

Table 1. ST2 Levels on Day 14 after Transplantation in Three Cohorts of Patients.*

Condition	Cohort 1 (N=95)		Cohort 2 (N=110)		Cohort 3 (N=107)	
	Median Values	P Value	Median Values	P Value	Median Values	P Value
TA-TMA vs. no TA-TMA	96.6 ng/ml vs. 53.4 ng/ml	0.02	199.7 ng/ml vs. 99.7 ng/ml	0.03	81.3 ng/ml vs. 40.3 ng/ml	<0.001
Acute GVHD vs. no acute GVHD	118.6 ng/ml vs. 58.3 ng/ml	0.29	112.2 ng/ml vs. 90.7 ng/ml	0.62	76.7 ng/ml vs. 49.7 ng/ml	0.007
Nonrelapse death vs. no nonrelapse death at 6 mo	NA	NA	263.4 ng/ml vs. 104.9 ng/ml	0.009	290.3 ng/ml vs. 50.7 ng/ml	0.001

* Cohort 1 includes patients who had survived for at least 1 year after hematopoietic stem-cell transplantation (HSCT). Cohort 2 includes consecutive patients who had undergone HSCT from November 2010 through May 2014 who were not included in cohort 1. Cohort 3 includes consecutive patients who had undergone HSCT from June 2014 through October 2016 and who were not included in cohort 1. All the analyses were performed with the use of enzyme-linked immunosorbent assay (plasma R&D Systems ELISA in cohorts 1 and 3 and serum Critical Diagnostics ELISA in cohort 2). GVHD denotes graft-versus-host disease, NA not applicable, and TA-TMA transplant-associated thrombotic microangiopathy.

patients with GVHD might be mistakenly classified as glucocorticoid-resistant GVHD, perhaps leading to the reported association between the condition and elevated ST2 levels. In our clinical experience, specific treatment of both TA-TMA and GVHD is needed for full resolution of symptoms when both disease processes are present. We would propose that the careful evaluation of transplant recipients with glucocorticoid-resistant GVHD for signs of TA-TMA might identify additional therapeutic options.

Seth J. Rotz, M.D.

Christopher E. Dandoy, M.D.

Stella M. Davies, M.B., B.S., Ph.D.

Cincinnati Children's Hospital Medical Center
Cincinnati, OH
stella.davies@cchmc.org

Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

1. Vander Lugt MT, Braun TM, Hanash S, et al. ST2 as a marker for risk of therapy-resistant graft-versus-host disease and death. *N Engl J Med* 2013;369:529-39.
2. Jodele S, Davies SM, Lane A, et al. Diagnostic and risk criteria for HSCT-associated thrombotic microangiopathy: a study in children and young adults. *Blood* 2014;124:645-53.
3. Dietrich S, Falk CS, Benner A, et al. Endothelial vulnerability and endothelial damage are associated with risk of graft-versus-host disease and response to steroid treatment. *Biol Blood Marrow Transplant* 2013;19:22-7.
4. Changsirikulchai S, Myerson D, Guthrie KA, McDonald GB, Alpers CE, Hingorani SR. Renal thrombotic microangiopathy after hematopoietic cell transplant: role of GVHD in pathogenesis. *Clin J Am Soc Nephrol* 2009;4:345-53.
5. Rachakonda SP, Penack O, Dietrich S, et al. Single-nucleotide polymorphisms within the thrombomodulin gene (THBD) predict mortality in patients with graft-versus-host disease. *J Clin Oncol* 2014;32:3421-7.

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Fish Oil in Pregnancy and Asthma in Offspring

TO THE EDITOR: Bisgaard et al. (Dec. 29 issue)¹ report a significant reduction of early childhood asthma and wheeze after fish-oil supplementation during the third trimester of pregnancy in women without endocrine, heart, or kidney disorders. A positive family history of asthma is an established risk factor for the development of childhood asthma.² Therefore, we would like to know how many of the pregnant women in the two study groups had a history of asthma or wheeze or had active asthma or wheeze during their preg-

nancy, because a skewed distribution of asthma or wheeze among study probands may have influenced the study results. Also, how many women gave fish-oil supplements to their children during the postintervention surveillance period of 5 years, especially since the study participants were made aware of group assignment after 3 years?

Clemens Tempfer, M.D.

