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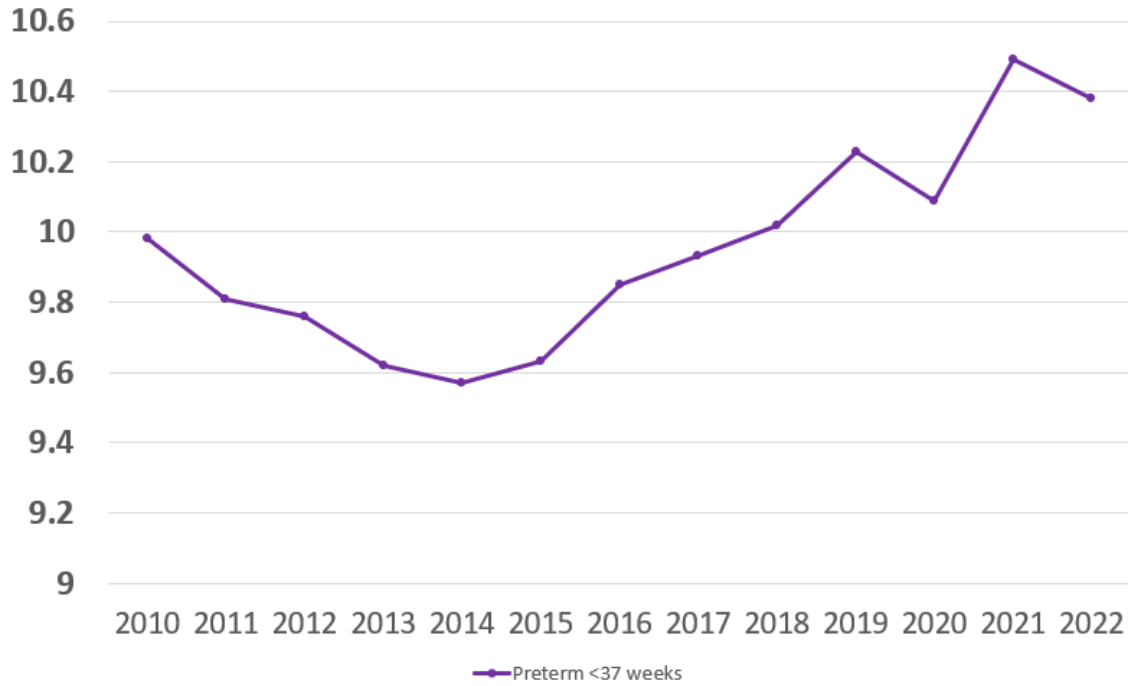
**September 26, 2024**

