HHS Public Access

Author manuscript

Neonatology. Author manuscript; available in PMC 2019 March 07.

Published in final edited form as:

Neonatology. 2018 ; 113(4): 366–378. doi:10.1159/000487388.

Update on Vitamin E and its Potential Role in Preventing or Treating Bronchopulmonary Dysplasia

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Abstract

Vitamin E is obtained only through the diet and has a number of important biological activities, including functioning as an antioxidant. Evidence that free radicals may contribute to pathological processes such as bronchopulmonary dysplasia (BPD), a disease of prematurity associated with increased lung injury, inflammation and oxidative stress, led to trials of the antioxidant vitamin E (α-tocopherol) to prevent BPD with variable results. These trials were all conducted at supraphysiologic doses and two of these trials utilized a formulation containing a potentially harmful excipient. Since 1991, when the last of these trials was conducted, both neonatal

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Disclosures: The authors have no financial relationships relevant to this article to disclose.

Ethical Approval: Not applicable, review of the literature

Conflict of Interests: The authors have no conflicts of interest to disclose.

Contributors' Statement:
Dr. Stone and Dr. Hartert: conceived of the topic for review, conducted literature searches and research, wrote the paper, have primary responsibility for final content
Dr. McEvoy, Dr. Aschner, and Dr. Walsh: conducted literature searches and research, edited paper, contributed to paper's neonatology content
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Dr. Rosas-Salazar and Dr. Moore- conducted literature searches and research, contributed to paper's pulmonology content
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All authors read and approved the final manuscript.

management strategies for minimizing oxygen and ventilator related lung injury and our understanding of vitamin E isoforms in respiratory health have advanced substantially. It is now known that there are differences between the effects of vitamin E isoforms α-tocopherol and γ-tocopherol on the development of respiratory morbidity and inflammation. What is not known is whether improvements in physiologic concentrations of individual or combinations of vitamin E isoforms during pregnancy or following preterm birth might prevent or reduce BPD development. The answers to these questions require adequately powered studies targeting pregnant women at risk of preterm birth or their premature infants immediately following birth, especially in certain subgroups that are at increased risk of vitamin E deficiency (e.g. smokers). The objective of this review is to compile, update, and interpret what is known about vitamin E isoforms and BPD since these first studies were conducted, and suggest future research directions.

Keywords

BPD; Bronchopulmonary dysplasia; chronic lung disease of prematurity; vitamin E; alpha-tocopherol; gamma-tocopherol; tocopherol; oxidative stress

Introduction

Bronchopulmonary dysplasia (BPD) is a form of chronic lung disease associated with premature birth, most commonly seen among extremely preterm infants (prior to 28 weeks of gestation) requiring treatment for respiratory distress syndrome (RDS). The United States has the highest rate of preterm birth among high income countries.[1] Advances in neonatal care have improved the survival of extremely preterm infants who are at the highest risk of developing BPD. In spite of major advances in the treatment of RDS, the incidence of BPD has not changed over the last several decades. Substantial evidence suggests that oxidative stress likely plays an important role in the development of certain phenotypes of BPD.[2] Understanding the mechanisms underlying the role of oxidative stress as a risk factor for BPD or in the pathogenesis of BPD is of substantial interest, as interventions that safely prevent or ameliorate oxidative stress might serve as prevention strategies for this disease.

One such potential intervention is vitamin E, which is known to neutralize free radicals and reduce oxidative stress. Vitamin E is also well tolerated as an oral supplement throughout pregnancy and infancy, and is routinely present in total parenteral nutrition for premature infants, making it an attractive option for BPD prevention or treatment. This review will focus on outlining the association between oxidative stress, vitamin E, and BPD pathophysiology. We will then review new developments in understanding of individual vitamin E isoforms since the initial vitamin E trials were conducted in BPD. Finally, we will discuss knowledge gaps where future research should focus.

Bronchopulmonary Dysplasia

The most commonly applied definition of BPD is a requirement for oxygen at 36 weeks of corrected gestational age, although the physiologic usefulness of this definition has been questioned[3] and is being actively studied.[4,5] BPD was once thought to be a natural progression of respiratory distress syndrome (RDS) and therefore ameliorable by surfactant

administration; however, the incidence of BPD has not decreased since surfactant became widely available.[6] Despite a multifactorial approach involving antenatal steroid therapy, early administration of surfactant, careful oxygen saturation targeting, avoidance of volutrauma and atelectasis, and an emphasis on intubation avoidance and early extubation, the incidence of BPD has remained stable.[3,7–13] Demographically and pathologically, however, BPD is substantially different now.[12,14–16] In the current era, many infants diagnosed with BPD at 36 weeks gestational age have minimal respiratory distress at birth, [6,17] and the new clinical and histological picture of BPD is conceived as a failure or arrest of normal alveolar and lung vascular formation in the setting of extreme prematurity, uncommon in infants greater than 1200g and greater than 30 weeks gestation.[18,19] In addition it is increasingly recognized that there are different phenotypes of BPD with variable contributions of oxidative stress, lung injury, lung repair, genetic predisposition, and epigenetic influences among other factors.[3]

Bronchopulmonary Dysplasia and Oxidative Stress

Oxidative stress results from the disrupted balance between generation of free radicals (such as reactive oxygen species) and their removal by free radical scavenging systems.[20] Reactive oxygen species exist, therefore, in a delicate balance in the human body. They are generated by multiple enzyme systems and act as intermediates of normal cellular metabolism,[21] performing essential roles as second messengers,[22] in induction of cell death and apoptosis,[23] and as local mediators of infection control and inflammation.[24]

Multiple investigators have noted that in the first few days of life there is a difference in oxidation of lipids and proteins in preterm infants who develop BPD compared to full term infants and adults,[14] and compared to preterm infants who do not develop BPD.[2] These differences manifest as increased presence of free iron, transferrin, ferritin and lactoferrin in bronchoalveolar secretions, which in the presence of oxygen become free radicals.[25–28] In settings of local increases of reactive oxygen species, the imbalance triggers downstream damage to the neonatal lung, possibly via nitric oxide-dependent pathways of lung development[29,30] or another downstream pathway that causes activation of the immune system and local inflammatory destruction of lung architecture. Thus, multiple studies suggest a role for free radical generation and lipid peroxidation in the presence of inhaled oxygen either causing or being a biomarker for BPD development.[25–28]

Interventions that mitigate or control oxidative stress might therefore prevent the development of BPD in at-risk infants. Vitamin E is a potent antioxidant, known to be essential for human health, and its easy tolerability as a normal part of the diet represents a feasible and acceptable potential antioxidant intervention. In 2015, Miller *et al.* concluded that increasing first trimester maternal plasma α-tocopherol is associated with differential neonatal airway epithelial cell inflammatory mediator release, especially a decrease in Tumor Necrosis Factor-α (TNF-α) production, suggesting that α-tocopherol may be an important local anti-inflammatory factor in the neonatal lung.[31] Hereafter we will review what is known about vitamin E, its isoforms, and their potential role/ association in the development of BPD.

The Role of Vitamin E and its Isoforms

Vitamin E is one of the essential fat-soluble vitamins, but it is not synthesized by the human body and requires intake from food sources, typically oils. (FIGURE 1) There are 8 isoforms of vitamin E, known as α-, β-, γ-, and δ-tocopherol and α-, β-, γ-, and δ-tocotrienol.[32] The two best-studied isoforms of vitamin E are α-tocopherol and γ-tocopherol. Dietary consumption of each isoform varies by food source.[33] At present, many foods and the majority of neonatal formulas in the United States deliver much greater γ-tocopherol than α-tocopherol.[34] The functions of each isoform in the human body, while not fully described, appear to be different, some with anti-inflammatory and some with proinflammatory properties.[35] Human tissues preferentially retain α-tocopherol and metabolize the other forms at higher rates.[36,37] The main carrier vehicle for tocopherols in the body are lipid particles (chylomicrons, LDL and HDL).[38] Increased lipids can elevate measured plasma tocopherols, and decreased lipids can lower measured plasma tocopherols.[39] Premature infants on TPN can have elevations in measured cholesterol compared to infants on enteral breastmilk.[40] Simultaneous measurement of tocopherols and lipids is currently recommended for scientific investigations, and is important to identify measurements of plasma tocopherols that have been altered by extremes of lipid status.[39,41]