Ruhr University Bochum
Bochum, Germany
clemens.tempfer@rub.de

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1. Bisgaard H, Stokholm J, Chawes BL, et al. Fish oil–derived fatty acids in pregnancy and wheeze and asthma in offspring. *N Engl J Med* 2016;375:2530-9.
2. Fuchs O, Bahmer T, Rabe KF, von Mutius E. Asthma transition from childhood into adulthood. *Lancet Respir Med* 2016 September 22 (Epub ahead of print).

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TO THE EDITOR: In a large, well-conducted trial, Bisgaard et al. found that supplementation with n–3 long-chain polyunsaturated fatty acids (LCPUFAs) during pregnancy reduces the risk of persistent wheeze and asthma in offspring during the first 5 years of life. These results support the use of new primary prevention strategies to reduce the burden of respiratory disease. Remarkably, the placebo given to the control group was olive oil, which has known antiinflammatory, antioxidant, and nutrigenomic properties^{1,2} and has been shown to reduce the risk of wheezing in offspring when ingested during pregnancy.³ Olive oil is a key component of the Mediterranean diet, which is associated with a reduced risk of asthma in children.⁴

We wonder whether the use of olive oil instead of a placebo containing no fatty acids could have led to an underestimation of the effect of LCPUFAs in this study. The number needed to treat might also have been lower than 14.6 for the general population, making a stronger case for consideration of the use of LCPUFAs as part of a primary prevention strategy.

Eugenio Baraldi, M.D.

Alfonso Galderisi, M.D.

University of Padua
Padua, Italy
eugenio.baraldi@unipd.it

No potential conflict of interest relevant to this letter was reported.

1. Ciceralo S, Lucas LJ, Keast RS. Antimicrobial, antioxidant and anti-inflammatory phenolic activities in extra virgin olive oil. *Curr Opin Biotechnol* 2012;23:129-35.
2. Piroddi M, Albini A, Fabiani R, et al. Nutrigenomics of extra-virgin olive oil: a review. *Biofactors* 2017;43:17-41.
3. Castro-Rodriguez JA, Garcia-Marcos L, Sanchez-Solis M, Pérez-Fernández V, Martínez-Torres A, Mallol J. Olive oil during pregnancy is associated with reduced wheezing during the first year of life of the offspring. *Pediatr Pulmonol* 2010;45:395-402.
4. Garcia-Marcos L, Castro-Rodriguez JA, Weinmayr G, Panagiotakos DB, Priftis KN, Nagel G. Influence of Mediterranean diet on asthma in children: a systematic review and meta-analysis. *Pediatr Allergy Immunol* 2013;24:330-8.

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TO THE EDITOR: Bisgaard et al. found that supplementation with high doses of fish oil (2.4 g per day) in women in the third trimester of pregnancy reduces the absolute risk of persistent wheeze or asthma and infections of the lower respiratory tract in offspring by approximately 7%. In the accompanying editorial, Ramsden correctly warns against applying such high doses until long-term follow-up has been conducted.¹

Neither the authors nor Ramsden mention the potential increased risk of such supplementation in cases of extreme premature delivery. Fish oil inhibits platelet function and affects hemostasis.² These properties might be harmful in infants with extremely low birth weight who already have deranged coagulation profiles.³ Furthermore, intraventricular hemorrhage is a feared complication in these infants. Since infants with extremely low birth weight constitute 1 to 1.5% of all pregnancies, the study by Bisgaard et al. did not have the power to detect such a complication. The potential increased risk in case of extreme premature delivery should be taken into account when designing future studies in which pregnant women receive supplements with high doses of fish oil.

Ola D. Saugstad, M.D., Ph.D.

University of Oslo
Oslo, Norway
odsaugstad@rr-research.no

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1. Ramsden CE. Breathing easier with fish oil — a new approach to preventing asthma? *N Engl J Med* 2016;375:2596-8.
2. Wachira JK, Larson MK, Harris WS. n-3 Fatty acids affect haemostasis but do not increase the risk of bleeding: clinical observations and mechanistic insights. *Br J Nutr* 2014;111:1652-62.
3. Neary E, Okafor I, Al-Awaysheh F, et al. Laboratory coagulation parameters in extremely premature infants born earlier than 27 gestational weeks upon admission to a neonatal intensive care unit. *Neonatology* 2013;104:222-7.

