012b) is not expected with food.

Classification of vitamin D status

For the assessment of the vitamin D status, the 25(OH)D concentration is suitable because it includes both – dietary intake and endogenous synthesis of vitamin D (Ross et al. 2011). 25(OH)D has a half-life of approximately 15 days (Jones et al. 2014). However, there is no consistency about the vitamin D status that results in the highest health advantage in the general population (Souberbielle et al. 2010; Holick et al. 2011; Ross et al. 2011; Pludowski et al. 2013) and also during pregnancy and breastfeeding periods (Wagner et al. 2012; Pludowski et al. 2013). A 25(OH)D concentration < 25.0 nmol/L can be classified as deficiency for bone health (Zittermann & Gummert 2010). The DGE considers a vitamin D status of at least 50.0 nmol/L for bone health (Linseisen et al. 2011). This value is also

recommended by the Institute of Medicine to ensure the requirements of 97.5% of the population (Ross et al. 2011). However, there is also an evidence that a 25(OH)D concentration of ≥ 75.0 nmol/L should be achieved (CPS 2007; Souberbielle et al. 2010; Holick et al. 2011; Vieth 2011) (**Table 2**).

Table 2 Classification of vitamin D status depending on the 25-hydroxyvitamin D concentration.

25(OH)D concentration [nmol/L][1]	Biochemical modifications
< 25.0	Rickets, osteomalacia, calcium malabsorption, severe hyperparathyroidism, low $1,25(OH)_2D$ concentrations, muscular diseases, death, dysfunction of immune and cardiovascular system?
25.0 - 49.9	Reduced bone mineral density, impaired muscle function, low absorption of calcium, increased PTH concentrations, slightly decreased $1,25(OH)_2D$ levels, increased mortality ratio
50.0 - 74.9	Low bodily stores of vitamin D, slightly increased PTH levels
≥ 75.0	No disturbance of vitamin D dependent functions, assurance of skeletal health, lower risk of fractures and falls, assurances of optimal health in case of an increased risk for cancer, cardiovascular disease, muscoskeletal disorders, autoimmune disorders
> 125.0	Increased mortality rate ratio
> 372.0	Hypercalcemia, acute toxicity

Table was designed in accordance with Melamed et al. 2008; Priemel et al. 2010; Souberbielle et al. 2010; Zittermann & Gummert 2010; Ross et al. 2011; Vieth 2011.
Abbreviations: $1,25(OH)_2D$, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; PTH, parathyroid hormone.
[1] Conversion in ng/ml: divided by 2.496 nmol/L

In addition to the endogenous vitamin D synthesis and the vitamin D intake, the vitamin D status is influenced by several factors. The following factors have a negative impact on the vitamin D status:

- Higher body fat mass (Oliai Araghi et al. 2015) and obesity (Tonnesen et al. 2016)
- Smoking (Shinkov et al. 2015; Tonnesen et al. 2016)
- Physical inactivity (Daly et al. 2012; Tonnesen et al. 2016)
- Genetics (Wang et al. 2010) as shown by the vitamin D dependent rickets type 1B (Thacher & Levine 2016)
- Diseases such as inflammatory bowel diseases (Del Pinto et al. 2015), granuloma-forming diseases (Adams & Hewison 2012), primary and secondary hyperparathyroidism (Clements et al. 1992) and chronic kidney diseases (Oh et al. 2012)
- Drugs like anti-epileptics, which increase the decomposition of vitamin D (Wang et al. 2013)

Supply situation with vitamin D

An inadequate vitamin D status is common in the general population of Europe as well as in pregnant and breastfeeding women. In the **general population** of Europe, a total of 40.4% show 25(OH)D concentrations below 50.0 nmol/L (Cashman et al. 2016), and in Germany, the frequency is approximately between 50.8% and 75.0% (Hintzpeter et al. 2008; Zittermann et al. 2009; Richter et al. 2014; Rabenberg et al. 2015). Only 17.5% of the German women aged 18 - 44 years demonstrate 25(OH)D concentrations ≥ 75.0 nmol/L (Rabenberg et al. 2015).

Information on the vitamin D status for **pregnant and breastfeeding women** in Germany are only available at the end of pregnancy (34th week of pregnancy). 44.4% of these women show 25(OH)D levels below 50.0 nmol/L (Weisse et al. 2013). Moreover, another study demonstrates that in 77.0% of German women after birth the vitamin D status is below 50.0 nmol/L (Wuertz et al. 2013).

1.3. Long-chain omega-3 fatty acids

1.3.1. Structure and metabolism

Fatty acids consist of a carbon (C) chain and a carboxyl (COOH) group. The chain length, number of double bonds and location of the double bond from the end of the methyl are characteristic of the fatty acids. The different structures result in the specific functions of the fatty acids. The n-3 PUFAs have their first double bond between carbon atoms 3 and 4. The most important n-3 PUFAs are α-linoleinic acid (ALA, C18:3n-3) and the LC n-3 PUFAs eicosapentaenoic acid (EPA, C20:5n-3) and docosahexaenoic acid (DHA, C22:6n-3) (Bazinet & Laye 2014).

After the intake from the diet, the LC n-3 PUFAs are emulsified in the stomach and transported to the small intestine. Here, the LC n-3 PUFAs are enzymatically cleaved to free FAs and 2-monoacylglycerides. Both reach the enterocytes in the form of micelles. A re-esterification of the n-3 FAs to triacylglycerides (TG) ensues. In chylomicrons, the TGs enter the systemic circulation. From there, TGs are transported via blood to the target tissues (Schuchardt & Hahn 2013).

Humans can convert ALA to EPA and DHA by desaturation, elongation and oxidation (**Figure 2**) (Baker et al. 2016). However, the conversion rate is very low (ALA to DHA < 1%) (Plourde & Cunnane 2007; Brenna et al. 2009) and several factors influence the necessary enzymes for this conversion process:

- **Co-factors** such as zinc (Eder & Kirchgessner 1996), iron (Zhou et al. 2011), magnesium (Mahfouz & Kummerow 1989), folate and vitamin B_{12} (Wadhwani et al. 2012) as well as vitamin B_6 (Tsuge et al. 2000)show a positive impact on the fatty acid desaturase.

- **Insulin** promotes (Arbo et al. 2011) and glucagon suppresses the fatty acid desaturase (Rimoldi et al. 2001).
- **Estrogen** may enhance the conversion (Burdge & Wootton 2002; Giltay et al. 2004; Kitson et al. 2013).
- **Genetic polymorphisms** of the elongase (Zhang et al. 2016a) and fatty acid desaturase (Horiguchi et al. 2016; Zhang et al. 2016a) inhibit the synthesis.
- **The omega-6 (n-6) PUFA linoleic acid** (LA, C18:2n-6) competes for the same conversion enzymes and is therefore a limiting factor in the conversion of LC n-3 PUFAs (Portolesi et al. 2007) (**Figure 2**).

Moreover, a retroconversion of DHA to EPA is possible (Stark & Holub 2004; Plourde et al. 2011; Park et al. 2016).

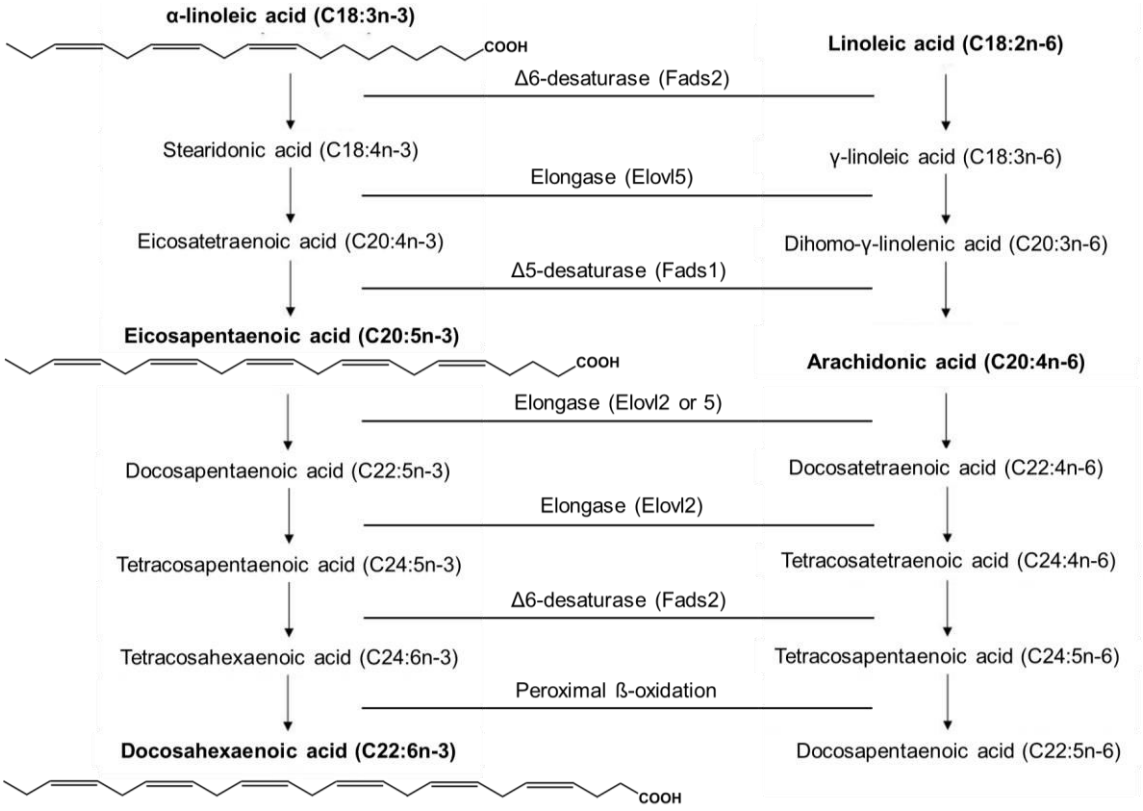

Figure 2 Biosynthesis of omega-3 fatty acids and omega-6 fatty acids.