Both α-tocopherol and γ-tocopherol have been called anti-inflammatory, but their downstream effects appear to be different, outlined in TABLE 1. α-tocopherol has been more extensively studied as has its documented anti-inflammatory profile.[42] γ-tocopherol also has anti-inflammatory effects,[42] especially in animal models and subjects with neutrophilic inflammation.[43–51] However, γ-tocopherol has also been reported to promote Type II inflammation in the lungs and in other organs.[33,52,53] In human subjects with asthma increased serum concentrations are associated with lower forced expiratory volume in 1 second (FEV1).[54] Supplementation of primarily γ-tocopherol was shown to reduce plasma and urine concentrations of α-tocopherol via undefined competitive mechanisms.[55] Subsequently, α- and γ-tocopherol were noted by Marchese *et al.* to have different primary roles in lung inflammation, with the isomers appearing to antagonize each other's metabolism.[54] In human studies, higher α-tocopherol is associated with a significantly decreased risk of asthma development, but the relationship of γ-tocopherol with asthma development is unclear.[56]

Vitamin E and Fetal Lung Development

Maternal prenatal factors including nutrition play a vital role in fetal and infant lung growth, and the normal development of the lungs may be interrupted by preterm birth. Amongst other nutrients, maternal α-tocopherol intake during pregnancy has been shown to be an important growth factor for fetal respiratory system development and other outcomes (FIGURE 2).[57] Murine models of BPD show accelerated growth in hypoplastic lung, increased lung complexity, and increased air surface with maternal supplementation of vitamin E containing α-tocopherol and γ-tocopherol.[58,59]

Vitamin E Concentrations in Prematurity

Falciglia *et al.* noted in 1988 that premature infants born at less than 33 weeks gestational age with RDS who went on to develop BPD had lower total plasma vitamin E at 3 days of life (0.58 ± 0.43 mg/dL) compared to those with RDS who recovered without the development of BPD (1.29 ± 0.54 mg/dL, $p<0.05$).[60–62] Decreased cord blood α-tocopherol and selenium concentrations in premature infants less than 30 weeks gestation who were on a standardized respiratory and ventilatory protocol for RDS were subsequently found to predict increased risk of developing BPD.[61] Haga *et al.* reported that even healthy, term infants appear to have a lower transport capacity for vitamin E compared with adults, resulting in lower plasma concentrations in cord blood samples compared to maternal plasma concentrations at delivery.[63] Initial plasma concentrations of vitamin E in infancy have been shown to be associated with maternal concentrations prior to birth.[64–66] Placental transfer of tocopherol isoforms to the infant is limited due to maternal metabolism of excess tocopherols compared to postnatal breastfeeding. [64–66] Preterm infants who are not receiving breastmilk may also have lower measured α-tocopherol concentrations after birth. Breastfeeding typically provides a higher α- tocopherol content in colostrum and transitional milk compared with formula and TPN. [67,68]

Wu *et al.* measured α- and γ-tocopherol isoforms and lipid concentrations from venous blood in term infants of 38–42 weeks gestation and preterm infants of 28–34 weeks gestation to establish a comparison between the two infant groups. The 28 to 34 week gestation infants had significantly lower serum mean α-tocopherol concentrations compared to the older infants, but they had similar ratios of overall vitamin E to total lipids.[65] There was a statistically significant correlation between neonatal and maternal vitamin E to total lipids ratios.[65] Better understanding of effects of postnatal supplementation with various tocopherol isoforms will be crucial, because at the present time dietary supplementation of vitamin E in neonatal care may be predominantly γ- and δ-tocopherol based, as is also the case with prenatal vitamins.[69]

Vitamin E Supplementation and the Development of Bronchopulmonary Dysplasia

Vitamin E has been extensively studied as an essential nutrient for the growth and development of infants, especially in its role as a potent antioxidant. It was hypothesized to be important in decreasing lung damage caused by the toxic effects of oxidant stress and oxygen toxicity.[70] Early studies, such as that by Ehrenkranz *et al.*, measured infant vitamin E concentrations following birth and demonstrated a protective effect of higher vitamin E concentrations on pressure-related lung injury.[70,71] These early observational studies did not account for the interaction (and likely opposing effects) of the vitamin E isoforms α- and γ-tocopherol on airway inflammation and lung disease risk that have subsequently been demonstrated.[33,54,72]

Investigators hypothesized that α-tocopherol supplementation might prevent either the oxidative lung injury or altered lung growth seen in preterm infants with bronchopulmonary dysplasia, and seven randomized controlled trials of α-tocopherol supplementation in

preterm infants were conducted for the prevention of BPD, four of which studied development of BPD as the primary outcome[70,71,73,74] and three which studied it as a secondary outcome[75–77] (TABLE 2). The results of these studies differ, with one reporting statistically significant reductions in BPD, and six showing nonsignificant reductions in BPD or no difference. A Cochrane meta-analysis of these same studies reported no association between vitamin E and BPD, (Estimated RR 0.91, CI 0.73, 1.14; Risk Difference −0.02, CI −0.07, +0.03) with wide confidence intervals suggesting that studies of BPD and vitamin E have been underpowered, even when combined in this way.[78] What all seven studies have in common is utilization of high dose vitamin E supplementation rather than normalization of deficiency, lack of prestratification of participants into categories at risk for vitamin E deficiency, delivery of the intervention in the neonatal period rather than during pregnancy, and failure to quantify and account for an interaction effect of γ-tocopherol or its potential presence in the product being delivered.[33] Of note, all seven provided α-tocopherol formulated by one company. Of more concern, two of the negative studies, in particular the same two with reported increased side effects of necrotizing enterocolitis, utilized a preparation which included a carrier of polyoxyethylated castor oil.[75,77] Polyoxyethylated castor oil is not biologically inert, as was believed at the time, and may cause serious adverse reactions, including direct epithelial damage.[79]

There is hesitancy on the part of neonatologists to reopen investigations into vitamin E isoforms, due to reported adverse events such as necrotizing enterocolitis, noted during the trial period in which the investigational product was being administered.[77] In undertaking this review, however, it appears that side effects may have been more likely related to the carrier vehicles,[79,80] to osmolality of preparations,[81] or to selection of supraphysiologic doses and target levels (TABLE 2). Lower concentrations of vitamin E are routinely included in the enteral feeds and total parenteral nutrition given to preterm infants without increased adverse effects, suggesting that more careful selection of vehicles and cautious dose finding trials prior to use would protect against adverse effects seen in previous trials. In addition, supportive pilot trials of specific vitamin E isoforms demonstrating improvements in established biomarkers for the development of BPD would be important prior to initiating large randomized controlled trials.

It is also important to acknowledge that there are some studies in opposition to the hypothesis that supplementation of α-tocopherol is sufficient to protect against the development of BPD. The predictive model of Falciglia *et al.* for which preterm human infants went on to develop BPD did not demonstrate the protective effect of α-tocopherol to be independent of the effect of selenium.[61] As selenium deficient rats had been shown to have increased metabolism of vitamin E,[82] this group speculated that vitamin E may be metabolized more quickly due to selenium deficiency in preterm infants under conditions of oxidative stress.[61] In another study Berger *et al.* administered high doses of α-tocopherol to premature baboons exposed to prolonged hyperoxia (FiO2 of 1.0) and, despite increasing α-tocopherol plasma concentrations, BPD was not prevented.[83] In one of the human trials, done by Watts *et al.*, additional supplementation of 16 mg d-l α-tocopherol, an amount less than what is currently contained in daily consumption of standard infant formula, starting in the first week of life to 266 infants weighing less than 1500g, did not prevent BPD, defined at that time as continued oxygen requirement at 28 days of postnatal life.[73] It is

noteworthy that at least 40% of both the control and treatment groups in this study were receiving inspired oxygen concentrations that were much higher (FiO2 >0.8) than those typically used with close oxygen saturation targeting in neonatal intensive care units today.[84] Watts *et al.* speculated that their study might have been underpowered for effect size, and that the lack of response could possibly be explained by the fact that predisposition for BPD may require vitamin E deficiency to be both severe and chronic (i.e., present in utero), with exposure therefore dependent on maternal status (and not infant status) at birth.[73] Another possible explanation for some of the contradictory studies is that beyond a certain concentration of hyperoxia, antioxidant defenses, no matter how replete, may simply be inadequate to compensate for the damage caused by high fractions of inspired oxygen, free radical generation and inflammation. A third explanation is that the current definition of BPD could encompass some phenotypes which are mechanistically connected to oxidative stress, and others which are not.[3] Demonstrating a protective dose response or threshold effect of α-tocopherol based on delivered inspired oxygen concentrations may be helpful in delineating this relationship.