# New Consensus Clinical Practice Guidelines to Reduce Risk of Preterm Births

Susan E. Carlson, PhD

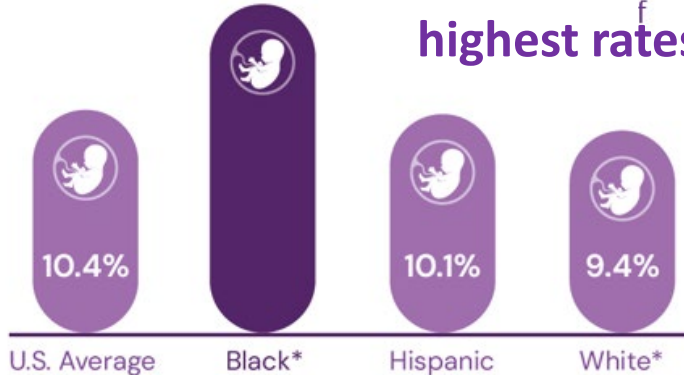
University of Kansas Medical Center

# US Preterm Birth Rates are on the Rise



Osterman 2024 CDC data

**14.6%** Non-Hispanic Black women have the highest rates of preterm birth



Pre-term Births as a percentage of births, 2022

\*Non-Hispanic

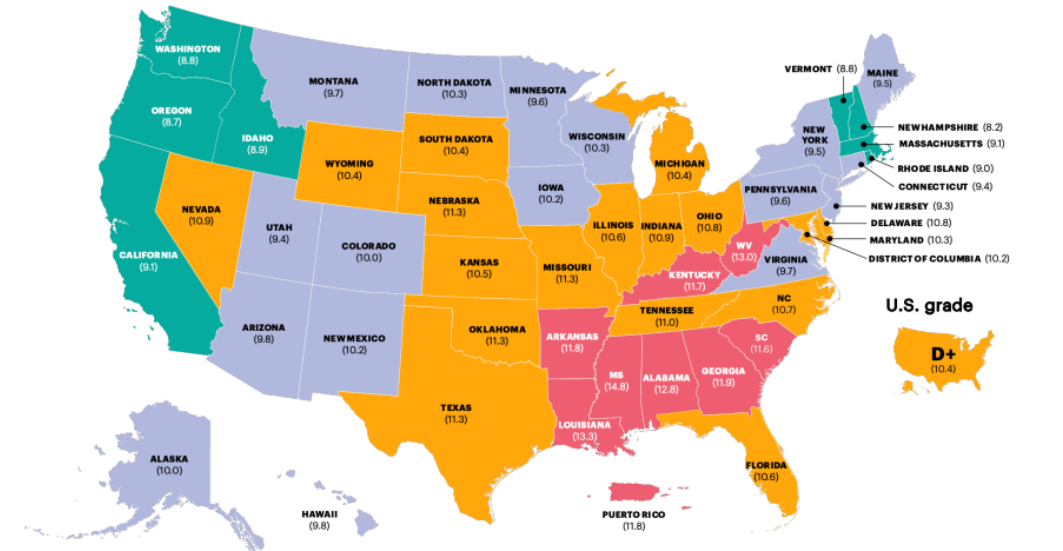
# March of Dimes grades the US a D+ for preterm birth



## 2023 MARCH OF DIMES REPORT CARD UNITED STATES

The preterm birth grade was **D+** in 2022; the worst grades occurred in the southern region of the U.S.

Preterm birth rate (born before 37 weeks gestation) and grade by state, 2022



### GRADE AND PRETERM BIRTH RATE

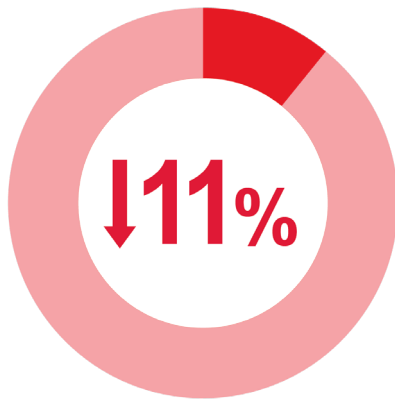
<b>A</b>	<b>A-</b>	<b>B+</b>	<b>B</b>	<b>B-</b>	<b>C+</b>	<b>C</b>	<b>C-</b>	<b>D+</b>	<b>D</b>	<b>D-</b>	<b>F</b>
7.7% or less	7.8 to 8.1%	8.2 to 8.5%	8.6 to 8.9%	9.0 to 9.2%	9.3 to 9.6%	9.7 to 10.0%	10.1 to 10.3%	10.4 to 10.7%	10.8 to 11.1%	11.2 to 11.4%	11.5% or greater

# A 2018 Cochrane Review Found Strong Evidence Omega-3 Fatty Acids Reduce Preterm Birth (PTB) and Early PTB

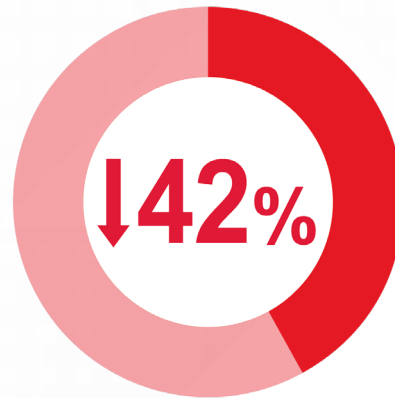
## Omega-3 supplementation during pregnancy\*