This figure was modified according to Bazinet & Laye 2014 and Baker et al. 2016.
Abbreviations: C, carbon; COOH, carboxyl group; Elovl2 or 5; elongation of very long-chain fatty acids 2 or 5; Fads1 or 2, fatty acid desaturase 1or 2; N-3, omega-3; N-6, omega-6.

1.3.2. Function

DHA exists in many organs such as in the brain, retina and testis (Sassa & Kihara 2014). Several physiologic effects are associated with the LC n-3 PUFAs (**Table 3**). Therefore, LC n-3 PUFAs have various benefits on the health of the general population (**Table 4**). However, more intervention studies are partly necessary to determine the evidence for these potential effects.

Table 3 Physiologic mechanism of long-chain omega-3 fatty acids.

Mechanism of LC n-3 PUFAs	
Membrane fluidity	• DHA is incorporated in lipid rafts (Schley et al. 2007) and enhances their membrane fluidity (Aliche-Djoudi et al. 2013). DHA leads to a modification of the fatty acid composition and decreases epidermal growth factor receptor in the lipid rafts (Schley et al. 2007).
Neurite Growth	• LC n-3 PUFAs enhance the neurite outgrowth in adults and aged neurons, as shown in sensory neuronal culture of dorsal root ganglia from rat (Robson et al. 2010). The effects are the result from the incorporation of LC n-3 PUFAs in Apo E containing lipoproteins in the form of fatty acid moiety of phospholipids. These lipoproteins promote the number of branches and therefore the neurite outgrowth (Nakato et al. 2015)
Synaptogenesis	• DHA increases the synaptic transmission (Connor et al. 2012) and improves the PSD95 level as well as the expression of synaptophysin (Tao et al. 2016)
Gene expression	• LC n-3 PUFAs regulate the expression of several genes, which regulate the inflammation, neuronal processes or the fatty acid metabolism, such as CD36 (Vedin et al. 2012), RAR, RXRα, RXRß (Dyall et al. 2010), PPARα, HNF6 and HNF1ß (Schmidt et al. 2012)
Neurogenesis	• LC n-3 PUFAs improve the number of S-phase cells in the neurons (Beltz et al. 2007) and neurogenesis (Beltz et al. 2007; Dyall et al. 2010)
Oxylipin synthesis	• LC n-3 PUFAs can be metabolized to oxygenated metabolites (oxylipins) by cyclooxygenase, lipoxygenase and cytochrome P450 pathway (Wang et al. 2014). For example, eicosanoids are formed, such as the DHA metabolite 17-HDHA (resolvin D1 precursor) (Shearer et al. 2010; Fischer et al. 2014), which has anti-inflammatory effects (Neuhofer et al. 2013; Erdinest et al. 2014).

Abbreviations: 17-HDHA, 17-hydroxydocosahexaenoic acid; CD36, cluster of differentiation 36; ApoE, Apolipoprotein E; DHA, docosahexaenoic acid; HNF1ß, hepatocyte nuclear factor 1 beta; HNF6, hepatocyte nuclear factor 6; LC n-3 PUFAs, long-chain omega-3 polyunsaturated fatty acids; PPARα, peroxisome proliferator-activated receptor alpha; PSD95, postsynaptic density protein 95; RAR, retinoic acid receptor; RXRα or ß, retinoid X receptor α or ß; S-phase; synthesis phase.

Table 4 Effects of long-chain omega-3 fatty acids on the health in the general population.

Effects in the general population	
Cardiovascular diseases	• Higher LC n-3 PUFAs status is related with a lower incidence of elevated blood pressure (RR 0.67; 95% CI 0.55, 0.83) (Yang et al. 2016). • LC n-3 PUFAs supplementation (≥ 1000 mg/day, ≥ 12 months) is associated with a lower risk for cardiac death (RR 0.68; 95% CI 0.56, 0.83) and myocardial infarction (RR 0.75; 95% CI 0.63, 0.88) in patients with cardiac diseases in the past (Casula et al. 2013). • LC n-3 PUFAs supplementation (450 - 4500 mg/day, average intake of 56 days) improves the flow-mediated dilation (WMD 2.3; 95% CI 0.89, 3.72) (Wang et al. 2012).
Cognitive decline	• LC n-3 PUFAs supplementation (400 - 1800 mg/day for 3 - 40 months) reduces the Mini-Mental State Examination score (WMD 0.15; 95% CI 0.05, 0.25) (Zhang et al. 2016b). • LC n-3 PUFAs supplementation (2.2 g/day for 26 weeks) enhances executive functions and white matter microstructure (Witte et al. 2014).
Depressive symptoms	• Higher n-3 PUFAs intake is related with a reduced risk of depressive symptoms (Beydoun et al. 2015). • Inverse relation between omega-3 index and depressive symptoms in subjects with increased oxidative stress (ß -1.74 ± 0.88) (Bigornia et al. 2016).
Breast cancer	• The highest quantile of n-3/n-6 intake (> 0.03 - 14.76 g) versus the lowest quantile (< 0.005 - < 5.48 g) is associated with a lower risk (RR 0.90; 95% CI 0.82, 0.99) (Yang et al. 2014).
Bone and the risk of fracture	• Intake of 4000 mg/day LC n-3 PUFAs for three months decreases bone resorption (Hutchins-Wiese et al. 2014). • DHA downregulates the expression of osteoclast-specific genes in osteoclasts, as shown in vitro (Kasonga et al. 2015). • Inverse association between the total n-3 PUFA status and the risk of hip fracture (HR 0.55; 95% CI 0.30, 1.01) (Orchard et al. 2013).
Type 2 diabetes	• The omega-3 index is negatively related with the risk in women under the age of 70 (Harris et al. 2016). • Δ5-desaturase activity is negatively and Δ6-desaturase activity is positively associated with the risk (Harris et al. 2016). • The evidence is inconclusive (Wu et al. 2012; Zhang et al. 2013).
Rheumatoid arthritis	• Long-term LC n-3 PUFAs intake of > 210 mg/day is associated with a lower risk (RR 0.48; 95% CI 0.33, 0.71) (Di Giuseppe et al. 2014).
All-cause mortality	• Each 300 mg/day increase of LC n-3 PUFAs intake reduces the risk (RR 0.94; 95% CI 0.89, 0.99) (Chen et al. 2016).

Abbreviations: ß, standardized coefficient; CI, confidence interval; DHA, docosahexaenoic acid; HR, hazard ratio; LC n-3 PUFAs, long-chain omega-3 fatty polyunsaturated acids; N-3, omega-3; N-6, omega-6; Omega-3 index, relative eicosapentaenoic acid and docosahexaenoic acid concentration in relation to total fatty acids in erythrocyte membranes; RR, relative risk; WMD, weighted mean difference.

Effects during the pregnancy and breastfeeding period

LC n-3 PUFAs, and especially DHA, have a particular importance during the pregnancy and breastfeeding period (**Table 5**). In addition to the n-6 PUFA arachidonic acid (AA, 20:4n-6), DHA influences the visual and cognitive development (Koletzko et al. 2008). High rates of DHA accumulate in the fetal brain, liver and retina during late pregnancy, which continues in the infant brain until the second year of life (Martinez 1992).

Usually, the fetus (Chambaz et al. 1985; Rodriguez et al. 1998), placenta (Cho et al. 1999) and infant (Carnielli et al. 2007) can synthesize DHA. However, the fetus and infant are also supplied by the maternal LC n-3 PUFA status via transfer by the placenta (Gil-Sanchez et al. 2010) or breast milk (Meldrum et al. 2012). An average of 40 mg DHA in the last weeks of pregnancy (Kuipers et al. 2012) and approximately 110 mg DHA during breastfeeding period (Kent et al. 2006; Brenna et al. 2007; Brenna & Lapillonne 2009) are transferred every day to the fetus and an exclusively breastfed infant, respectively.

Physiological changes may be covered the additional maternal requirement. Pregnant rats show a higher activity of the Δ6-destaurase and DHA concentration than non-pregnant rats (Kitson 2013). It is suggested that the higher Δ6-desaturase activity results by estrogen (Kitson 2013), whose concentration increases during pregnancy (Schock et al. 2016). However, the positive effect of estrogen on the conversion rate during pregnancy may no longer exist during the breastfeeding period (Burdge 2004) because the estrogen concentration decreases postpartum (Rasmussen & Kjolhede 2004).

1.3.3. Nutritional requirements, recommendations and supply situation

N-3 PUFA and n-6 PUFA intake

National dietary reference recommendations of n-3 PUFAs for the German healthy population exist only for the essential FA ALA as EPA and DHA can convert from ALA. The recommended intake of ALA should be sufficient to ensure an adequate LC n-3 PUFA supply (D-A-CH 2015).