Future Research Directions

Fifty years after the original description of BPD, it remains a major complication of premature birth.[85,86] However, not all extremely premature infants develop BPD, suggesting that BPD can be prevented, if premature birth cannot. The original hypotheses driving studies of vitamin E on BPD are worth revisiting, even in the presence of conflicting and negative trials. Previous trials conducted utilizing lower dose oral supplements of vitamin E were underpowered,[73,74] and studies utilizing parenteral dosing remain in the shadow of adverse outcomes related to supraphysiologic doses with a possibly toxic vehicle.[75–77] Lastly, none of the trials targeted prenatal supplementation, as all were delivered postnatally.

As vitamin E is a required vitamin, and deficiency is associated with increased BPD risk, a definitive understanding of the role vitamin E isoforms play in BPD development is needed to inform potential prevention efforts. TABLE 3 outlines what we know about vitamin E and BPD, and important remaining gaps in our knowledge. Observational studies could identify infants and mothers at risk of vitamin E deficiency and BPD, such as those born to mothers who smoke[87] and could determine the optimal concentration ranges of each isoform to minimize BPD risk in premature neonates. Proof of concept studies could reveal the optimal timing of vitamin E isoform delivery on biomarkers of BPD risk, and demonstrate potential mechanisms of action of individual isoforms. Mechanistic studies could help to elucidate how individual vitamin E isoforms affect lung growth and lung inflammation. Any future tocopherol based intervention will have to account for and quantify the content of individual isoforms. In particular, we feel that renewed study of the α-tocopherol isoform should be considered given its protective association with development of respiratory health outcomes such as asthma, allergic airway inflammation, and with improved lung growth parameters, compared with γ-tocopherol.[33,57,88]

As part of this strategy, properly conducted epidemiology studies to identify subgroups of mothers and infants at greater risk of vitamin E deficiency should take higher initial priority.

In addition to vitamin E, vitamin C and selenium are also known to be important in the interdependent human antioxidant system.[32,82] Infants of mothers who smoke have already been shown to gain significant increases in lung function and decreased likelihood of wheezing in a randomized controlled trial of supplementation of another antioxidant micronutrient, vitamin C, during pregnancy.[89,90] Status of vitamin E isoforms, vitamin C, and selenium should be examined in the maternal, infant and cord blood of smoking mothers who deliver preterm, in order to determine their association with risk of subsequent BPD.

Proof of concept studies will also be of great value moving forward. Determining the optimal timing and delivery of a tocopherol intervention will be especially important. Maternal supplementation may only lead to increased transmission of tocopherol metabolites,[66] as only very specific isomers of α-tocopherol cross the placenta.[91,92] This does not necessarily mean that the antioxidant activity is diminished, as the primary transmissible metabolite (alpha-carboxyethyl hydroxychroman) has also been shown to have good *in-vitro* antioxidant activity,[93] but with limited evidence of *in vivo* antioxidant activity.[94] Prenatal supplementation favoring very specific placentally transmissible isomers of α-tocopherol, such as naturally derived RRR-α-tocopherol,[91,92] in a supplement with high overall α-tocopherol to γ-tocopherol ratio may yield the best strategy for influencing postnatal lung outcomes. For infants at risk in the postnatal environment, administration of tocopherol interventions may need to occur immediately after birth to prevent, rather than treat, lung damage leading to BPD. Because the intravenous route of administration of vitamin E in very low birth weight infants may carry an increased risk of sepsis and other adverse outcomes, and because poor vehicle selection may have contributed to toxicity in the past, we think that future intervention trials should focus on the enteral route or on modification of existing TPN formulas, and be appropriately cautious with the target dose.[78]

Conclusions

At present, there is insufficient evidence about the benefits and risks of vitamin E in BPD prevention to make evidence-based recommendations about supplementation. However, new data on the effects of the individual vitamin E isoforms on lung health should make us relook at this essential dietary factor as a potential preventive or treatment intervention for BPD. Adequately powered studies will be needed to address whether supplementation of specific vitamin E isoforms either in pregnant women at risk of preterm birth, or in at-risk premature infants immediately following birth, reduces the development of BPD and subsequent long-term pulmonary morbidity in childhood and adult life.

Acknowledgments

Funding Sources: NIH/NHLBI T32 HL87738 (CS), UG3OD023288, HL105447, and HL129060 (CTM), UG3OD023320 (JA), U01HL101456 (JA, PM, TH), NIH K24 AI 077930, 7 UG3 OD023282 (TH)

Abbreviations

BPD	bronchopulmonary dysplasia

RDS	respiratory distress syndrome
FiO2	fraction of inspired oxygen
ROP	retinopathy of prematurity
PO	by mouth

References

1. Aschner J, Patrick S, Stark A, Lee S. The Scope and Organization of Neonatology: North American and Global Comparisons. Avery's Neonatology: Pathophysiology and Management of the Newborn, LWW (7). 2015
2. Perrone S, Tataranno M, Buonocore G. Oxidative Stress and Bronchopulmonary Dysplasia. J Clin Neonatol. 2012; 1:109–114. [PubMed: 24027702]
3. McEvoy C, Jain L, Schmidt B, Abman S, Bancalari E, Aschner J. Bronchopulmonary dysplasia: NHLBI Workshop on the Primary Prevention of Chronic LUng Diseases. Ann Am Thorac Soc. 2014; 11:S146–153. [PubMed: 24754823]
4. Pryhuber G, Maitre N, Ballard R, Cifelli D, Davis S, Ellenberg J, Greenberg J, Kemp J, Mariani T, Panitch H, Ren C, Shaw P, Taussig L, Hamvas A. Prematurity and respiratory outcomes program (PROP): study protocol of a prospective multicenter study of respiratory outcomes of preterm infants in the United States. BMC Pediatr. 2015; 15
5. Higgins R, Jobe A, Koso-Thomas M, Bancalari E, Viscardi R, Hartert T, Ryan R, Kallapur S, Steinhorn R, Konduri G, Davis S, Thebaud B, Clyman R, Collaco J, Martin C, Woods J, Finer N, Raju T. Executive Summary of the Workshop on Bronchopulmonary Dysplasia The Journal of Pediatrics. J Pediatr. 2018 White Paper- In Press.
6. Bancalari E, del Moral T. Bronchopulmonary dysplasia and surfactant. Biol Neonate. 2001; 80:7–13.
7. Campbell K. Intensive oxygen therapy as a possible cause of retrolental fibroplasia; a clinical approach. Med J Aust. 1951; 2:48–50. [PubMed: 14874698]
8. Carlo W, Finer N, Walsh M, Rich W, Gantz M, Laptook A, Yoder B, Faix R, Das A, Poole W, Schibler K, Newman N, Ambalavanan N, Frantz I, Piazza A, Sánchez P, Morris B, Laroia N, Phelps D, Poindexter B, Cotten C, Van Meurs K, Duara S, Narendran V, Sood B, O'Shea T, Bell E, Ehrenkranz R, Watterberg K, Higgins R. Target ranges of oxygen saturation in extremely preterm infants. N Engl J Med. 2010; 362:1959–1969. [PubMed: 20472937]
9. Stevens T, Blennow M, Myers E, Soll R. Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome. Cochrane Database of Systematic Reviews. 2007; 4 http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD14003063.pub14651853/abstract.
10. Wheeler K, Klingenberg C, McCallion N, Morley C, Davis P. Volume-targeted versus pressure-limited ventilation in the neonate. Cochrane Database of Systematic Reviews. 2010; 11 http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD14003666.pub14651853/abstract.
11. Shalish W, Sant'Anna G, Natarajan G, Sanjay C. When and How to Extubate Premature Infants from Mechanical Ventilation. Curr Pediatr Rep. 2014; 2:18–25.
12. Auten R, Davis J. Oxygen Toxicity and Reactive Oxygen Species: The Devil is in the Details. Nature. 2009; 66:121–127.
13. Guy L, Lanman J, Dancis J. The possibility of total elimination of retrolental fibroplasia by oxygen restriction. Pediatrics. 1956:2.
14. Welty SE. Is there a role for antioxidant therapy in bronchopulmonary dysplasia? Journal of Nutrition. 2001; 131:947S–950S. [PubMed: 11238792]
15. Northway WJ, Rosan R, Porter D. Pulmonary disease following respiratory therapy of hyaline-membrane disease. Bronchopulmonary dysplasia. N Engl J Med. 1967; 276:357–368. [PubMed: 5334613]