**PTB <37 weeks:** 10,304 participants

**Early PTB <34 weeks:** 5,204 participants



High quality evidence for an **11% reduction**



High quality evidence for a **42% reduction**

Two new trials conducted after prenatals with DHA were marketed found it was those with low intake at enrollment who benefited with lower early PTB

However, when added to the Cochrane Review the evidence remained strong for both PTB and early PTB

**High quality evidence means no further research trials are necessary to show causality**

\*Middleton et al., Omega-3 fatty acid supplementation during pregnancy, Cochrane Review 2018.

## DHA intake is very low among US pregnant women

- DHA found in few food sources
- Intake is low in those who do not consume seafood or take a supplement
- ACOG and DGA recommend 8 to 12 oz of seafood/week (equivalent to 200-250 mg/day of DHA)
- Some organizations recommend 200-250 mg/d DHA
- **However, 0%** of the 1180 pregnant women in an NHANES survey analysis consumed at least 8oz of seafood per week\*
- The usual DHA intake is between 54\*\* and 84\*\*\* mg/day

Food	DHA (mg)
3 oz pink salmon	638
3 oz white tuna	535
3 oz crab	196
12 large shrimp	96
3 oz tuna salad	47
2 pieces chicken	37
1 large egg	19-50

USDA, ARS 2003; USDA Nutrient Database for Standard Reference. Release 16.

\* Zhang Z, Fulgoni III, VL, Kris-Etherton PM, Mitmesser SA. Nutrients 2018; 10:416

\*\*Benisek D et al., J Am Coll Nutr 1999;18:543-4; \*\*\*Crawford SA et al., Nutrients 2023;15:3228

# Can DHA intake be used instead of a blood sample?

- A validated 7-question food frequency questionnaire (DHA-FFQ) provides an estimate of DHA intake in pregnancy\*
- The 7 questions ask amount and frequency of intake of fish (in 3 categories of DHA content), egg yolk, chicken, liver and supplements containing DHA.
- Women in two RCTs (n=1305) completed the DHA-FFQ. Baseline intake <150 mg/day benefited from high dose supplementation.