ALA is found in different oils such as soya, walnut, rapeseed, linseed or pumpkin seed (Souci et al. 2015). An ALA intake of 0.5% of the energy intake is recommended for women, which is approximately 0.9 - 1.7 g/day (D-A-CH 2015). Data of the German nutrition report 2012 show that the average intake of ALA is 1.0 g/day in women (15 - 80 years) (DGE 2012).

Fish such as herring, salmon, sardine and mackerel are the primary food sources for **EPA** and **DHA** (Souci et al. 2015). In addition, micro algae (Ryckebosch et al. 2014) and Antarctic krill (Gigliotti et al. 2011) are also LC n-3 PUFAs sources. In contrast to Germany, an additional recommendation intake of EPA and DHA is suggested from other authoritative

Table 5 Effects of long-chain omega-3 fatty acids on the course of pregnancy, development and health of the fetus and infant and the mother's health.

Effects on the course of pregnancy and development and health of the fetus and infant	
Preterm birth	• Per 1% increase of the relative DHA level, the gestational age is 1.6 day longer (Harris et al. 2015). • LC n-3 PUFAs supplementation (> 100 mg/day, ~second trimester until end of gestation) is related with a lower risk of early preterm birth (< 34th week of gestation) (RR 0.74; 95% CI 0.82, 1.01) (Imhoff-Kunsch et al. 2012).
Birth outcome	• Maternal supplementation of 600 mg DHA/day during pregnancy is associated with an increase of birth weight (172 g) and head circumference (0.5 cm) (Carlson et al. 2013). • Maternal supplementation of 600 mg DHA/day from the 20th week of gestation until delivery is associated with an increase of the gestational length of about 4.0 - 4.5 days (Harris et al. 2015). • The results are inconsistent (Delgado-Noguera et al. 2015).
Cognitive and visual development	• Positive association between the cord DHA level and the visual function (Jacques et al. 2011), memory function (Boucher et al. 2011), motor function (Bakker et al. 2009) and neurological development (Jong et al. 2015). • Maternal seafood intake ≤ 340 g/week versus > 340 g/week during pregnancy is related with a higher risk of a low verbal intelligence quotient in children between 6th month and 8th year of life (OR 1.09; 95% CI 0.92, 1.29) (Hibbeln et al. 2007).
Immune system	• Maternal supplementation of 400 mg DHA/day from the 18th - 22th week of gestation until delivery reduces the incidence of colds (OR 0.76; 95% CI 0.58, 1.00) and results in a shorter duration of cough, phlegm and wheezing during the infant's first month of life (Imhoff-Kunsch et al. 2011).
Asthma and allergy	• Maternal LC n-3 PUFAs supplementation during pregnancy is associated with a lower risk of childhood asthma (OR 0.35; 95% CI 0.15, 0.79) (Klemens et al. 2011). • LC n-3 PUFAs supplementation is related with a lower risk of allergy in infants between the age of 12 - 36 months (OR 0.66; 95 % CI 0.44, 0.98) (Gunaratne et al. 2015). • The evidence is inconclusive (Best et al. 2016).
Blood pressure	• Higher maternal LC n-3 PUFAs status during the second trimester shows a lower childhood systolic blood pressure at the age of 6 year (ß -0.28; 95% CI -0.54, -0.03) (Vidakovic et al. 2015).
Influence on maternal health	
Postpartum depression	• Lower maternal omega-3 index in the 28th week of pregnancy is associated with a higher occurrence of depressive symptoms (ß 0.39; $p < 0.01$) (Markhus et al. 2013). • Lower n-3 PUFAs and DHA levels in women with postpartum depression (Vriese et al. 2003). • Higher DHA concentration in breastmilk is related with a lower prevalence of postpartum depression (Hibbeln 2002).

Abbreviations: ß, standardized coefficient; CI, confidence interval; DHA, docosahexaenoic acid; LC n-3 PUFAs, long-chain omega-3 polyunsaturated fatty acids; N-3 PUFA, omega-3; OR, odds ratio; omega-3 index, relative eicosapentaenoic acid and docosahexaenoic acid concentration in relation to total fatty acids in erythrocyte membranes; P, probability; RR, relative risk.

bodies and expert scientific organizations, which range from 250 to 500 mg/day for the general population, which are partly recommended for the prevention of cardiovascular diseases (ISSFAL 2004; Kris-Etherton et al. 2007; EFSA 2010; DeSalvo et al. 2016). For pregnant and breastfeeding women, the D-A-CH society recommends 200 mg DHA/day (D-A-CH 2015). The daily intake in German women is an average of 58 mg of EPA and 107 mg of DHA (DGE 2012). Moreover, an average of 105 g fish/week is ingested (DGE 2012) in contrast to the recommended intake of 150 - 220 g/week (Oberritter et al. 2013).
An UL does not exist for DHA and EPA due to insufficient data (EFSA 2012a).

The intake of **LC n-6 PUFAs** is also crucial for the assessment of the LC n-3 PUFA status due to the same conversion enzymes (Portolesi et al. 2007). A specific ratio for the intake of n-3/n-6 is not justifiable (EFSA 2010). National dietary reference value for the ALA intake does not exist. A LA intake of 2.5% of the energy intake (4.7 - 8.6 µg/day) is assumed to be sufficient for an adequate AA synthesis (D-A-CH 2015). Meat and fatty fish contain high amounts of LA and AA . Moreover, LA is found in different oils, such as sunflower (Souci et al. 2015). In German women (15 - 80 years), the average daily intake of LA is 7.3 g and that of AA is 128 g (DGE 2012).

Classification of LC n-3 PUFA status

A biochemical measurement of LC n-3 PUFAs reflects the total LC n-3 PUFA status – synthesized and ingested EPA and DHA (Tu et al. 2013). The analysis in the erythrocyte membranes reflects the long-term status of LC n-3 PUFAs (Harris & Schacky 2004; Sun et al. 2007). The investigation of the omega-3 index comprises the relative EPA and DHA concentration in relation to the total fatty acids in erythrocyte membranes (Harris & Schacky 2004). The categorization of the omega-3 index is shown in **Table 6**. Originally, the omega-3 index was used in the cardiology field in which the risk of death from coronary heart disease is the lowest at an omega-3 index of ≥ 8% and the highest risk at an omega-3 index of ≤ 4% (Harris & Schacky 2004). For pregnant and breastfeeding women, no biochemical reference values are available. However, an omega-3 index ≤ 5% during pregnancy is probably a risk factor for postpartum depression (Markhus et al. 2013).

Table 6 Classification of long-chain omega-3 fatty acids by the omega-3 index.

Classification	Omega-3 index (%)
Very low	≤ 4
Low	> 4 - 6
Moderate	> 6 - 8
High	> 8

Table was designed in accordance with the classification of Stark et al. 2016.
Abbreviation: Omega-3 index, relative eicosapentaenoic acid and docosahexaenoic acid concentration in relation to the total fatty acids in erythrocyte membrane.

The status of LC n-3 PUFAs depends on several factor values and is negatively affected, for example, by smoking (Scaglia et al. 2016; Zaparoli et al. 2016) and positively affected by age (Harris et al. 2013) and physical capacity (Moyers et al. 2011).

Supply situation with LC n-3 PUFAs

The LC n-3 PUFA status is very low or low in the most parts of the world (Stark et al. 2016). Extrapolated data of the general **German population** also show a low LC n-3 PUFA status (Stark et al. 2016). However, these data are partially based on studies with a small sample size (n ≤ 166), include both genders with an average of 50 years or specific groups, such as vegetarian subjects (Geppert et al. 2005; Dawczynski et al. 2010; Baghai et al. 2011).

National information on the LC n-3 PUFA status do not exist for **pregnant and breastfeeding women**. Studies from other countries like Norway show an average EPA level of 0.8 ± 0.1% and an average DHA level of 6.0 ± 0.3% in pregnant women at the 28th of gestation (Markhus et al. 2015). Moreover, Norwegian breastfeeding women, who breastfed since six months, demonstrate an average EPA level of 0.9 ± 0.1% and an average DHA level of 5.9 ± 0.3% (Markhus et al. 2015).

1.4. Iron

1.4.1. Structure and metabolism

The micronutrient iron occurs heme-bound (bivalent iron, ferrous, Fe^{2+}) as part of the red blood cell hemoglobin (Hb) and the muscle protein myoglobin as well as nonheme-bound (trivalent iron, ferric Fe^{3+}) (Steinbicker & Muckenthaler 2013).

Iron is metabolized primarily in the duodenum (Munoz et al. 2011) (**Figure 3**). In contrast to heme-bound iron, the nonheme-bound iron form is not soluble in its oxidized form (Gulec et al. 2014) and must be reduced to Fe^{2+} before absorption (Steinbicker & Muckenthaler 2013). In the enterocytes, heme oxygenase-1 (HO-1) releases iron from heme (Munoz et al. 2011). Here, Fe^{2+} is stored as ferritin or is released into the blood plasma.

The absorption of Fe^{2+} in blood plasma is regulated by hepcidin, which influences the expression of the necessary iron exporter ferroportin 1 (FPN1) (Steinbicker & Muckenthaler 2013). In the blood plasma, iron is transported via transferrin. Iron is absorbed in the target cells by transferrin receptor (TfR) 1 or 2 or divalent metal transporter 1 (DMT1). There, it is either directly needed or is stored as ferritin in the cytosol or as hemosiderin in the lysosomes (Munoz et al. 2011).