16. Jobe A, Bancalari E. Bronchopulmonary Dysplasia. Am J Respir Crit Care Med. 2001; 163:1723–1729. [PubMed: 11401896]
17. Rojas M, Gonzalez A, Bancalari E, Claure N, Poole C, Silva-Neto G. Changing trends in the epidemiology and pathogenesis of neonatal chronic lung disease. J Pediatr. 1995; 126:605–610. [PubMed: 7699543]
18. Balinotti J, Tiller C, Llapur C, Jones M, Kimmel R, Coates C, Katz B, Nguyen J, Tepper R. Growth of the lung parenchyma early in life. Am J Respir Crit Care Med. 2009; 179:134–137. [PubMed: 18996997]
19. Jobe A. The New Bronchopulmonary Dysplasia. Curr Opin Pediatr. 2011; 23:167–172. [PubMed: 21169836]
20. Betteridge D. What is oxidative stress? Metabolism. 2000; 49:3–8.
21. Papa S, Skulachev V. Reactive oxygen species, mitochondria, apoptosis and aging. Mol Cell Biochem. 1997; 174:305–319. [PubMed: 9309704]
22. Lambeth J. Nox enzymes, ROS, and chronic disease: an example of antagonistic pleiotropy. Free Radical Biology and Medicine. 2007; 43:332–347. [PubMed: 17602948]
23. Fleury CH, Mignote B, Vayssiere J. Mitochondrial reactive oxygen species in cell death signaling. Biochemie. 2002; 84:131–141.
24. van der Vliet A. NADPH oxidases in lung biology and pathology: host defense enzymes and more. Free Radical Biology and Medicine. 2008; 44:938–955. [PubMed: 18164271]
25. Gerber C, Bruchelk G, Stegmann H, Schweinsberg F, CP S. Presence of bleomycin-detectable free iron in the alveolar system of preterm infants. Biochem Biophys Res Commun. 1999; 257:218–222. [PubMed: 10092536]
26. Nycyk J, Drury J, Cooke R. Breath pentane as a marker for lipid peroxidation and adverse outcomes in preterm infants. Arch Dis Child Fetal Neonatal Ed. 1998; 79:F67–F69. [PubMed: 9797630]
27. Ogihara T, Hirano K, Morinobu T, Kim H, Hiroi M, Ogihara H, Tamai H. Raised concentration of aldehyde lipid peroxidation products in premature infants with chronic lung disease. Arch Dis Child Fetal Neonatal Ed. 1999; 80:F21–F25. [PubMed: 10325806]
28. Ogihara T, Okamoto R, Kim H, Nagai A, Morinobu T, Moji H, Kamegai H, Hirano K, Ogihara H, Tamai H, Mino M. New evidence for the involvement of oxygen radicals in triggering neonatal chronic lung disease. Pediatric Research. 1996; 39:117–119. [PubMed: 8825395]
29. Han R, Stewart D. Defective lung vascular development in endothelial nitric oxide synthase deficient mice. Trends Cardiovasc Med. 2006; 16:29–34. [PubMed: 16387628]
30. Afshar S, Gibson L, Yuhanna I, Sherman T, Kerecman J, Grubb P, Yoder B, McCurnin D, Shaul P. Pulmonary NO synthase expression is attenuated in a fetal baboon model of chronic lung disease. Am J Physiol Lung Cell Mol Physiol. 2003; 284:L749–L758. [PubMed: 12676765]
31. Miller D, Turner S, Spiteri-Cornish D, Scaife A, Danielian P, Devereux G, Walsh G. Maternal vitamin D and E intakes during early pregnancy are associated with airway epithelial cell responses in neonates. Clinical Exp Allergy. 2015; Accepted Author Manuscript. doi: 10.1111/cea.12490
32. Institute of Medicine Report: Dietary reference intakes for vitamin C, vitamin E, selenium, and carotenoids. Washington, DC: National Academy Press; 2000. p. 186-283.
33. Cook-Mills JM, Abdala-Valencia H, Hartert T. Two Faces of Vitamin E in the Lung. American Journal of Respiratory and Critical Care Medicine. 2013; 188:279–284. [PubMed: 23905522]
34. Jiang Q, Christen S, Shigenaga M, Ames B. Gamma-tocopherol, the major form of vitamin E in the US, deserves more attention. Am J Clin Nutr. 2001; 74:714–722. [PubMed: 11722951]
35. Jiang Q. Natural forms of vitamin E: metabolism, antioxidant, and anti-inflammatory activities and their role in disease prevention and therapy. Free Radical Biology and Medicine. 2014; 72:76–90. [PubMed: 24704972]
36. Sontag T, Parker R. Cytochrome P450 omega-hydroxylase pathway of tocopherol catabolism. Biol Chem. 2002; 277:25290–25296.
37. Leonard S, Patterson E, Atkinson J, Ramakrishnan R, Cross C, Traber M. Studies in humans using deuterium-labeled alpha- and gamma-tocopherols demonstrate faster plasma gamma-tocopherol

disappearance and greater gamma-metabolite production. Free Radical Biology and Medicine. 2005; 38:856–866.

38. Herrera E, Barbas C. Vitamin E: action, metabolism and perspectives. Journal of physiology and biochemistry. 2001; 57:43–56.
39. Horwitt M, Harvey C, Dahm C Jr, Searcy M. Relationship between tocopherol and serum lipid levels for determination of nutritional adequacy. Annals of the New York Academy of Sciences. 1972; 203:223–236. [PubMed: 4633111]
40. Rochow N, Moller S, Fusch G, Drogies T, Fusch C. Levels of lipids in preterm infants fed breast milk. Clin Nutr. 2010; 29:94–99. [PubMed: 19666201]
41. Thurnham D, Davies J, Crump B, Situnayake R, Davis M. The use of different lipids to express serum tocopherol: lipid ratios for the measurement of vitamin E status. Annals of clinical biochemistry. 1986; 23(Pt 5):514–520. [PubMed: 3767286]
42. Reiter E, Jiang Q, Christen S. Anti-inflammatory properties of α- and γ-tocopherol. Molecular Aspects of Medicine. 2007; 28:668–691. [PubMed: 17316780]
43. Burbank A, Duran C, Almond M, Wells H, Jenkins S, Jiang Q, Yang C, Wang T, Zhou H, Hernandez M, Peden D. A short course of gamma-tocopherol mitigates LPS-induced inflammatory responses in humans ex vivo. JACI. 2017
44. Burbank A, Duran C, Pan Y, Burns P, Jones S, Jiang Q, Yang C, Jenkins S, Wells H, Alexis N, Kesimer M, Bennett W, Zhou H, Peden D, Hernandez M. Gamma tocopherol-enriched supplement reduces sputum eosinophilia and endotoxin-induced sputum neutrophilia in volunteers with asthma. The Journal of allergy and clinical immunology. 2017
45. Eldridge M, Peden D. Allergen provocation augments endotoxin-induced nasal inflammation in subjects with atopic asthma. The Journal of allergy and clinical immunology. 2000; 105:475–481. [PubMed: 10719296]
46. Hernandez M, Wagner J, Kala A, Mills K, Wells H, Alexis N, Lay J, Jiang Q, Zhang H, Zhou H, Peden D. Vitamin E, γ-tocopherol, reduces airway neutrophil recruitment after inhaled endotoxin challenge in rats and in healthy volunteers. Free Radic Biol Med. 2013; 60:56–62. [PubMed: 23402870]
47. Mills K, Lay J, Wu W, Robinette C, Kesic M, Dreskin S, Peden D, Hernandez M. Vitamin E, gamma-tocopherol, diminishes ex vivo basophil response to dust mite allergen. Allergy. 2014; 69:541–544. [PubMed: 24697338]
48. Wagner J, Harkema J, Jiang Q, Illek B, Ames B, Peden D. Gamma-tocopherol attenuates ozone-induced exacerbation of allergic rhinosinusitis in rats. Toxicologic pathology. 2009; 37:481–491. [PubMed: 19389874]
49. Wagner J, Jiang Q, Harkema J, Ames B, Illek B, Roubey R, Peden D. Gamma-tocopherol prevents airway eosinophilia and mucous cell hyperplasia in experimentally induced allergic rhinitis and asthma. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 2008; 38:501–511. [PubMed: 17970781]
50. Wagner J, Jiang Q, Harkema J, Illek B, Patel D, Ames B, Peden D. Ozone enhancement of lower airway allergic inflammation is prevented by gamma-tocopherol. Free Radic Biol Med. 2007; 43:1176–1188. [PubMed: 17854713]
51. Wiser J, Alexis N, Jiang Q, Wu W, Robinette C, Roubey R, Peden D. In vivo gamma-tocopherol supplementation decreases systemic oxidative stress and cytokine responses of human monocytes in normal and asthmatic subjects. Free Radic Biol Med. 2008; 45:40–49. [PubMed: 18405673]
52. Berdnikovs S, Abdala-Valencia H, McCary C, Somand M, Cole R, Garcia A, Bryce P, Cook-Mills J. Isoforms of Vitamin E have opposing immunoregulatory functions during inflammation by regulating leukocyte recruitment. J Immunol. 2009; 182:4395–4405. [PubMed: 19299740]
53. McCary C, Abdala-Valencia H, Berdnikovs S, Cook-Mills JM. Supplemental and highly elevated tocopherol doses differentially regulate allergic inflammation: reversibility of α-tocopherol and γ-tocopherol's effects. The Journal of Immunology. 2011; 186:3674–3685. [PubMed: 21317387]
54. Marchese M, Kumar R, Colangelo L, Avila P, Jacobs D, Gross M, Sood A, Liu K, Cook-Mills J. The vitamin E isoforms α-tocopherol and γ-tocopherol have opposite associations with spirometric parameters: the CARDIA study. Respir Res. 2014; 15:31. [PubMed: 24629024]