<https://redcap.kumc.edu/surveys/?s=M3CDMMKK9X3TWCPY>

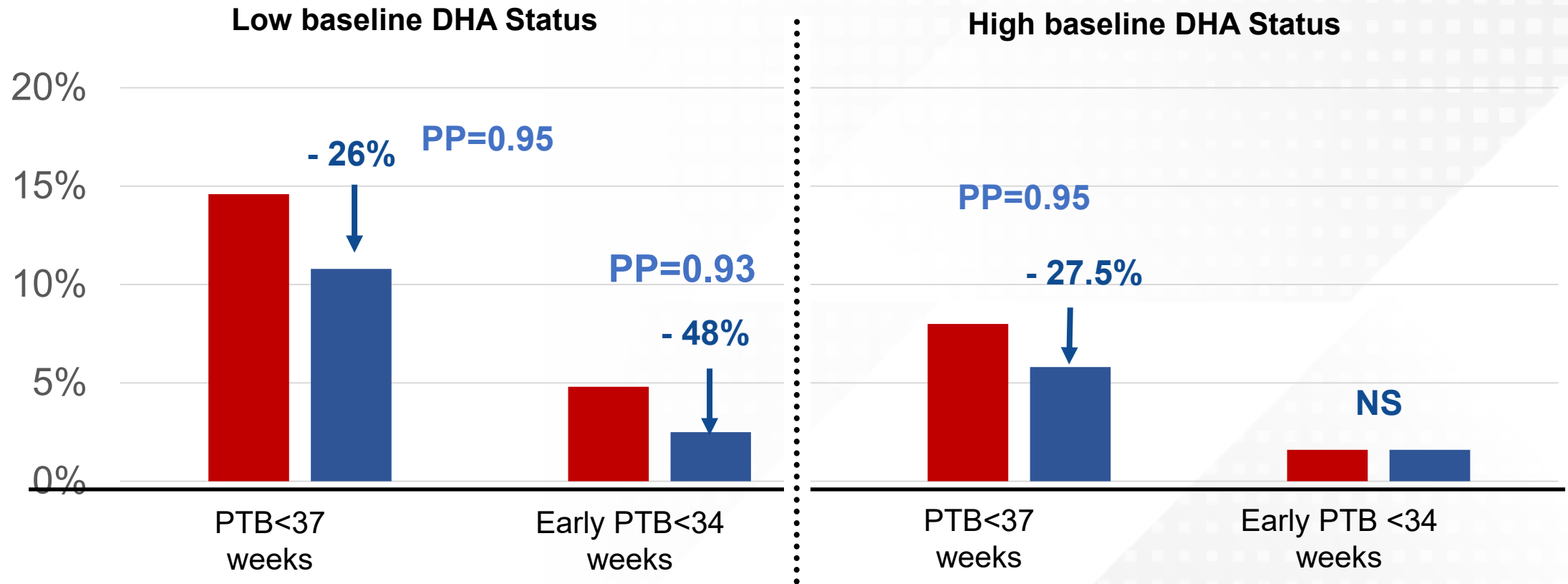
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\*Crawford et al., PLEFA 2022 (PMC8825687); Christifano et al., PLEFA 2022 (PMC8825685)

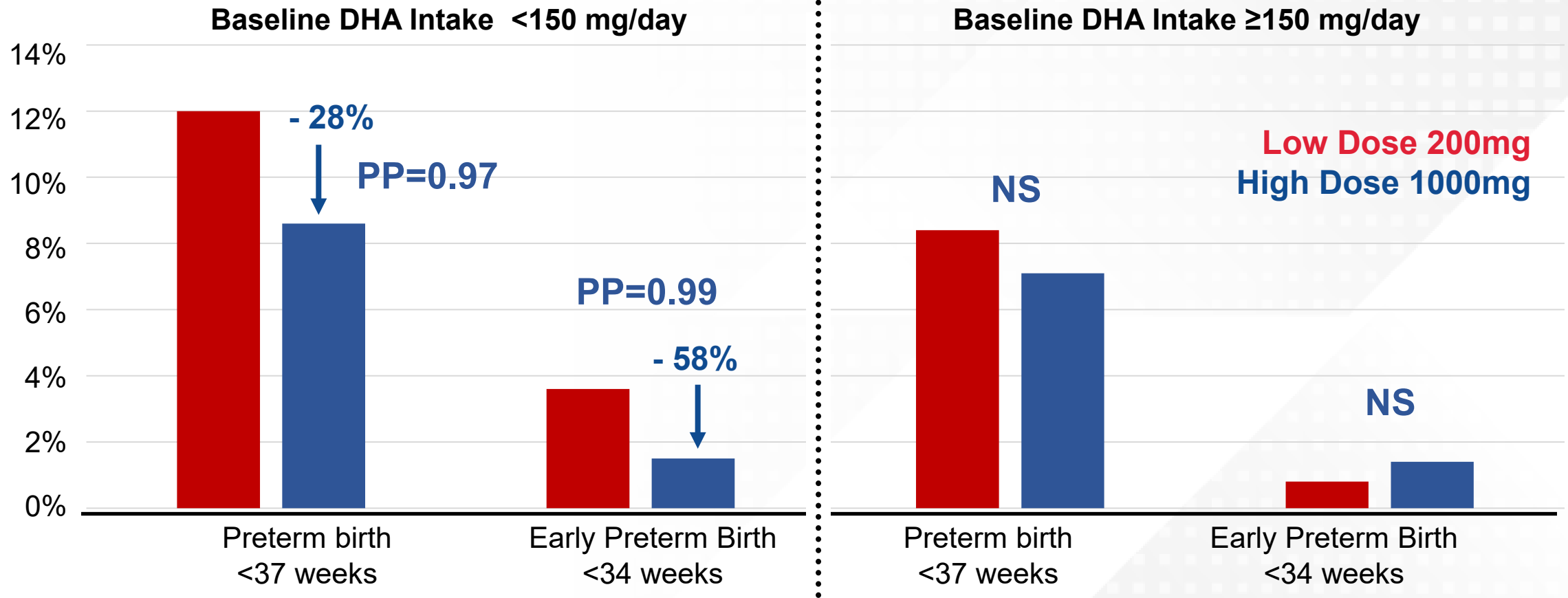
# PTB and Early PTB by Baseline DHA Status and Assigned DHA Dose