The majority of iron (~ 65.0%) is present as Hb in the erythrocytes. The iron requirements for the de novo synthesis of Hb (erythropoiesis) in the bone marrow (20 - 30 mg/day) (Munoz et al. 2011) is primarily achieved by iron recycling. Erythrocytes are reprocessed in macro-

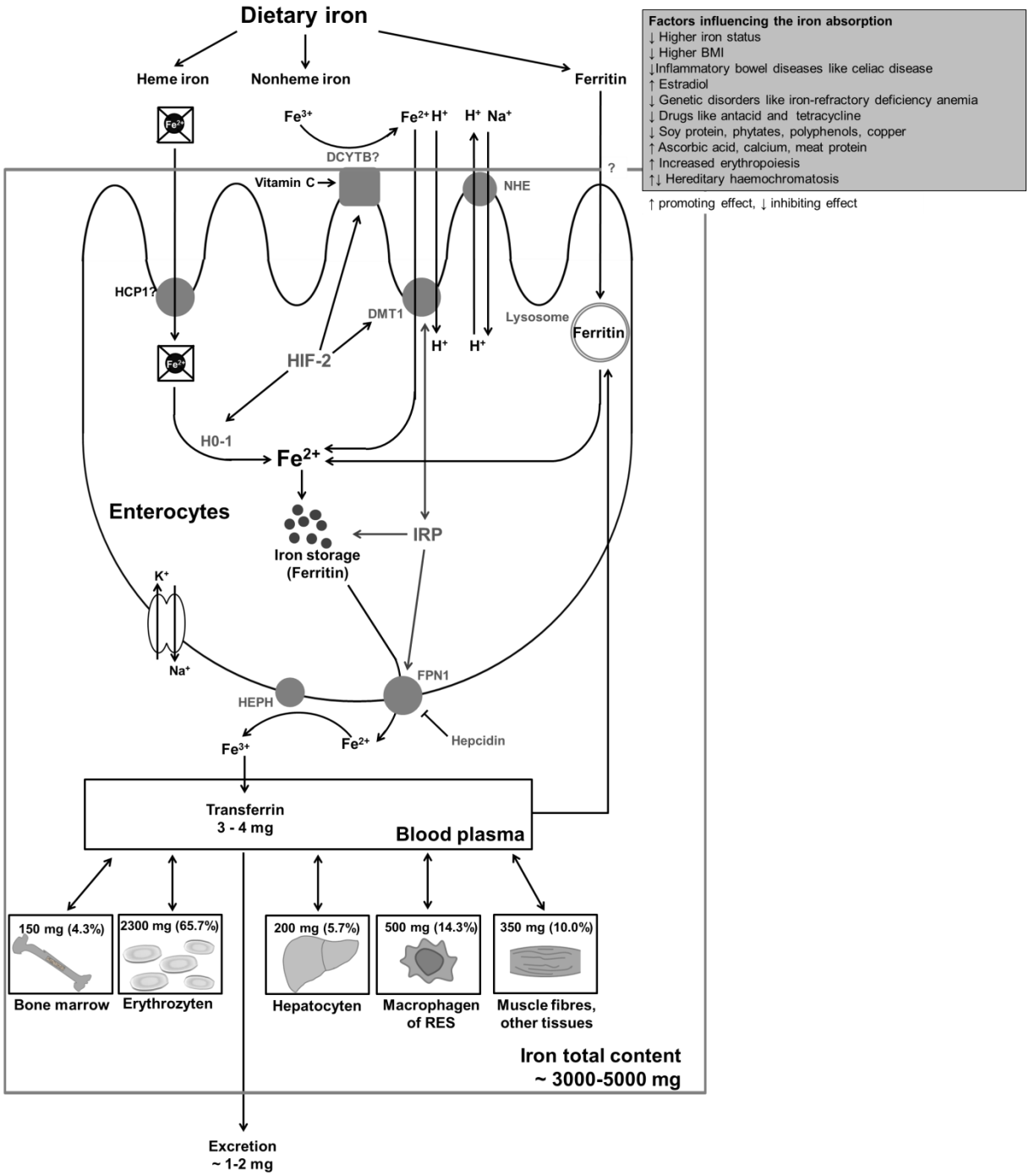

Figure 3 Iron metabolism.

Figure was modified according to Munoz et al. 2011; Steinbicker & Muckenthaler 2013, Gulec et al. 2014 and with addition of Neuvonen et al. 1975; O'Neil-Cutting & Crosby 1986; Hallberg et al. 1991; Skikne & Cook 1992; Petry et al. 2010; Yang et al. 2012; Collings et al. 2013; Heeney & Finberg 2014; Cepeda-Lopez et al. 2015; Freeman 2015; Weinborn et al. 2015; Olivares et al. 2016.
Abbreviations: BMI, body mass index; DMT1, divalent metal transporter 1; DCYTB, duodenal cytochrome B; Fe^{2+}, bivalent iron; Fe^{3+}, trivalent iron; FPN1, ferroportin 1; H^+, hydrogen ion; HCP1, heme carrier protein 1; HEPH, hephaestin; HIF-2, hypoxia inducible factor-2; HO-1, heme oxygenase-1; IRP, iron regulatory protein; K^+, potassium ion; Na^+, sodium ion; NHE, sodium-hydrogen exchanger; RES, reticuloendothelial system.

phages at approximately 120 days. Therefore, the iron intake by food is principally needed to replenish the daily loss of iron (1 - 2 mg/day) through urinary excretion, sweating, blood and skin desquamation (Steinbicker & Muckenthaler 2013).

1.4.2. Function

Iron is important for the supply of oxygen and cellular energy. Moreover, iron influences the deoxyribonucleic acid synthesis, cellular proliferation and differentiation as well as the gene expression. As a component of different enzymes, such as oxidases, catalases and peroxidases, iron is involved in the antioxidative defense (Ekmekcioglu & Marktl 2006).
The great relevance of iron for health becomes obvious in the negative effects on health in the case of an inadequate iron status (**Figure 4**). Initially, unspecific symptoms appear like fatigue (Brutsaert et al. 2003; Krayenbuehl et al. 2011), hair loss (Deloche et al. 2007), 2007), depression, lack of concentration and irritability (Rangan et al. 1998). With a progressive imbalance, the endurance capacity (Brownlie et al. 2004) and the cognitive planning ability (Murray-Kolb & Beard 2007; Blanton et al. 2013) are also impaired. Moreover, restless leg syndrome occurs, which leads to sleep disturbance and its consequences (Allen et al. 2013).
Iron has also beneficial effects during pregnancy, and its inadequate status is negatively associated with maternal and infantile health as well as with the course of pregnancy (Breymann 2015; Pratt & Khan 2016; Rahman et al. 2016).

In contrast to these positive effects, iron also catalyzes the formation of hydroxyl radical (Kehrer 2000). An iron overload could lead to oxidative stress or lipid peroxidation, which may result in organ damage, such as of the liver (Sengsuk et al. 2014) or brain (Piloni et al. 2013).

1.4.3. Nutritional requirements, recommendations and supply status

The assurance of iron requirement is rather complex as numerous factors affect the iron status:

- **Iron absorption** has a large variation (0.7 - 22.9%) (Collings et al. 2013) due to several factors that influence the iron absorption rate (Collings et al. 2013; Cepeda-Lopez et al. 2015) (**Figure 3**). The average iron absorption is assumed to be approximately 15.5% (Armah et al. 2015). Thereby, the absorption of heme iron is higher (~ 20.0%) (Bezwoda et al. 1983) than that of nonheme iron (~ 5.6%) (Armah et al. 2015) caused by the numerous factors that influence the nonheme iron absorption (cf. **Figure 3**).
- **Blood losses** through blood donation (Rigas et al. 2014) or gastrointestinal bleeding adversely impact the iron status (Reyes et al. 1999).

- **Menstruation-related blood losses** are a determining factor in the iron status of premenopausal women. Thereby, an average of 17.6 ml blood is lost during a menstruation cycle with an iron loss of approximately 0.43 mg/day (Harvey et al. 2005).
- **Use of contraceptives** appears to be a relevant factor on the menstruation-related blood losses, and therefore, it is a factor of the iron status:
  - Use of **hormonal oral contraceptives (OC)** is associated with shorter bleedings time (Milman et al. 1998) and less blood loss (Fraser et al. 2012). The use of OCs may be positively associated with the iron status (Milman et al. 1998; Miller 2014; Haile et al. 2016), however, the effect is inconclusive (Casabellata et al. 2007).
  - Use of **levonorgestrel intrauterine systems** (LNG-IUS) is indicated to improve the Hb (Rana et al. 2012; Lowe & Prata 2013) and ferritin concentration (Rana et al. 2012) possibly because the use is associated with a decrease in the severity of dysmenorrhea (Lindh & Milsom 2013) and menstrual duration (Rana et al. 2012).
  - Use of **copper intrauterine device** (IUD) results in a decrease of the Hb (Lowe & Prata 2013) and ferritin concentration (Rana et al. 2012).

Iron intake

A high iron content is found in meat (especially in offal), wheat bran, millet, soya and quinoa (Souci et al. 2015). In animal sources, non-heme and heme-bound iron are available, whereas in plant sources exist nonheme-bound iron (Hurrell & Egli 2010). The reference value for the iron intake of women considers an iron absorption rate of 10.0 - 15.0% and the physiological status (menstruating/non-menstruating) (D-A-CH 2015). According to the German nutrition report of 2012, the average intake of iron in women lies below the iron recommendation of 15.0 mg/day in menstruating women. In women 19 - 25 years of age the average iron intake is 8.6 mg/day, and in women aged 25 - 34 years it is 9.5 mg/day (DGE 2012).