55. Yoshikawa S, Morinobu T, Hamamura K, Hirahara F, Iwamoto T, Tamai H. The effect of gamma-tocopherol administration on alpha-tocopherol levels and metabolism in humans. European Journal of Clinical Nutrition. 2005; 59:900–905. [PubMed: 15928686]
56. Larkin E, Gao Y, Gebretsadik T, Hartman T, Wu P, Wen W, Yang G, Bai C, Jin M, Roberts L, Gross M, Shu X, Hartert T. New risk factors for adult-onset incident asthma. A nested case-control study of host antioxidant defense. Am J Respir Crit Care Med. 2015; 191:45–53. [PubMed: 25408961]
57. Turner SW, Campbell D, Smith N, Craig LCA, McNeill G, Forbes SH, Harbour PJ, Seaton A, Helms PJ, Devereux GS. Associations between fetal size, maternal alpha-tocopherol and childhood asthma. Thorax. 2010; 65:391–397. [PubMed: 20435859]
58. Islam S, Narra V, Cote GM, Manganaro TF, Donahoe PK, Schnitzer JJ. Prenatal vitamin E treatment improves lung growth in fetal rats with congenital diaphragmatic hernia. Journal of Pediatric Surgery. 1999; 34:172–176. [PubMed: 10022166]
59. Peroni DG, Bonomo B, Casarotto S, Boner AL, Piacentini GL. How changes in nutrition have influenced the development of allergic diseases in childhood. Italian Journal of Pediatrics. 2012; 38
60. Falciglia HS, Johnson JR, Sullivan J, Hall CF, Miller JD. Complex Antioxidant Relationships and Derangements in Premature Infants with Respiratory-Distress Syndrome and Bronchopulmonary Dypslasia. Pediatric Research. 1994; 35:A51–A51.
61. Falciglia HS, Johnson JR, Sullivan JA, Hall CF, Miller JD, Riechmann GC, Falciglia GA. Role of antioxidant nutrients and lipid peroxidation in premature infants with respiratory distress syndrome and bronchopulmonary dysplasia. American Journal of Perinatology. 2003; 20:97–107. [PubMed: 12660915]
62. Falciglia H, Ginn-Pease M, Falciglia G, Lubin A, Frank D, Chang W. Vitamin E and selenium levels of premature infants with severe respiratory distress syndrome and bronchopulmonary dysplasia. J Pediatr Perinat Nutr. 1988; 2:35–49. [PubMed: 3216334]
63. Haga P, Ek J, Kran S. Plasma tocopherol levels and vitamin E/β-lipoprotein relationships during pregnancy and in cord blood. Am J Clin Nutr. 1982; 36:1200–1204. [PubMed: 6890762]
64. Hoppu U, Salo-Vaananen P, Lampi A-M, Isolauri E. Serum Alpha and Gamma Tocopherol Levels in Atopic Mothers and their Infants are Correlated. Biol Neonate. 2005; 88:24–26. [PubMed: 15731552]
65. Wu S, Chou Y. Measurement of serum vitamin E isomers in fullterm and preterm infants. Chang Gung Med J. 2001; 24:793–798. [PubMed: 11858395]
66. Didenco S, Gillingham M, Go M, Leonard S, Traber M, McEvoy C. Increased vitamin E intake is associated with higher α-tocopherol concentration in the maternal circulation but higher α-carboxyethyl hydroxychroman concentration in the fetal circulation. Am J Clin Nutr. 2011; 93:368–373. [PubMed: 21159788]
67. Romeu-Nadal M, Morera-Pons S, Castellote AI, Lopez-Sabater MC. Determination of gamma- and alpha-tocopherols in human milk by a direct high-performance liquid chromatographic method with UV-vis detection and comparison with evaporative light scattering detection. Journal of Chromatography A. 2006; 1114:132–137. [PubMed: 16574129]
68. Lima M, Dimenstein R, Ribeiro K. Vitamin E concentration in human milk and associated factors: a literature review. Jornal de pediatria. 2014; 90:440–448. [PubMed: 24953721]
69. Elisia I, Kitts D. Differences in Vitamin E and C Profile Between Infant Formula and Human Milk and Relative Susceptibility to Lipid Oxidation International. Journal for Vitamin and Nutrition Research. 2013; 83:311–319.
70. Ehrenkranz R, Bonta B, RC A, Warshaw J. Amelioration of Bronchopulmonary Dysplasia after Vitamin E administration- a Preliminary Report. N Engl J Med. 1978; 299:564–569. [PubMed: 355877]
71. Ehrenkranz RA, Ablow R, Warshaw J. Prevention of bronchopulmonary dysplasia with vitamin E administration during the acute stages of respiratory distress syndrome. The Journal of Pediatrics. 1979; 95:873–878. [PubMed: 490265]