Low Dose 200mg  
High Dose 1000mg



From Carlson et al., Higher dose docosahexaenoic acid supplementation during pregnancy and early preterm birth: A randomized, double-blind, adaptive-design superiority trial. EclinMed 36(2021) 100905. Low baseline status defined as <6% RBC-PL-DHA

# If baseline DHA Intake was <150 mg/day per the FFQ, high dose DHA reduced PTB and EPB compared to a low dose



Christifano et al., Clin Nutr ESPEN 2023;53:93-99. Participants from ADORE and PANDA trials are included (n=1310)



# Clinical practice guideline development

- **Charitable Child Health Foundation**/Stiftung Kindergesundheit at LMU Univ. Hospitals Munich, agreed to organize & support guideline development
- **Steering committee:** Prof. Irene Cetin, Univ. Milan; Prof. Susan Carlson, Univ. Kansas; Prof. Berthold Koletzko, Univ. Munich
- **Scientific manager:** Dr. Franziska Feldi

# Guideline Published in February 2024

Expert Review

## Omega-3 fatty acid supply in pregnancy for risk reduction of preterm and early preterm birth



### Seven organizations already back the guideline

1. European Board & College of Obstetrics and Gynaecology
2. European Academy of Paediatrics
3. European Society for Paediatric Research
4. Asia Pacific Health Association (Pediatric-Neonatology Branch)
5. International Society for Developmental Origins for Health and Disease
6. Child Health Foundation (Stiftung Kindersgesundheit)
7. European Foundation for the Care of Newborn Infants (Parent Organization)

### 24 Authors from 15 countries & all continents



# Methods

- Steering committee, scientific manager and a guideline group member reviewed available publications, drafted a summary of the evidence, questions, and proposed conclusions
- Consensus meeting on May 5, 2023 discussed/revised outline and conclusions, followed by further written comments and suggestions
- Anonymous voting on 10 proposed conclusions
- Subsequent additional voting on an 11<sup>th</sup> conclusion (addressing informing of women and their partners, developed during the further discussions)

# Definition of Consensus based on voting results

Rating	Support by
Strong consensus	>95%
Consensus	> 75-95%
Majority approval	>50-75%
Not supported	<50%

*Based on medical guideline standards of the German Working Group of Medical Scientific Societies (Arbeitsgemeinschaft-der-Wissenschaftlichen-Medizinischen-Fachgesellschaften. Ständige Kommission „Leitlinien“ der Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF). Das AWMF-Regelwerk Leitlinien. AWMF, Marburg, 2020. Version 2.0. . Marburg: AWMF-Institut für Medizinisches Wissensmanagement. 2020.) and adopted by European learned societies (Bischoff SC, Singer P, Koller M, Barazzoni R, Cederholm T, van Gossum A. Standard operating procedures for ESPEN guidelines and consensus papers. Clin Nutr. 2015;34(6):1043-51.)*