An UL does not exist for iron; originated from missing evidence of an association between iron status and chronic diseases (EFSA 2006).

Classification of iron status

Different blood parameters should be taken into consideration to evaluate the iron status because the iron content is distributed (**Figure 3**). The classification is shown in **Figure 4**.

Ferritin is an indicator of iron stores (Skikne et al. 1990) and its level already decreases at the beginning of an inadequate iron balance (Clark 2008). A sustained imbalance might result in a restricted erythropoiesis (iron deficient-erythropoiesis) (Clark 2008). At this time, the **soluble TfR** (sTfR) increases (Flowers et al. 1989). Moreover, sTfR also reflects the tissue iron deficiency (Skikne et al. 1990). The analysis of the **sTfR-ferritin** (sTfR-F) **index**

(sTfR/$\log_{10}$ ferritin) specifies the iron depletion as it combines ferritin and sTfR (Punnonen et al. 1997). A progressive iron deficiency leads to a manifestation of anemia with a modification of the erythrocytes – microcytic and hypochromic (Clark 2008). Consequently, the **Hb** concentration is decreased, which is an indicator of anemia (WHO 2001). In addition, several other forms of anemia exist, such as the megaloblastic anemia with decreased levels of vitamin B_{12} and folate (Yadav et al. 2016).

In contrast, a severe risk of iron overload exists at a ferritin concentration of > 150 µg/L (WHO 2001).

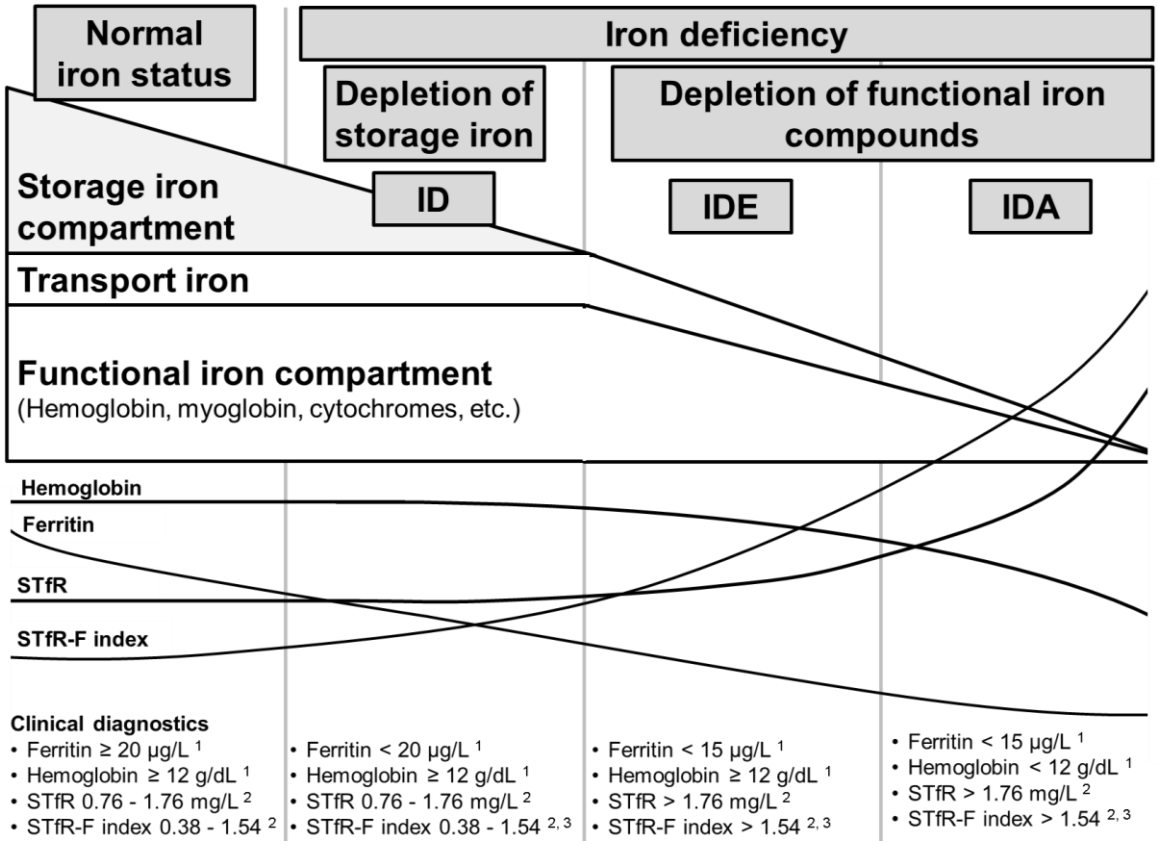

Figure 4 Classification of iron status and health consequences.

Figure was modified according to Suominen et al. 1998 and with addition of WHO 2001 and Brutsaert et al. 2003 [3].

Abbreviations: sTfR, soluble transferrin receptor; sTfR-F index, soluble transferrin receptor-ferritin index; ID, iron deficiency non-anemic; IDE, iron-deficient erythropoiesis; IDA, iron-deficiency anemia.

[1] The reference values relate to the recommendations for women; [2] reference value depends on the measurement method and therefore corresponds to the value of laboratory (Siemens Healthcare Diagnostics Products GmbH 2011); [3] calculated by sTfR/log10 ferritin iron (Punnonen et al. 1997).

Supply situation with iron

Iron stores are lower in premenopausal women than in men (Dainty et al. 2014). The prevalence of iron deficiency in non-pregnant women (< 50 years) of different countries varies between 9.7% and 43.0% (Milman et al. 1998; Lahti-Koski et al. 2003; Pynaert et al. 2007; Miller 2014; Fonseca et al. 2016). Anemia (Hb < 12 µg/L) exists in 22.0% of the European non-pregnant women (15 - 49 years) (Stevens et al. 2013).

2. Scientific publications

2.1. Vitamin D

2.1.1. Paper I: Higher prevalence of vitamin D deficiency in German pregnant women compared with non-pregnant women

Gellert S, Ströhle A, Hahn A (2017). Higher prevalence of vitamin D deficiency in German pregnant women compared with non-pregnant women. Arch Gynecol Obstet, 296 (1): 43-51.

https://link.springer.com/article/10.1007%2Fs00404-017-4398-5

2.1.2. *Paper II:* Breastfeeding woman are at higher risk of vitamin D deficiency than non-breastfeeding women – insights from the German VitaMinFemin study

Gellert S, Ströhle A, Hahn A (2017). Breastfeeding woman are at higher risk of vitamin D deficiency than non-breastfeeding women - Insights from the German VitaMinFemin study. Int Breastfeed J, 12 (19).

https://internationalbreastfeedingjournal.biomedcentral.com/articles/10.1186/s13006-017-0105 -1

2.2. Long-chain omega-3 fatty acids

2.2.1. *Paper III:* Higher omega-3 index and DHA status in pregnant women compared to lactating women – Results from a German nation-wide cross-sectional study

Gellert S, Schuchardt JP, Hahn A (2016). Higher omega-3 index and DHA status in pregnant women compared to lactating women – Results from a German nation-wide cross-sectional study. Prostaglandins Leukot Essent Fatty Acids, 109 (6): 22-28.

http://www.sciencedirect.com/science/article/pii/S0952327816300217?via%3Dihub

2.2.2. *Paper IV:* Low long-chain omega-3 fatty acid status in middle-aged women

Gellert S, Schuchardt JP, Hahn A (2017). Low long chain omega-3 fatty acid status in middle-aged women. Prostaglandins Leukot Essent Fatty Acids, 117 (2): 54-59.

http://www.sciencedirect.com/science/article/pii/S0952327816301600?via%3Dihub

2.3. Iron

2.3.1. *Paper V*: Iron status in relation to oral contraceptive use in women of reproductive age

Gellert S, Hahn A (2017). Iron status in relation to oral contraceptive use in women of reproductive age. Insights in nutrition and dietetics, Austin J Womens Health, 4 (1): 1025.

http://austinpublishinggroup.com/womens-health/download.php?file=fulltext/ajwh-v4-id1025.pdf

3. General discussion

The aim of this dissertation thesis was to assess the vitamin D, LC n-3 PUFA and iron status for the first time in German women during a specific lifetime. The collection was confirmed in the framework of the nationwide cross-sectional “vitamin and mineral status among German women” (VitaMinFemin) study, which investigated the status of selected nutrients that have a special relevance to certain life phases of women. According to the results of the nationwide survey “National Nutrition Survey II (2008)“ of the Federal Research Institute of Nutrition and Food (MRI 2008), those nutrients were determined for which the supply status is suspected to be marginal or inadequate. A total of 2367 women (18 - 66 years of age) were recruited between April 2013 and March 2015 by 125 general practitioners and gynecologists. The necessary blood samples were collected during a routine or diagnostically relevant examination. Moreover, nutrient-related aspects, that are required for the assessment of the nutrient status, were also evaluated.