72. Behrman R, Saldanha RL, Cepeda EE, Poland RL. The effect of vitamin E prophylaxis on the incidence and severity of bronchopulmonary dysplasia. The Journal of Pediatrics. 1982; 101:89–93. [PubMed: 7045320]
73. Watts JL, Milner R, Zipursky A, Paes B, Ling E, Gill G, Fletcher B, Rand C. Failure of supplementation with vitamin-E to prevent bronchopulmonary dysplasia in infants less than 1500 g birth weight. European Respiratory Journal. 1991; 4:188–190. [PubMed: 2044736]
74. Milner, R., Watts, J., Paes, B., Zipursky, A. RLF in <1500 gram neonates. Part of a randomized clinical trial of the effectiveness of Vitamin E: Retinopathy of Prematurity Conference; Ross Laboratories; Columbus, OH. 1981; p. 703-716.
75. Hittner H, Godio L, Rudolph A, Adams J, Garcia-Prats J, Friedman Z, Kautz J, Monaco W. Retrolental fibroplasia: efficacy of vitamin E in a double-blind clinical study of preterm infants. N Engl J Med. 1981; 305:1365–1371. [PubMed: 7029275]
76. Speer M, Bilfeld C, Rudolph A, Chadda P, Holbein M, Hittner H. Intraventricular hemorrhage and vitamin E in the very low-birth-weight infant: evidence for efficacy of early intramuscular vitamin E administration. Pediatrics. 1984; 74:1107–1112. [PubMed: 6504632]
77. Johnson L, Quinn G, Abbasi S, Otis C, Goldstein D, Sacks L, Porat R, Fong E, Delivoria-Papadopoulos M, Peckham G, Schaffer D, Bowen JF. Effect of sustained pharmacologic vitamin E levels on incidence and severity of retinopathy of prematurity: a controlled clinical trial. The Journal of Pediatrics. 1989; 114:827–838. [PubMed: 2654350]
78. Brion L, Bell E, Raghuveer T. Vitamin E supplementation for prevention of morbidity and mortality in preterm infants. Cochrane Database of Systematic Reviews. 2003; 2003 CD003665.
79. Kiss L, Walter F, Bocsik A, Veszelka S, Ozsvari B, Puskas L, Szabo-Revesz P, Deli M. Kinetic analysis of the toxicity of pharmaceutical excipients Cremophor EL and RH40 on endothelial and epithelial cells. Journal of pharmaceutical sciences. 2013; 102:1173–1181. [PubMed: 23362123]
80. Campos F, Victorino V, Martins-Pinge M, Cecchini A, Panis C, Cecchini R. Systemic toxicity induced by paclitaxel in vivo is associated with the solvent cremophor EL through oxidative stress-driven mechanisms. Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association. 2014; 68:78–86. [PubMed: 24657178]
81. Finer N, Peters K, Hayek Z, Merkel C. Vitamin E and necrotizing enterocolitis. Pediatrics. 1984; 73:387–393. [PubMed: 6546616]
82. Fischer WC, Whanger PD. EFFECTS OF SELENIUM DEFICIENCY ON VITAMIN-E METABOLISM IN RATS. Journal of Nutritional Science and Vitaminology. 1977; 23:273–280. [PubMed: 915559]
83. Berger TM, Frei B, Rifai N, Avery ME, Suh J, Yoder BA, Coalson JJ. Early high dose antioxidant vitamins do not prevent bronchopulmonary dysplasia in premature baboons exposed to prolonged hyperoxia: A pilot study. Pediatric Research. 1998; 43:719–726. [PubMed: 9621979]
84. Vento M, Moro M, Escrig M, Arruza L, Villar G, Izquierdo I, Roberts L, Arduini A, Escobar J, Sastre J, Asensi M. Preterm resuscitation with low oxygen caues less oxidative stress, inflammation and chronic lung disease. Pediatrics. 2009; 124:e439–449. [PubMed: 19661049]
85. Johnson T, Patel A, Jegier B, Engstrom J, Meier P. The Cost of Morbidities in Very Low Birth Weight Infants. J Pediatr. 2013; 162:243–249. e241. [PubMed: 22910099]
86. Miller V, Rice J, DeVoe M, Fos P. An analysis of program and family costs of case managed care for technology-dependent infants with bronchopulmonary dysplasia. J Pediatr Nurs. 1998; 13:244–251. [PubMed: 9753910]
87. Stone C Jr, Qiu Y, Kurland I, Slaughter J, Moore P, Cook-Mills J, Hartert T, Aschner J. Effect of maternal smoking on plasma and urinary measures of vitamin E isoforms in the first month after extreme preterm birth. Journal of Pediatrics. 2018 In Press: Publication Online Ahead of Print.
88. Cook-Mills J, Gebretsadik T, Abdala-Valencia H, Green J, Larkin E, Dupont W, Shu X, Gross M, Bai C, Gao Y, Hartman T, Rosas-Salazar C, Hartert T. Interaction of vitamin E isoforms on asthma and allergic airway disease. Thorax. 2016; 71:954–956. [PubMed: 27257004]
89. McEvoy C, Schilling D, Clay N, Jackson K, Go M, Spitale P, Bunten C, Leiva M, Gonzales D, Hollister-Smith J, Durand M, Frei B, Buist A, Peters D, Morris C, Spindel E. Vitamin C Supplementation for Pregnant Smoking Women and Pulmonary Function in their Newborn Infants: A Randomized Clinical Trial. JAMA. 2014; 311:2074–2082. [PubMed: 24838476]

90. Ortega R, López-Sobaler A, Martinez R, Andrés P, Quintas M. Influence of smoking on vitamin E status during the third trimester of pregnancy and on breast-concentrations in Spanish women. Am J Clin Nutr. 1998; 68:662–667. [PubMed: 9734745]
91. Acuff R, Dunworth R, Webb L, Lane J. Transport of deuterium-labeled tocopherols during pregnancy. Am J Clin Nutr. 1998; 67:459–464. [PubMed: 9497190]
92. Debier C, Larondelle Y. Vitamins A and E: metabolism, roles and transfer to offspring. British Journal of Nutrition. 2005; 93:153–174. [PubMed: 15788108]
93. Betancor-Fernandez A, Sies H, Stahl W, Polidori M. In vitro antioxidant activity of 2,5,7,8-tetramethyl-2-(2'-carboxyethyl)-6-hydroxychroman (alpha-CEHC), a vitamin E metabolite. Free Radic Res. 2002; 36:915–921. [PubMed: 12420750]
94. Uto-Kondo H, Kiyose C, Ohmori R, Saito H, Taguchi C, Kishimoto Y, Machida N, Hasegawa M, Yoshioka E, Saita E, Hirata Y, Igarashi O, Kondo K. The coantioxidative effects of carboxyethyl-6-hydroxychromans and alpha-Tocopherol. J Nutri Sci Vitaminol (Tokyo). 2007; 53:301–305.
95. Contin D, Munne-Bosch S. Interspecific variation in vitamin E levels and the extent of lipid peroxidation in pioneer and non-pioneer species used in tropical forest restoration. Tree physiology. 2016; 36:1151–1161. [PubMed: 27052435]
96. Meydani S, Barklund M, Liu S, Meydani M, MIller R, Cannon J, Morrow F, Rocklin R, Blumberg J. Vitamin E supplementation enhances cell-mediated immunity in healthy elderly subjects. Am J Clin Nutr. 1990; 52:557–563. [PubMed: 2203257]
97. Hsieh C, Huang C, Lin B. Low and high levels of alpha-tocopherol exert opposite effects on IL-2 possibly through the modulation of PPAR-gamma, IkappaBalpha, and apoptotic pathway in activated splenocytes. Nutrition. 2006; 22:433–440. [PubMed: 16472984]
98. Jiang Q, Ames B. Gamma-tocopherol, but not alpha-tocopherol, decreases proinflammatory eicosanoids and inflammation damage in rats. FASEB J. 2003; 17:816–822. [PubMed: 12724340]
99. Jiang Q, Elson-Schwab I, Courtemanche C, Ames B. Gamma tocopherol and its major metabolite, in contrast to alpha tocopherol, inhibit cyclooxygenase activity in macrophages and epithelial cells. Proc Natl Acad Sci USA. 2000; 97:11494–11499. [PubMed: 11005841]
100. Wu D, Meydani M, Beharka A, Serafini M, Martin K, Meydani S. In vitro supplementation with different tocopherol homologues can affect the function of immune cells in old mice. Free Radical Biology and Medicine. 2000; 28:643–651. [PubMed: 10719246]
101. Boscoboinik D, Chatelin E, Bartoli G, Azzi A. Molecular basis of alpha-tocopherol inhibition of smooth muscle proliferation in vitro. EXS. 1992; 62:164–177. [PubMed: 1450584]
102. Kempna P, Reiter E, Arock M, Azzi A, Zingg J. Inhibition of HMC-1 mast cell proliferation by vitamin E: involvement of the protein kinase B pathway. J Biol Chem. 2004; 279:50700–50709. [PubMed: 15385541]
103. Gerondakis S, Siebenlist U. Roles of the NF-kB Pathway in Lymphocyte Development and Function. Cold Spring Harb Perspect Biol. 2010; 2:a000182. [PubMed: 20452952]
104. Oh H, Ghosh S. NF-kB: roles and regulation in different CD4(+) T-cell subsets. Immunol Rev. 2013; 252:41–51. [PubMed: 23405894]
105. Devaraj S, Jialal I. Low-density lipoprotein postsecretory modification, monocyte function, and circulating adhesion molecules in type 2 diabetic patients with and without macrovascular complications: the effect of alpha-tocopherol supplementation. Circulation. 2000; 102
106. Devaraj S, Li D, Jialal I. The effects of alpha tocopherol supplementation on monocyte function. Decreased lipid oxidation, interleukin 1 beta secretion, and monocyte adhesion to endothelium. J Clin Invest. 1996; 98:756–763. [PubMed: 8698868]
107. Abdala-Valencia H, Berdnikovs S, Soveg F, Cook-Mills J. α-Tocopherol supplementation of allergic female mice inhibits development of CD11c+CD11b+ dendritic cells in utero and allergic inflammation in neonates. Am J Physiol Lung Cell Mol Physiol. 2014; 307:L482–496. [PubMed: 25015974]
108. Abdala-Valencia H, Soveg F, Cook-Mills J. γ-Tocopherol supplementation of allergic female mice augments development of CD11c+CD11b+ dendritic cells in utero and allergic inflammation in neonates. Am J Physiol Lung Cell Mol Physiol. 2016; 310:L759–771. [PubMed: 26801566]

109. Puklin J, Simon R, Ehrenkranz R. Influence on retrolental fibroplasia of intramuscular vitamin E administration during respiratory distress syndrome. Opthalmology. 1982; 89:96–103.