1. Intakes of **up to 1000 mg/day of DHA & EPA**, or of **up to 1000 mg/day of DHA alone**, do not raise safety concerns in the general population and in pregnant women (*Consensus, supported by 89.5%*)

## Conclusions 1-3

2. Observational studies and randomized controlled trials in pregnant women show **lower intakes of fish** and **lower blood levels of the omega-3 fatty acids DHA and EPA** found in fish associated with a **significantly increased risk of preterm and early preterm birth** (*Consensus, 85%*)

3. **Women of childbearing age** should aim to obtain a **regular supply** of omega-3 fatty acids from foods providing these fatty acids, including fish and **oily fish**, and/or from **supplements providing DHA & EPA, or DHA alone** (*Strong consensus, 100%*)



# Conclusions 4-5



4. For the general population, including **women in their childbearing years**, a regular intake of **at least 250 mg/day DHA plus EPA**, as recommended by the European Food Safety Authority, is desirable (*Strong consensus, 100%*)

5. For **pregnant women**, an **additional intake of at least 100-200 mg DHA/day**, as recommended by the European Food Safety Authority, is desirable (*Strong consensus, 100%*)

# Conclusions 6-8

6. Pregnant women with **low DHA intake** and/or **low DHA blood levels** are at increased risk of preterm and early preterm birth and should receive a regular supply of **about 600-1000 mg/day of DHA plus EPA, or DHA alone**, based on results of randomized controlled trials demonstrating significant reduction in preterm and early preterm birth (*Consensus, 90%*)

7. This additional supply should preferably **begin in the 2<sup>nd</sup> trimester** of pregnancy and **not later than ~20 weeks** of gestation (*Consensus, 85%*)

8. High dose supplementation with the goal of risk reduction for preterm birth should continue as long as there is a risk of preterm birth, i.e. **until about 37 weeks** of gestation, **or until childbirth** if before 37 weeks (*Consensus 80%*)





# Conclusions 9-11

9. Identification of women at increased risk of preterm and early preterm birth due to low DHA intake and/or low DHA blood levels is achievable by screening with a **few questions on dietary intake** of foods rich in DHA and EPA and on use of omega-3 supplements (*Consensus, 90%*)



10. DHA measurement from a **blood lipid component** is an additional option to identify women with low status, however **further standardization of laboratory methods and of appropriate cutoff values** is needed (*Consensus, 85%*)



11. It is important to provide women of childbearing age, **pregnant women and their partners** with **evidence-based information**, preferably both verbally and in writing, on how to achieve an appropriate intake of DHA or DHA + EPA for women of childbearing age and pregnant women (*Strong consensus, 100%*)