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THE AUTHORS REPLY: We concur with Tempfer that maternal asthma is one of the strongest risk factors for childhood asthma, a trend that was replicated in our study (see Table S4 in the Supplementary Appendix, available with the full text of the article at NEJM.org). As reported (see Table S2 in the Supplementary Appendix of the article), there was a slightly lower prevalence of asthma among mothers in the treatment group than

among those in the placebo group (24.1% vs. 28.1%). However, the association between the fish-oil intervention and asthma in offspring remained statistically significant in analyses that adjusted for the main risk factors for asthma, including maternal asthma (Table S11 in the Supplementary Appendix of the article).

Previous observational and randomized studies suggest that prenatal rather than postnatal fish-oil exposure is an important factor in the risk of asthma among offspring, and we did not collect data on postnatal fish-oil supplementation. However, we believe that such supplementation is not likely to have biased the results of the trial. First, the treatment effect was largely unchanged before and after participants were made aware of group assignment. Second, one would expect that any increased postnatal intake in children that resulted from parents' knowledge of the study results would have occurred in the placebo group and would have been more likely to result in an underestimation of the treatment effect (type 2 error).

We agree with Baraldi and Galderisi that hypothetically, any protective effect from olive oil (the placebo) could in principle have caused an underestimation of the protective effect of LCPUFAs. The choice of olive oil as placebo was based on the assumption that this is a safe supplement with no significant health effects when taken in addition to a normal "westernized" diet. The amount of oleic acid (the main constituent of olive oil) provided in our study corresponds to only approximately 16% of the normal intake in Danish women (3 g per day vs. 19 g per

day),¹ and the amount of linoleic acid, which may have a proinflammatory effect owing to the processing of arachidonic acid, corresponds to less than 5% of the normal daily intake (0.4 g per day vs. 9 g per day).¹ We would not expect such small relative changes to affect disease risk.

We agree with Saugstad that the risk of rare adverse events cannot be ruled out and should be carefully monitored in future trials and at the population level. In relation to preterm birth and low birth weight, it has been hypothesized that fish-oil supplementation during pregnancy might prevent both outcomes. A recent systematic review of 21 randomized, controlled trials suggested that fish-oil supplementation during pregnancy reduces the risk of both preterm delivery and low birth weight.² It is therefore possible that the positive effect in relation to preterm birth might outweigh the potential for an increased risk of hemorrhage.

Hans Bisgaard, M.D., D.M.Sc.

Klaus Bønnelykke, M.D., Ph.D.

Copenhagen Prospective Studies on Asthma in Childhood
Copenhagen, Denmark
bisgaard@copsac.com

Since publication of their article, the authors report no further potential conflict of interest.

1. Hulshof KF, van Erp-Baart MA, Anttolainen M, et al. Intake of fatty acids in western Europe with emphasis on trans fatty acids: the TRANSFAIR Study. *Eur J Clin Nutr* 1999;53:143-57.

2. Chen B, Ji X, Zhang L, Hou Z, Li C, Tong Y. Fish oil supplementation improves pregnancy outcomes and size of the newborn: a meta-analysis of 21 randomized controlled trials. *J Matern Fetal Neonatal Med* 2016;29:2017-27.

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Genetic Risk, Lifestyle, and Coronary Artery Disease

TO THE EDITOR: In their assessment of cardiovascular risk, Khera et al. (Dec. 15 issue)¹ include single-nucleotide polymorphisms that are associated with lipid levels in the genetic risk score, even though lipid levels are included in conventional risk-prediction equations for coronary heart disease. Furthermore, the score was not scaled to the average population risk by taking into account the distribution of the risk alleles in the population.² In the example provided in Table S2 in the Supplementary Appendix of the article

(available at NEJM.org), the person has two risk alleles at the 9p21 locus (rs4977574). The reported odds ratio for the risk allele (G) at this locus is 1.29, and the odds ratio for two risk alleles (as compared with AA) is 1.665. However, if one considers the risk-allele frequency (0.49), then the odds ratio for this locus in the general population is 1.304 (Fig. 1), and the scaled odds ratio for GG (as compared with the population average) is 1.665 divided by 1.304, or 1.277. Such refinements will be important when a genetic risk