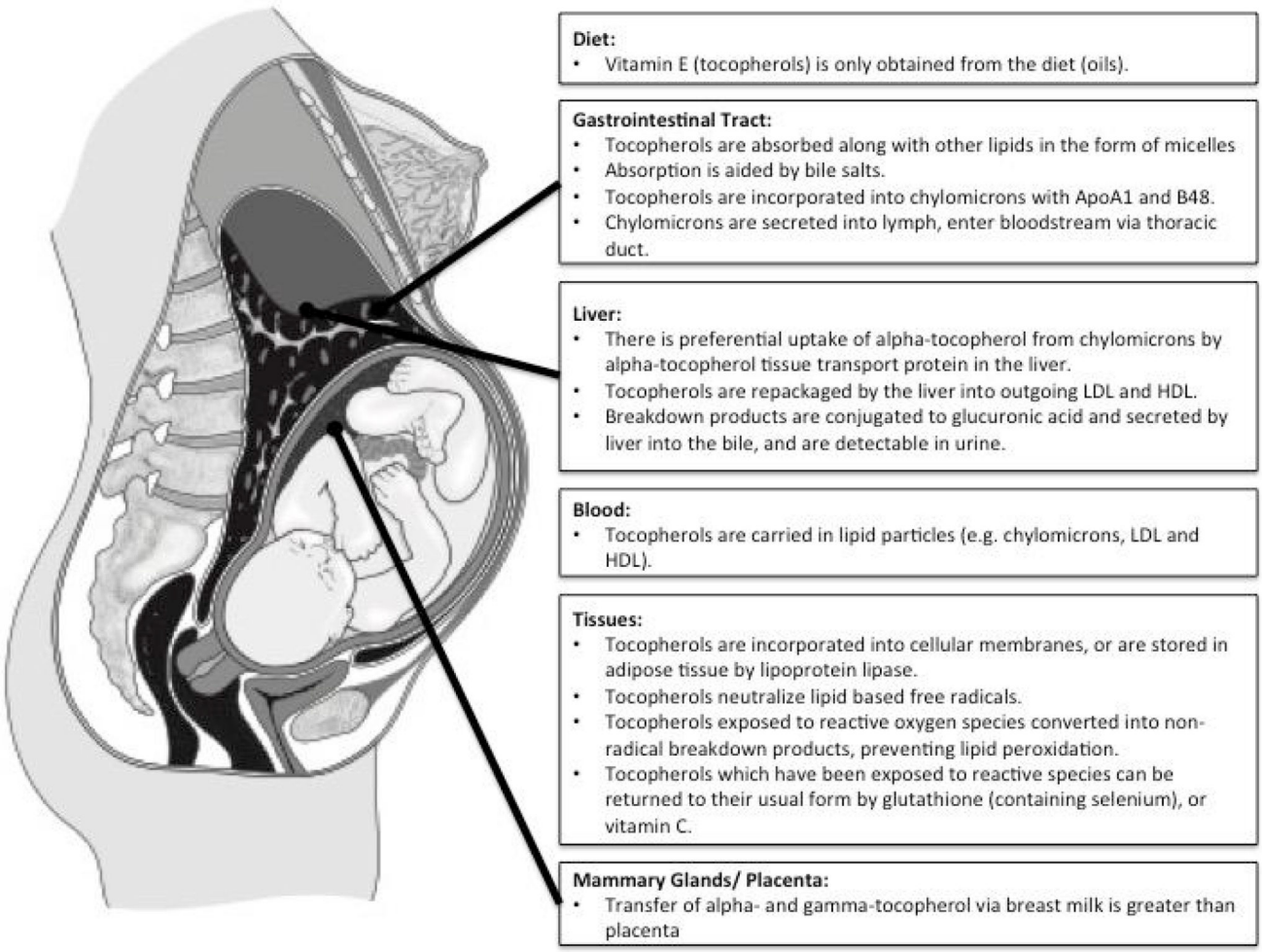

Figure 1.

Metabolism of vitamin E isoforms α- and γ-tocopherol during pregnancy. Tocopherols are found only in the diet and are transported via lipid pathways. The main site of tocopherol action is in tissues, where they are incorporated into cellular membranes and act to stabilize lipids and prevent lipid peroxidation by free radicals. Drawing modified from public image (Image modified with licensed permission. Artist: Blamb, source: www.shutterstock.com)

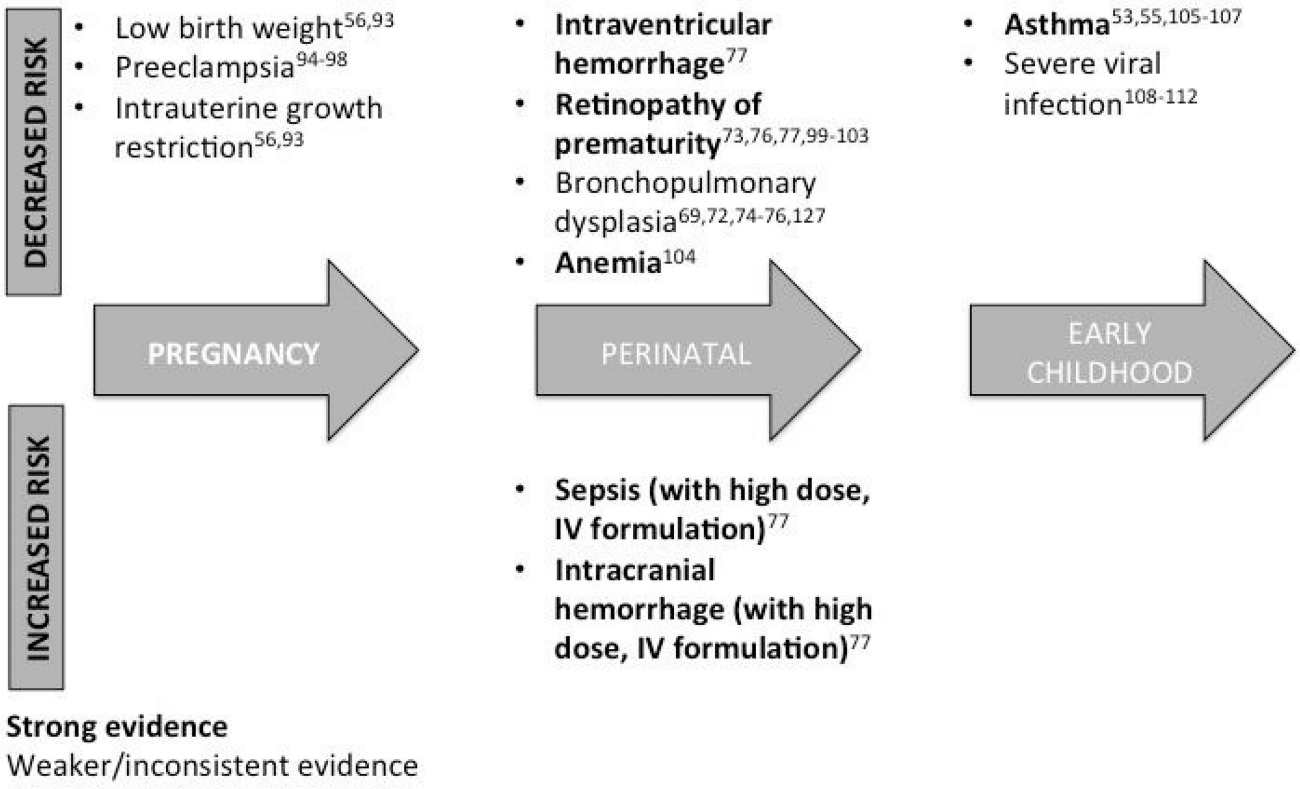

Figure 2.