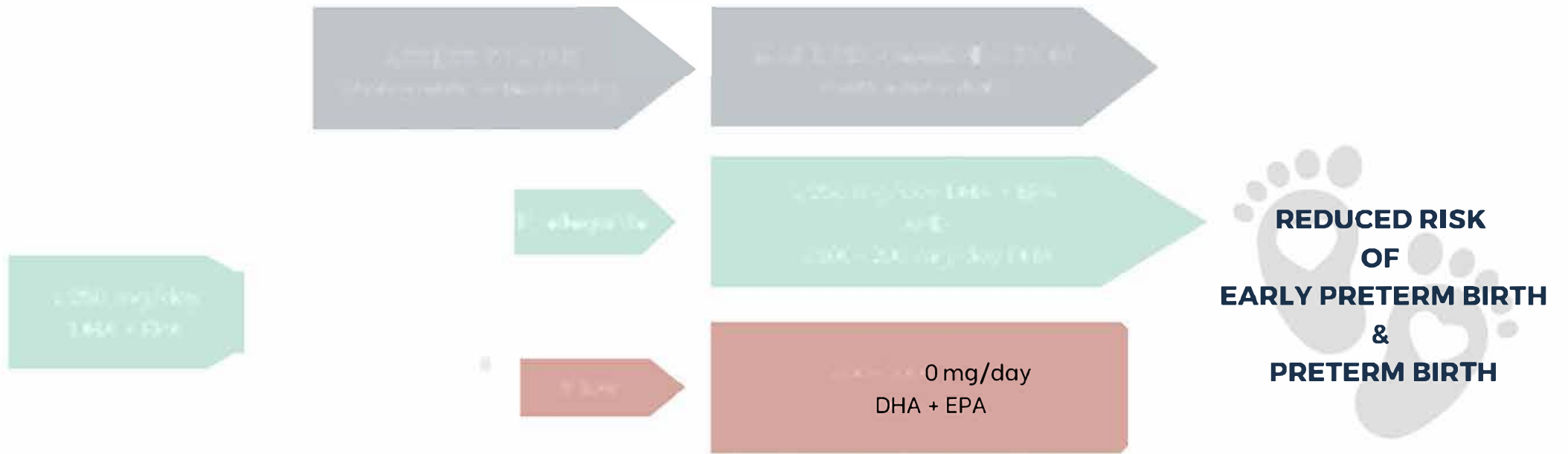


TABLE 1

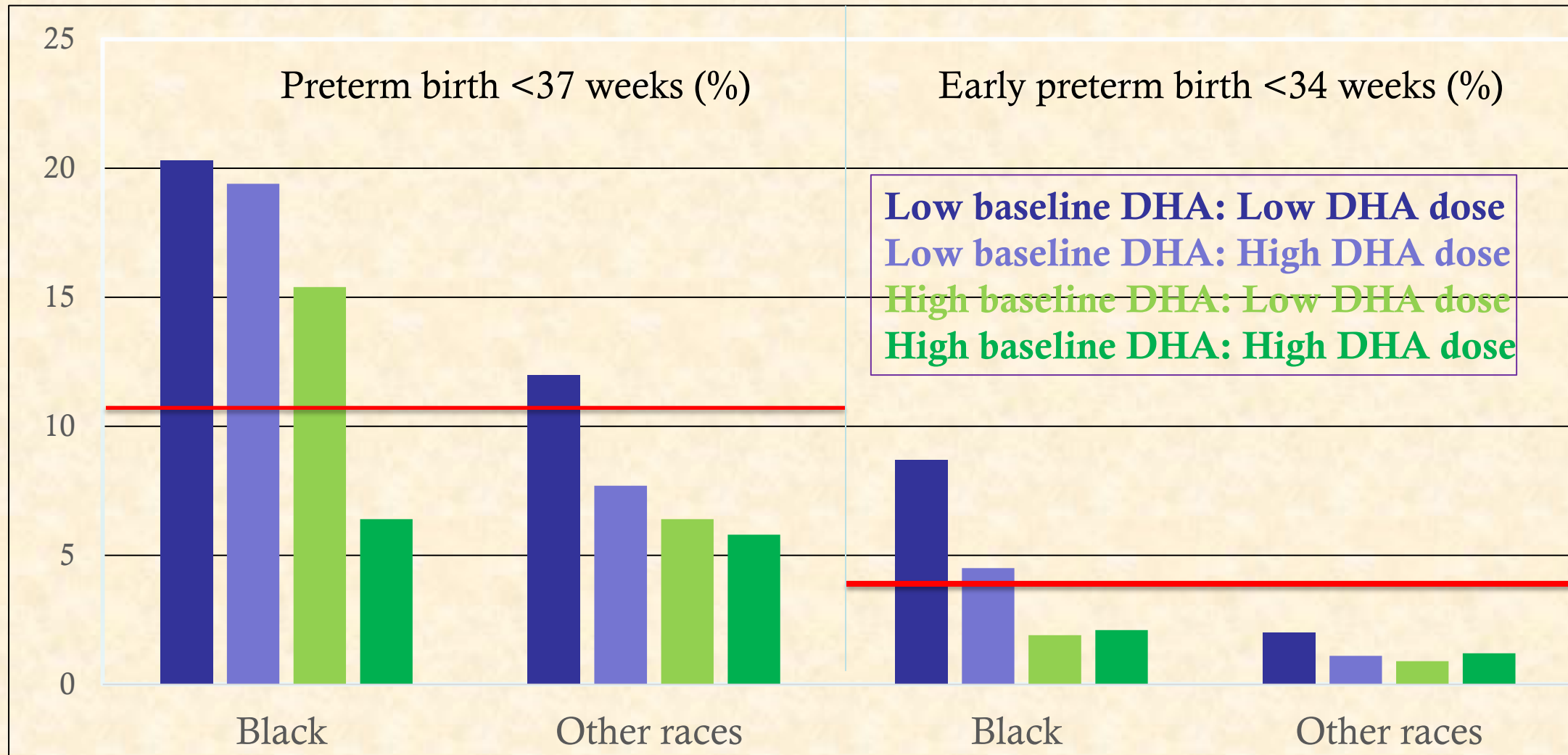
## Categories of selected foods based on content of omega-3 eicosapentaenoic and docosahexaenoic acid (mg/100 g)