The results of this dissertation thesis are presented in the associated scientific publications (chapter 2).
The supply situation of **vitamin D** in **pregnant** (n = 429) **and breastfeeding women** (n = 124) in comparison with the status of NP and NB women of the same age, region and recruited season are shown in *Papers I* and *II* (chapter 2.1).
The **LC n-3 PUFA** status was assessed in **pregnant women in the third trimester** (n = 213), **breastfeeding women** (n = 127) and **middle-aged women** (40 - 60 years) (n = 446). The results are discussed in *Papers III* and *IV* (chapter 2.2).
In **women of reproductive age** (n = 178, 18 - 34 years), the **iron** status was determined with consideration of OCs and several other potential factors (*Paper V*, chapter 2.3).

In the following section, the results of this nutrient survey are discussed and compared with previous studies.

3.1. Vitamin D status in pregnant and breastfeeding women compared to non-pregnant and non-breastfeeding women (*Papers I and II*)

The status of vitamin D is inadequate in the general population of Germany as shown in previous studies (Hintzpeter et al. 2008; Richter et al. 2014; Rabenberg et al. 2015) and in these NPNB women. Approximately 56.0% of these NPNB women demonstrated 25(OH)D levels that were below 50.0 nmol/L and only around 12.0% showed a vitamin D status ≥ 75.0 nmol/L (*Paper I and II*). This finding could be linked to the fact that only a few foods contain appreciable vitamin D contents (Souci et al. 2015). Moreover, even if the endogenous vitamin D synthesis could supply an adequate vitamin D amount (Seckmeyer et al. 2013), 30% of the women avoid midday sun for sun protection (Gavin et al. 2012), where

the synthesis rate is the most effective (Serrano et al. 2017). Additionally, 56% of German women use sunscreens (Richter et al. 2014), which reduce the formation (Matsuoka et al. 1987).

Therefore, there is the assumption that pregnant and breastfeeding women are also inadequately supplied with vitamin D, however, nationwide data are missing. During pregnancy and breastfeeding periods, the supply of vitamin D is important for the course of pregnancy, the development and health of the fetus (Aghajafari et al. 2013) and infant (Zhu et al. 2014) as well as for maternal health (Achkar et al. 2015; Lu et al. 2016).

Main results and assessments compared with previous studies

These are the first data of the vitamin D status in German women at different points of pregnancy (*Paper I*) and breastfeeding periods (*Paper II*).

- The **majority** of women demonstrated **25(OH)D concentrations below 50.0 nmol/L** (pregnant women: 78.1%; breastfeeding women: 75.8%).
- Vitamin D status **≥ 75.0 nmol/L** was only present in **4.9 % of the pregnant women** and **5.6 % of the breastfeeding women**.
- A total of **36.8% of the pregnant women** showed 25(OH)D concentrations below **25.0 nmol/L** (vitamin D deficiency) and the risk of this level was significantly **3.7-fold higher** (95% confidence interval [CI] 2.5, 5.4) **than in NPNB women** in an adjusted model (season, region [longitude] of recruiting, recent holidays, age, body mass index [BMI] and trimester).
- In **breastfeeding women**, a total of **26.6%** of the women showed 25(OH)D concentrations **below < 25.0 nmol/L** (vitamin D deficiency) and the risk for this level was significantly **4.0 times higher** (95% CI 1.8, 8.7) than in **NPNB women** in an adjusted model (season, region [longitude] of recruiting and BMI).
- **None** of the pregnant and breastfeeding women had 25(OH)D concentrations ≥ 125.0 nmol/L.

The high prevalence of an inadequate vitamin D status has also been shown in a previous monocentric study of German women after delivery (77.0% < 50.0 nmol/L) (Wuertz et al. 2013). Moreover, the prevalence of 25(OH)D concentrations below 50.0 nmol/L in pregnant or breastfeeding women was equal or even higher in other European countries, such as in Ireland (80.0%) (Zhang et al. 2014), the United Kingdom (95.0%) (Jones et al. 2016), Italy (70.6%) (Cadario et al. 2015) and Poland (91.9%) (Czech-Kowalska et al. 2015). Consistently, Holmes et al. (2009) also showed a higher prevalence of insufficient vitamin D status in pregnant women in the United Kingdom compared with NP women (75.0% vs. 42.0%).

Possible explanations for the lower vitamin D status during pregnancy and breastfeeding period

The lower vitamin D status of pregnant and breastfeeding women compared to NPNB women in this study could be caused by the additional nutritional requirement of the fetus via placenta (Olmos et al. 2016) and infant via breastmilk (Narchi et al. 2010). Moreover, it is expected that pregnancies often start with an inadequate vitamin D status – 60.7% of the women of childbearing age show 25(OH)D concentrations below 50.0 nmol/L (Pilz et al. 2017). Interestingly, the risk of a vitamin D status < 25.0 nmol/L was significantly lower (odds ratio 0.5; 95% CI 0.3, 0.9) in breastfeeding women than in pregnant women in an adjusted model (season and region [longitude] of recruiting). However, previously data demonstrated a decrease of the 25(OH)D concentration from pregnancy to breastfeeding period (Jones et al. 2016). It is certainly conceivable that the intensity of breastfeeding had an influence on the maternal vitamin D status. Narchi et al. (2010) indicated that the prevalence of an inadequate vitamin D status in breastfeeding women six month postpartum is slightly higher in exclusively breastfeeding women compared to partially breastfeeding women (Narchi et al. 2010). Therefore, a lower intensity of breastfeeding in this breastfeeding women might be the reason for the lower risk of vitamin D status < 25.0 nmol/L, but information about the intensity of breastfeeding were not collected in this study.

Influencing factors on the vitamin D status

Some of the previous studies of pregnant and breastfeeding women showed a similar prevalence of an inadequate vitamin D status, however, other European studies like Denmark, Sweden or Spain also demonstrated an insufficient vitamin D status but with a lower prevalence (18.0 - 44.4%) (Milman et al. 2012; Brembeck et al. 2015; Rodriguez et al. 2016). Interestingly, a European-wide comparison of the general population showed a higher prevalence of vitamin D deficiency in Germany and other mid-latitude countries (Cashman & Kiely 2016). Differences in the prevalence may be caused by factors that influence the endogenous vitamin D synthesis and, therefore, the vitamin D status. Some of them were determined in this study:

- **Season** was associated with vitamin D status in both **pregnant and breastfeeding women** in an adjusted model (factors see above), as previously shown in pregnant women (Vandevijvere et al. 2012; Rodriguez et al. 2016), breastfeeding women (Czech-Kowalska et al. 2015) and the general population (Richter et al. 2014; Rabenberg et al. 2015). The risk of 25(OH)D concentrations below 25.0 nmol/L in pregnant and breastfeeding women was lower in the summer (June - August) and autumn (September - November) months. This result may be originated from the limited endogenous synthesis in Germany during October and March (Engelsen et al. 2005). However, even in the summer months, when

sufficient vitamin D synthesis is feasible (Seckmeyer et al. 2013), 25(OH)D concentrations below 50.0 nmol/L were prevalent in approximately 64.0% of the pregnant and breastfeeding women.

- Higher **longitude of recruiting**, but not latitude, was related to a lower risk of 25(OH)D concentrations below 25.0 nmol/L in **pregnant and breastfeeding women** (even after adjustment: factors see above). However, previously results in Germany indicated that a lower latitude have a positive effect on the vitamin D status (Rabenberg et al. 2015) due to a higher UVB radiation availability in lower latitudes (O'Neill et al. 2016). The influence of longitude in this study may be explained by regional differences in the sunshine duration. Based on collected data of the German Meteorological Service (DWD 2013-2015), own calculations showed that the sunshine duration is higher in East Germany (higher longitude) than in West Germany (lower longitude).

Various other determinants may be also responsible for the higher prevalence of an inadequate vitamin D status in this study compared with other studies of European pregnant and breastfeeding women:

- **Vitamin D intake** and prevalence of **supplementation and fortification**: This study did not analyzed the dietary intake. However, in the general population, the vitamin D intake of German women is lower in comparison to other countries like Sweden (1.5 - 1.7 µg/day versus 6.7 µg/day) (DGE 2012; Brembeck et al. 2015). Besides, none of this study population supplemented vitamin D and only 6.5% of the German women in the general population take vitamin D supplements (average intake of 3.5 µg/day) (DGE 2012). In contrast, for example in Swedish breastfeeding women the prevalence of vitamin D supplementation is higher (31.0%) and also the resulting intake (average intake of 7.0 µg/day) (Brembeck et al. 2015). Moreover, there is no general vitamin D fortification in Germany thus far, even though it is authorized, whereas Sweden as well as other countries fortify certain foods with vitamin D (EC 2006).
- **Measurement method of the 25(OH)D concentration** also influences the vitamin D status (Koning et al. 2013). The prevalence of a sufficient vitamin D status could be higher than detected in this study due to the measurement of the 25(OH)D concentration by chemiluminescence immunoassay. This methodology underestimates the vitamin D status in comparison with the liquid chromatography-mass spectrometry method (Koning et al. 2013). However, the relative difference between the two measurement methods is uncertain (Cashman et al. 2016). Moreover, this circumstance affects all of the analyses and therefore does not influence the general result that pregnant and breastfeeding women had a lower vitamin D status compared with NPNB women.

Owing to the different factors that have an impact on the vitamin D status, the assessment of the vitamin D status is very complex. The influence of several other factors, such as recent holidays (Richter et al. 2014) or skin type (Webb & Engelsen 2006), were also determined in this study. However, no influence was detected. Moreover, other factors cannot be quantified in detail, for example, the residence outside, where time of day is important (Serrano et al. 2017).