Beneficial and adverse effects of α-tocopherol on pregnancy, perinatal and early childhood outcomes, with strength of evidence. Low birth weight[57,94] Preeclampsia[95–99] Intrauterine growth restriction[57,94] intraventricular hemorrhage[78] retinopathy of prematurity[74,77,78,100–104] bronchopulmonary dysplasia anemia[105] sepsis[78] intracranial hemorrhage[78] asthma[54,56,106–108] viral infection[109–113]

Table 1

Comparing the Effects of Alpha- and Gamma- Tocopherol Isoforms of Vitamin E on Lung Growth and Lung Inflammation

Effect	Alpha-Tocopherol	Gamma-Tocopherol
Infant FEV1 and FVC[54]	Increased infant α-tocopherol associated with increases in FEV1 and FVC	Increased γ-tocopherol associated with decreases in FEV1 and FVC
Effect on lipid peroxidation[69,95]	Associated with greater reductions in lipid peroxidation	Associated with lesser reductions in lipid peroxidation
Effect on IL-2 production[96,97]	Increased production by stimulated peripheral blood mononuclear cells	Unknown
Effect on cyclooxygenase enzymes[96,98–100]	Decreased prostaglandin E2 synthesis	Decreased prostaglandin E2 synthesis
Effect on intracellular pathways[97,101–104]	Inhibition of protein kinase B and C, reduced nuclear factor kappa B	Inhibition of protein kinase B, with mixed inhibition/activation of protein kinase C
Effect on leukocyte trafficking/ adhesion[53,105,106]	Decreased expression of VCAM-1	Increased expression of VCAM-1
Effect on offspring cytokine production after allergen challenge in infant murine models (maternal supplementation)[107,108]	Decreased IL-4, IL-33, TSLP, CCL11, and CCL24	Increased CCL11, amphiregulin, activin A, and IL-5
Effect on prevalent Type I inflammation[43,44,46–50,98,107,108]	Decreases neutrophilic inflammation	Decreases neutrophilic inflammation more than α-tocopherol, reduced tumor necrosis factor-α
Effect on prevalent Type II inflammation[43,44,46–50,98]	Decreases recruitment of dendritic cells and eosinophils	Increases recruitment of dendritic cells and eosinophils in some models Decreases eosinophil and basophil recruitment in other models Reductions in leukotriene B4

Table 2

Randomized Controlled Trials of Vitamin E Supplementation in Premature Neonates for Prevention of BPD

Author and year	Intervention Studied	Other supplements	N	Group Allocation	Patient Characteristics	BPD Studied as Primary or Secondary Outcome?	Results
Ehrenkranz et al, 1979[70]	20mg/kg intramuscular Vitamin E daily until FiO2 requirement less than 0.4 (vehicle contained propylene glycol and polysorbate 80)	none	n=34 infants analyzed	18 in control group, and 16 in treatment group	Premature infants with diagnosed respiratory distress syndrome who survived for 10 days or more (to allow differentiation of radiographic criteria between RDS and BPD).	Primary	Increase of serum vitamin E from 0.28 +/− 0.02mg to 3.2+/− 0.28mg by the third dose administered, controls remained deficient at 0.28 +/− 0.06mg. Lower incidence of moderate to severe radiographic abnormalities in treatment group n=0, compared with n=6 in the control group. Infants in the treatment group demonstrated significant differences in duration of requirement for oxygen, positive pressure ventilation and endotracheal ventilation, despite statistically similar requirements during first 5 days of life
Ehrenkranz et al, 1982[109]	20mg/kg intramuscular Vitamin E at study admission, and 24, 48 and 168 hours later, then twice weekly until cessation of oxygen requirement (vehicle contained propylene glycol and polysorbate 80)	oral: 50 IU/day Vitamin E if weight was less than 1000 g and 25 IU/day if weight was greater than 1000 g. Given to all infants	n=80 infants analyzed	43 in control group, and 37 in treatment group	Premature infants with diagnosed respiratory distress syndrome who survived for 10 days or more (to allow differentiation of radiographic criteria between RDS and BPD).	Primary	Increase of serum vitamin E from baseline 0.45 +/− 0.04mg to 5.48+/− 0.6mg by the 72-hour dose, controls 0.6+/− 0.06mg at 72 hours. No BPD in infants who received less than 250 hours of oxygen therapy. No difference in incidence of BPD in the subset of infants who had greater than 250 hours of supplemental oxygen. In controls: 8 cases (40%) versus treatment group: 7 cases (33%), diagnosed by ongoing oxygen requirement at 30 days. Reanalysis of the 1978 Ehrenkranz study along with this publication reported possible diminished correlation of benefit due to the universal administration of some form of Vitamin E to all study participants. Even controls achieved normal adult serum values due to accessory supplements.
Hittner et al, 1981[75]	100mg/kg/day oral Vitamin E from day of life 0 to	none	n=101 infants analyzed	51 in control group, and 50	Premature infants weighing less than 1500	Secondary (Primary	No significant difference between incidence of BPD in controls: 13

Author and year	Intervention Studied	Other supplements	N	Group Allocation	Patient Characteristics	BPD Studied as Primary or Secondary Outcome?	Results
	discharge from the hospital (reported to be d/l alpha tocopherol) (vehicle contained propylene glycol and polysorbate 80.)			in treatment group	grams who required supplemental oxygen for respiratory distress syndrome. Excluded children who did not survive for four weeks due to need to observe retinal vascularization	Outcome Prevention of ROP)	cases (26%) versus treatment group: 15 cases (30%). Severity of illness/ BPD diagnostic criteria not reported.
Hittner et al, 1984[76]	15mg/kg intramuscular Vitamin E given on day 1 of life. 10mg/kg intramuscular Vitamin E given on day 2, 4, and 6 of life (reported to be d/l alpha tocopherol) (vehicle contained propylene glycol polysorbate 80, and polyoxyethylated castor oil.)	100mg/kg/day oral vitamin E given to all infants (control and treatment) daily until retinal vascularization was complete	n=168 infants analyzed	89 in control group, and 79 in treatment group	Premature infants weighing less than 1500 grams who required supplemental oxygen for respiratory distress syndrome. Excluded children who did not survive for four weeks due to need to observe retinal vascularization	Secondary (Primary Outcome Prevention of ROP)	No significant difference between incidence of BPD in controls: 17 cases (25.4%) versus treatment group 17 cases (25%). Severity of illness/ BPD diagnostic criteria not reported.
Johnson et al, 1989[77]	15mg/kg d/l alpha tocopherol Vitamin E given by IV with a lipid emulsion, PO, or intramuscular route, depending on the infant's feeding status. Dose titrated subsequently to keep serum concentrations close to 5mg/dl in treatment group (vehicle polyoxyethylated castor oil),	none	n=754 infants analyzed	384 in control group, and 370 in treatment group	Premature infants at gestational age <36 weeks and weighing less than 2000 grams, matched on birth weight.	Secondary (Primary Outcome Prevention of ROP)	No significant difference in duration of oxygen therapy or duration of ventilation requirements during hospitalization. No official diagnosis of BPD given. Reported increased incidence of necrotizing enterocolitis in infants <1500grams in the Vitamin E group after 8 days of treatment (few of whom were receiving enteral treatment)
Watts et al, 1981[74]	Oral Vitamin E supplement containing 16mg d/l alpha tocopherol given daily for six weeks (vehicle contained propylene glycol and polysorbate 80)	none	n=138 infants analyzed	71 in control group, and 67 in treatment group	Premature infants weighing less than 1500 grams expected to survive 48 hours.	Primary	No significant difference between incidence of BPD in controls: 17 cases (24%) versus treatment group: 15 cases (22%). BPD only occurred in mechanically ventilated infants
Watts et al, 1991[73]	Oral Vitamin E supplement containing 16mg d/l alpha tocopherol given daily for six weeks (vehicle contained polysorbate 80)	none	n=266 infants analyzed	134 in control group, and 132 in treatment group	Premature infants weighing less than 1500 grams expected to survive 48 hours.	Primary	20% reduction in cases of BPD with early death from 23% to 18% that was not statistically significant given power of the study. Incidence of BPD in controls: 27 cases (20%) compared to treatment group: 22 cases (17%). No increase in necrotizing enterocolitis observed with oral preparation.

Table 3

Use of Vitamin E Isoforms in Therapy or Prevention of BPD: Review of What is Known and Key Questions that Need to be Answered

Observational and RCTs	Proof of concept	Mechanism of Action
What is Known: • There is an association between decreased tocopherols and increased BPD.[59–61,64,69] • Trials have shown mixed results, but may have been affected by vehicle, route and dose.[69,72,74–76,127]	**What is Known:** • Alpha- and gamma- tocopherol have differing associations with childhood respiratory outcomes.[53,55,105–107]	**What is Known:** • Alpha- and gamma-tocopherol have differing effects on lung growth and lung inflammation. (Table 1)
What is not known: • Are there subpopulations of infants/mothers at greater risk of vitamin E deficiency and BPD? (Example: smokers) • Is there an optimal alpha- and gamma- tocopherol range associated with the lowest risk of BPD in premature neonates?	**What is not known:** • Does supplementation with a specific isoform of tocopherol during pregnancy or after premature birth protect against BPD development? • What are the dietary co-factors (vitamin C, selenium)? • What is the optimal route of delivery? Enteral vs. TPN? • When is the optimal timing of intervention? At-risk pregnancy or after premature birth?	**What is not known:** • How does supplementation with specific isoforms of tocopherol alter lung growth? • How does supplementation with alpha- and gamma-tocopherol alter oxygen induced lung inflammation in premature infants or in models of prematurity?