>1000 mg/100 g	500–1000 mg/100 g	250–500 mg/100 g	<250 mg/100 g
Herring (Atlantic, kippered): 2150	Sardine (Atlantic, canned): 982	Carp (cooked): 451	Grouper (mixed species, cooked): 248
Salmon (Atlantic, farmed, cooked): 2150	Bass (striped, cooked): 967	Pike (walleye, cooked): 398	Halibut (Atlantic and Pacific, cooked): 235
Anchovy (European, canned): 2052	Trout (mixed species, cooked): 936	Pollock (Alaska, cooked): 333	Liver, beef (grass-fed): 234
Herring (Atlantic, cooked): 2009	Salmon (sockeye, cooked): 859	Tuna (skipjack, cooked): 328	Cod (Atlantic, cooked): 158
Mackerel (Pacific and jack, cooked): 1853	Bass (fresh water, mixed species, cooked): 763	Liver, lamb (grass-fed): 326	Tilapia (cooked): 135
Salmon (Atlantic, wild, cooked): 1841	—	Perch (mixed species, cooked): 324	Tuna (fresh, yellowfin, raw): 100
Mackerel (Spanish, cooked): 1246	—	Hake (frozen, cooked): 280	Catfish (farmed, cooked): 89
Gilthead bream: 1160	—	Tuna (light, canned): 270	Cod (Pacific, cooked): 80
Salmon (coho, wild, cooked): 1059	—	—	Eggs (chicken, whole, cooked): 58
—	—	—	Chicken, dark meat (roasted): 50

Data extracted from Supplemental Table.<sup>39-41</sup>



# High baseline DHA and Randomization to High dose DHA Eliminated Much of the Racial Disparity in Preterm and Early Preterm Birth



# Key Takeaways

- The March of Dimes gives the US a D+ for preterm births (PTB).
- 1 in 10 babies in the US is a PTB, but 14.8% of Non-Hispanic Black women have a PTB. Most Black women appear to need high dose DHA to reduce PTB.
- New consensus statements published in the American Journal of Obstetrics and Gynecology - Maternal Fetal Medicine outlines intakes of omega-3s EPA+DHA to reduce risk of PTB  
[https://www.ajogmfm.org/article/S2589-9333\(23\)00393-2/fulltext](https://www.ajogmfm.org/article/S2589-9333(23)00393-2/fulltext)
- Low consumers provided 600-1000mg/day of omega-3s EPA+DHA from seafood, fish oil, algal oil could reduce risk of the earliest PTB by 2/3rds.
- Adopting these guidelines could save the US more than \$8B/year in healthcare costs.
- We need to get this information to expectant moms in the US to give all babies a healthy start to life!

# Omega-3 supplementation to reduce risk of preterm birth: New global expert clinical practice guideline

- Assess your DHA intake with our Food Frequency Questionnaire