3.2. Long-chain omega-3 fatty acid status in pregnant, breastfeeding and middle-aged women (*Papers III* and *IV*)

During pregnancy and breastfeeding period, LC n-3 PUFAs are essential, especially for the cognitive and visual development of the fetus and infant (Koletzko et al. 2008) and to reduce the risk of maternal postpartum depression (Markhus et al. 2013).

Moreover, several other positive effects are attributed to LC n-3 PUFAs, i.e., on the prevention of death from cardiovascular diseases (Harris & Schacky 2004), which is relevant due to the increasing prevalence of cardiovascular diseases in this age range (Mozaffarian et al. 2015).

Pregnant and breastfeeding women *(Paper III)*

- The average **DHA** level was **5.64 ± 1.43%** and the **omega-3 index** was **6.23 ± 1.48%**. For pregnant and breastfeeding women exist no omega-3 index reference values. There is an evidence that the risk for maternal postpartum depression is increased at an **omega-3 index of ≤ 5%** (Markhus et al. 2013), which was present in **22.1%** of these women. According to the classification of the LC n-3 PUFA status for the generally healthy population (Stark et al. 2016), a total of **87.1%** of the pregnant and breastfeeding women had **omega-3 index values below 8%**.
- The DHA level and omega-3 index were significantly **higher in pregnant women than in breastfeeding women** (DHA level: 6.10 ± 1.29% vs. 4.86 ± 1.31%; omega-3 index: 6.62 ± 1.39% vs. 5.57 ± 1.39%) and were **negatively associated** with the **gestation week** and **month of lactation**, respectively.

The LC n-3 PUFA status in this pregnant and breastfeeding women was similar to the results of previous studies (Markhus et al. 2013; Li et al. 2015; Markhus et al. 2015). Moreover, a cross-sectional (Li et al. 2015) and a longitudinal study (Al et al. 1995) also showed a decrease in the DHA level from the middle of pregnancy, which continues during the breastfeeding period until the 6 month postpartum (Markhus et al. 2015).

The additional requirement during pregnancy, especially at the end of gestation (Kuipers et al. 2012), could be a reason for the lower DHA level in breastfeeding women compared to

pregnant women. Moreover, in the breastfeeding period, the DHA loss via breast milk (about 100 mg/day) (Kent et al. 2006; Brenna et al. 2007; Brenna & Lapillonne 2009) is higher than in the last weeks of gestation, where the fetus accumulates approximately 40 mg/day DHA (Kuipers et al. 2012).

The current study measured only the relative LC n-3 PUFA status. However, even if the total lipid level increases during pregnancy (Mankuta et al. 2010), the absolute DHA level also decreases with the time of pregnancy (Li et al. 2015).

Middle-aged women *(Paper IV)*

- The average **DHA** level was **4.66 ± 1.01%** and the **omega-3 index** was **5.49 ± 1.17%**.
- A total of **62.8%** demonstrated a **low omega-3 index value (> 4 - 6%)**, and **high omega-3 index values (≥ 8%)** were only present in **2.7%** of the women.

The assessment of the LC n-3 PUFA status in both study collectives compared with previous studies

The results of the LC n-3 PUFA status in both collectives correspond with extrapolated data of German adults, where the LC n-3 PUFA is classified as very low (> 4 - 6%) (Stark et al. 2016). In a European-wide comparison of the general population, the LC n-3 PUFA status was lower in these both groups than the extrapolated LC n-3 PUFA status of other countries such as in Sweden and Finland, where a moderate omega-3 index (> 6 - 8%) is prevalent, or in Denmark and Norway, where the omega-3 index is high (> 8%) (Stark et al. 2016).

The plant n-3 PUFA intake in Germany is similar to these countries (Micha et al. 2014). However, the seafood **n-3 PUFA intake**, which reflects the EPA and DHA intake, is lower in German women compared to these countries. In Finland, the seafood n-3 PUFA intake is 450 - 549 mg/day, and in Denmark and Norway the intake is ≥ 550 mg/day (Micha et al. 2014). In contrast, the average intake of EPA and DHA of German women is less than 200 mg/day (DGE 2012) and therefore below the recommendations of at least 200 mg/day DHA alone or in combination with EPA (ISSFAL 2004; Koletzko et al. 2007; Kris-Etherton et al. 2007; EFSA 2010; D-A-CH 2015; DeSalvo et al. 2016).

The lower LC n-3 PUFA status in both groups could also be the result of a low prevalence of **LC n-3 PUFAs supplementation**. For example, a total of 56.0% of the general population in Norway supplement LC n-3 PUFAs (Saga et al. 2012). In this study, none of the middle-aged women took LC n-3 PUFA supplements, and in the pregnant and breastfeeding women, the prevalence of LC n-3 PUFA supplementation was 11.5%. In the general population of Germany, the prevalence of fish oil supplementation is below 1.0% (DGE 2012). Moreover, assuming that an omega-3 index ≥ 8% also applies for pregnant and breastfeeding women, a total of 59.0% of the pregnant and breastfeeding women in this study, who took the

recommended DHA supplementation (200 mg/day) (Koletzko et al. 2007; D-A-CH 2015), showed an omega-3 index below 8%. However, the beginning and regular intake of this supplementation was unknown.

Influencing factors on the LC n-3 PUFA status

Several factors were identified that affected the LC n-3 PUFA status:

- **Smoking** have a negative influence on the omega-3 index in **both study groups**, as shown previously, where smoking was inversely associated with the DHA level (Simon et al. 1996; Scaglia et al. 2016; Zaparoli et al. 2016) and omega-3 index (Block et al. 2008). Probably oxidative stress (Pasupathi et al. 2009) and a lower formation of PUFAs (Pawlosky et al. 1999) is responsible, but the exact effect of smoking is unknown.
- The influence of **age** was examined in **middle-aged women**, and was related with a higher EPA level and omega-3 index in women ≥ 50 years of age compared to women between 40 and 49 years of age. An increased intake of LC n-3 PUFAs with age is assumed to be the reason for the higher LC n-3 PUFA status (Harris et al. 2013). However, data of the German nutrition report demonstrated only a slightly higher intake of EPA and DHA in women 51 - 64 years of age in comparison with younger women (35 - 50 years) (EPA 65 versus 57 mg/day, DHA 119 versus 108 mg/day) (DGE 2012).
- **Hormonal contraceptive** users showed a lower EPA/ALA ratio and a higher DHA/EPA ratio in **middle-aged women** compared to women who did not use OCs. These findings might result from estrogen, which is suggested to increase the conversion from ALA to DHA by enhancement of the desaturation/elongation pathway (Burdge & Wootton 2002; Giltay et al. 2004; Kitson et al. 2013). A significant difference between the DHA level and omega-3 index were not detected in this study. Nevertheless, the probably positive effect of estrogen was shown in women who use hormonal replacement therapy (HRT) – their LC n-3 PUFA status did not vary from women who did not use hormones. This indicates that HRT is may be effective enough to compensate for the hormone deficiency during this life phase.

  The effect of estrogen may be also responsible for the higher prevalence of omega-3 index ≥ 8% in pregnant women (17.4%) than in middle-aged women (2.7%) and breastfeeding women (5.5%) due to the increase of the estrogen level during pregnancy (Schock et al. 2016).

3.3. Iron status in women of reproductive age (*Paper V*)

Iron is important in women of reproductive age due to menstruation-related iron losses (Napolitano et al. 2014) and the increased iron requirements in case of a potential forthcoming pregnancy (Bothwell 2000). The assurance of the iron status is challenging because several factors affect the iron status (Cable et al. 2012; Collings et al. 2013; Napolitano et al. 2014; Weinborn et al. 2015), and therefore the requirement of iron.

Main results and the assessment of iron status with previous studies

- An **inadequate iron status** was prevalent in **16.3 %** of the women (18 - 34 years). A total of **13.5%** demonstrated **iron deficiency without anemia** (ferritin < 20 µg/L, hemoglobin ≥ 12 g/dl), whereas **anemia** (Hb < 12 g/dL) was shown in **2.8 %**.
- The severe risk of **iron overload** (ferritin > 150 µg/L) was present in **1.1%** of the women.

A comparison with previous studies is difficult due to the inconsistent use of cutoffs for iron deficiency. The prevalence of iron deficiency in this study was possible lower compared to the most previous studies. For example, iron deficiency (ferritin < 12 µg/L) was prevalent in 20.0% of the Finnish women (< 50 years) (Lahti-Koski et al. 2003) and in 9.8% of the US women (18 - 49 years) (Miller 2014). Moreover, the prevalence of iron deficiency (ferritin < 15 µg/L) in Belgium women (18 - 39 years) was about 20.0% (Pynaert et al. 2007). In contrast, a total of 7.3% of the women in this study demonstrated ferritin concentration < 15 µg/L. It might be assumed that the prevalence of an inadequate iron status is lower in this study than detected due to the increase of ferritin during inflammation (Thurnham et al. 2010), however, therefore the sTfR concentration was measured.

With regarding to anemia, the cutoff agree between the studies (Hb < 12 g/dL). The prevalence of anemia was comparable with that of Danish women (2.2%) (Milman et al. 1998). However, the frequency was lower than in Belgian women (nearly 5.0%) (Pynaert et al. 2007), Finnish women (5.8%) (Lahti-Koski et al. 2003) and Portuguese women (30.5%) (Fonseca et al. 2016).

Factors that influence the iron status

The differences in the iron status in comparison with previous studies could also be explained by the many factors that influence the iron status. The following factors had an impact on the iron status in this study:

- **Dietary patterns** affect the iron status in this study, as shown previously (Haider et al. 2016). In omnivorous individuals in this study, the ferritin concentration was higher and the sTfR-F index was lower compared to vegetarians. This finding corresponds with the higher iron absorption in mixed-diet than in vegetarian diet (Hunt & Roughead 1999, Bach

Kristensen et al. 2005), which is possible due to the fact that plant foods contain iron inhibitors such as soy protein (Weinborn et al. 2015).

- **Blood donators** showed a higher prevalence of depleted iron stores than non-blood donators in this study. In previous studies, the prevalence of depleted iron stores (ferritin < 15 µg/L) in blood donators was between 39.0% and 50.0% (Booth et al. 2014; Rigas et al. 2014). Moreover, the sTfR-F index was also higher in blood donators of this study compared to non-blood donators, in such a way that a future iron imbalance could lead to an impaired erythropoiesis (Clark 2008).
- In the self-assessment of menstruation, a higher **amount of blood loss during menstruation** had an adversely effect on the iron status – ferritin concentration and sTfR-F index – in this study. These results were in accordance with recent findings where the collected menstruation blood loss had a negative impact on the ferritin level (Napolitano et al. 2014). Moreover, in this study, the ferritin concentration was also lower in the case of a shorter time frame since the last menstruation and a higher intensity of menstruation.
- The **use of OCs** was associated with a higher ferritin concentration in this study, which could be explained by shorter bleeding times (Milman et al. 1998) and less blood loss (Fraser et al. 2012) due to the use of OCs. However, the prevalence of depleted iron stores did not depend on OC use. The positive impact of OCs on the iron status only appears to be attributed with the use of OCs of micro pills (fourth progestin generation) like dienogest. These OCs have an antiandrogen activity (Schindler et al. 2003) that leads to a lower bleeding rate and rare intermenstrual bleeding (Golbs et al. 2002). In contrast, the OC of the second and third progestin generation had no influence on the iron status in this study, which is in accordance with a previous study that examined the influence of the OCs of the third progestin generation (Casabellata et al. 2007).

4. General conclusion and perspectives

The main results of this thesis are shown in **Figure 5**.

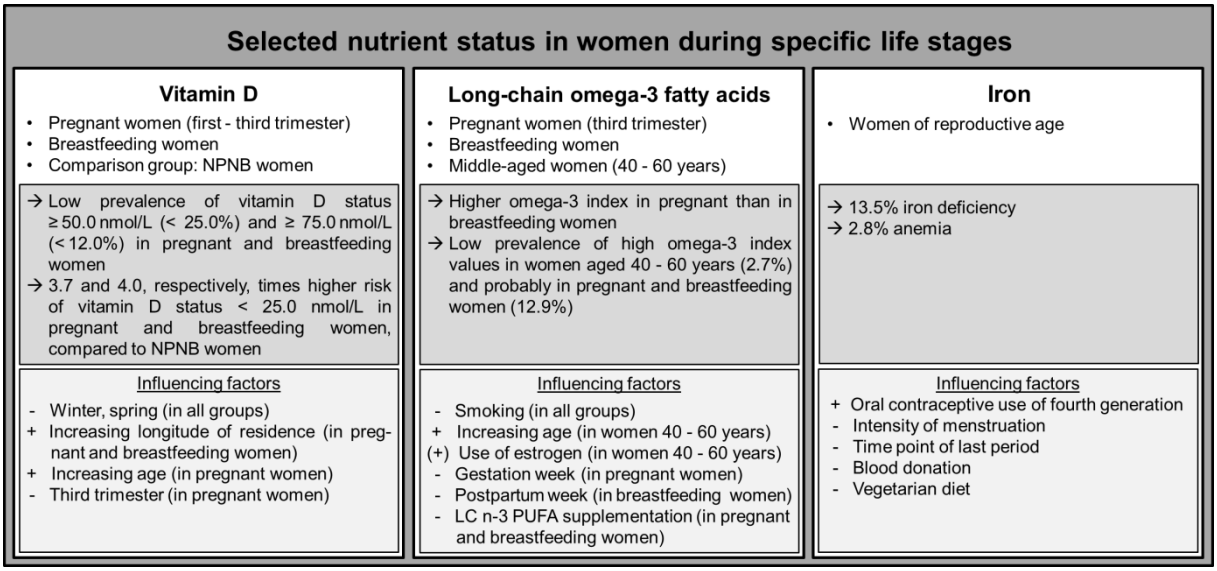

Figure 5 Status of specific nutrients in women during certain stages of life.

Abbreviations: -, negative influence; +, positive influence; (+), probably positive influence; anemia, hemoglobin < 12 g/dL; iron deficiency without anemia, ferritin < 20 µg/L and hemoglobin ≥ 12 g/dL; LC n-3 PUFA, long-chain omega-3 polyunsaturated fatty acids; NPNB, non-pregnant, non-breastfeeding women; omega-3 index, relative eicosapentaenoic acid and docosahexaenoic acid concentration in relation to the total fatty acids in erythrocyte membranes; high omega 3-index, omega-3 index ≥ 8%.

Pregnant and breastfeeding women demonstrated a high prevalence of an inadequate **vitamin D** status and are risk groups for vitamin D deficiency (25(OH)D < 25.0 nmol/L) compared to NPNB women (*Paper I* and *II*). Also, the majority of NPNB women showed a low vitamin D status. Firstly, the determination of the vitamin D status with the highest health advantage for these groups is required to ensure optimal health of mother, fetus and infant during pregnancy and breastfeeding period (Aghajafari et al. 2013; Zhu et al. 2014; Achkar et al. 2015; Lu et al. 2016). Nevertheless, the vitamin D status needs to be improved in most of these women, regardless of the target value (≥ 50.0 or ≥ 75.0 nmol/L). General strategies are required to ensure an adequate vitamin D status because foods contain only a small amount of vitamin D (Souci et al. 2015) and the endogenous vitamin D synthesis seems to be inadequate in this study population to ensure an adequate vitamin D status. As the use of sunscreen reduces the vitamin D synthesis capability (Matsuoka et al. 1987), one opportunity is the development of sunscreens that reduce erythema but also enhance the vitamin D synthesis. In vitro, the development of these sunscreens has been shown (Kockott et al. 2016). Another additional possibility is the vitamin D supplementation and fortification. The effectiveness of a vitamin D supplementation, which dose corresponds to the recommendation of DGE (20 µg/day), has been confirmed to achieve 25(OH)D concentrations ≥ 50.0 nmol/L in 99% of women of reproductive age (Pilz et al. 2017). In addition, a vitamin D fortification of staple food might be another opportunity to increase the

vitamin D status, as it has been shown in different interventions studies (Bakker et al. 2009; Black et al. 2012; Allen et al. 2015; Nikooyeh et al. 2016). Further studies are required to examine which foods are suitable to increase and maintain the vitamin D status. Furthermore, a correct selection of foods is necessary to ensure the improvement the vitamin D status of the whole population. Therefore, the EU-funded project “Food-based solutions for optimal vitamin D nutrition and health through the life cycle” has been initiated, which intention is the establishment of food-based strategies to avoid inadequate vitamin D status (Kiely et al. 2015).

The **LC n-3 PUFA** status is probably inadequate in the most pregnant and breastfeeding women (*Paper III*). Further studies are required to ascertain the accurate assessment of a favorable LC n-3 PUFA status during pregnancy and breastfeeding periods. In the majority of middle-aged women, the LC n-3 PUFA status is insufficient (*Paper IV*) and might be a risk factor for several health consequences, such as cardiovascular death (Harris & Schacky 2004). Therefore, the LC n-3 PUFA status in middle-aged women should be enhanced. Altogether, strategies should be developed to improve the LC n-3 PUFA status. The use of vegetable oils (source of ALA) does not appear to be sufficient (Egert et al. 2012; Salem & Eggersdorfer 2015) due to the limited conversion rate from ALA to DHA (Plourde & Cunnane 2007; Brenna et al. 2009). For this reason, reference values for the dietary intake of LC n-3 PUFAs are necessary. The consume of fish or a fish oil supplementation are supporting opportunities to improve the LC n-3 PUFA status. An intake of 1 g/day of fish or fish oil over 12 weeks increases the omega-3 index by an average of 1.01% and 1.70%, respectively (Brazionis et al. 2012). However, the present availability of fish oil and fish will not be sufficient to ensure a desirable LC n-3 PUFA status for the world population (Salem & Eggersdorfer 2015). Alternative sources of LC n-3 PUFAs are microalgae oil (Ryckebosch et al. 2014) or Antarctic krill (Gigliotti et al. 2011). An average microalgae oil intake of at least 2 g/day is already sufficient for the most microalgae species to ensure a daily consumption of 250 mg LC n-3 PUFA (Ryckebosch et al. 2014). Moreover, LC n-3 PUFAs fortification of foods is a further alternative to enhance the LC n-3 PUFA status (Egert et al. 2012).

The **iron** status in women of reproductive age was not worrying (*Paper V*). However, women in this life phase should still ensure the intake of sufficient iron in a highly available form to sustain the iron status, which is especially important when pregnancy is planned (Breymann 2015). Guidelines are necessary to instruct women about the different iron sources and their bioavailability.

Finally, educational work is required to inform the population about the critical supply situation with these nutrients and how these supply situation can be improved.

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Appendix II: Curriculum vitae

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