

New Perspective Allows New Solutions

For

TOBACCO SMOKING

Leading To Improved Health & Increased Longevity

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Disclosure

**Harlan Bieley, MD, MS, is the inventor/owner
U.S. Patent #8,889,194**

Our Purpose Today

1. Reveal that Tobacco Smoking and Secondhand Smoke Exposure depletes antioxidants, micronutrients, and has other losses.
2. Replenishing these losses in Smokers:
decreases morbidity and mortality
improves numerous bio-markers
giving people a fighting chance of
staying well and living longer.

Our Purpose Today

3. Reveal that N-acetylcysteine (NAC): helps with **relapse prevention** once smokers quit and has salutary effects.

About Harlan Bieleley

- "It is not that I am so smart. But I stay with the questions much longer." **Albert Einstein**
- I, 'lived inside the question' of how to help the smoker so that I can make a difference in their life.
(and tortured my family and friends throughout the process)

Evolution of a new idea

- To paraphrase the German philosopher Schopenhauer:
- Initially, it's ridiculed, it's gobbledygook.
- Then, it's obvious to everyone.
- Lastly, they will tell you that they said it to you first.

As doctors we typically consider...

- History of the Present Illness, HPI:
- Along with
- Allergies
- Medicines

Why?

- Because we would not want to give a drug to the patient who is obviously allergic to it.
- Also, we consider medicines that might cause a drug-drug interaction, side effect.

Unmet and Underappreciated

- An unmet and underappreciated need that the medical community needs to consider...
- Drug-Induced Nutrient Depletions.

Not typically considered: Drug-Induced Nutrient Depletions

source: Drug-Induced Nutrient Depletion Handbook Ross Pelton, James LaValle

Drug-Induced Nutrient Depletion

- About half the drugs used in clinical practice have documented nutrient depleting effects.
- Co-enzyme Q10, folic acid, B2, B6, Mg, Zn are nutrients most likely to be depleted.
- Mechanisms include impaired absorption or bioactivation; increased excretion.

Tobacco smoking- contains nicotine- a drug

- “**Nicotine** is a stimulant and potent parasympathomimetic alkaloid that is naturally produced in the nightshade family of plants. It is used for the treatment of **tobacco** use disorders as a smoking cessation aid and **nicotine** dependence for the relief of withdrawal symptoms.”
- -Wikipedia

Tobacco contains nicotine- an abused substance

- Nicotine is highly [addictive](#). It is one of the most commonly abused drugs.
- Tobacco laws regulate the sale of tobacco throughout the world.

- Grana R, Benowitz N, Glantz SA (May 2014). ["E-cigarettes: a scientific review"](#). *Circulation*. **129** (19): 1972–86.
- Holbrook BD (June 2016). "The effects of nicotine on human fetal development". *Birth Defects Research. Part C, Embryo Today*. **108** (2): 181–92.
- Sajja RK, Rahman S, Cucullo L (March 2016). ["Drugs of abuse and blood-brain barrier endothelial dysfunction: A focus on the role of oxidative stress"](#). *Journal of Cerebral Blood Flow and Metabolism*. **36** (3): 539–54.

Drug-Induced Nutrient Depletion

Tobacco Smoking and Secondhand Smoke:

- Vitamins: C, D3, E, A
- B-Vitamins: B2, B6, B12, biotin, folate
- Minerals: Calcium, Magnesium, Manganese, Selenium, Zinc, Copper
- Antioxidants: Glutathione, Superoxide Dismutase, Vitamins C, E
- Hormones and other substances: Melatonin, Choline, Serotonin agents, Dopamine, NAC, Glutathione Peroxidase, Carotenoids

Source: Harlan Bieleley, MD,MS References 1-115.

References and Abstracts available by request.

Centers for Disease Control

- The United States Surgeon General, in a **700 page** report concludes **that any exposure to tobacco smoke, even occasional smoking or exposure to secondhand smoke, causes *immediate* damage to your body.**
- **That damage can lead to serious illness or death.** [Regina M. Benjamin](#), MD, MBA VADM, USPHS, Surgeon General.
Exposure to Tobacco Smoke Causes Immediate Damage: A Report of the Surgeon General Public Health Rep. 2011 Mar-Apr; 126(2): 158–159.

What happens when you replenish depleted substances?

- What's the effect of replenishment of these depleted substances?
- We will answer these questions by looking at those who are exposed to secondhand smoke, tobacco smokers, pregnant smokers, and those who have made a quit attempt.

Secondhand Smoke Exposure and Replenishment

- Secondhand Smoke Exposure and Replenishment of Antioxidants and Micronutrients.

Vitamin C supplement for Secondhand smoke

- Exposure to environmental tobacco smoke (ETS) has been linked to increased risk of lung cancer and cardiovascular diseases in nonsmokers. Current research suggests that some of these diseases are associated with elevated oxidative stress.
- Plasma F2IsoP concentrations of subjects in the **Vitamin C** and mixture groups decreased significantly by 17.2 pmol/l ($P = 0.0105$) and 19.2 pmol/l ($P = 0.0083$) when compared with the placebo group (11.4% and 12.7%, respectively).
- Daily Anti-Oxidant supplementation (especially with **Vitamin C**) decreases this oxidative stress biomarker in passive smokers.
- This finding might be of importance for the prevention of ETS-associated adverse health effects in nonsmokers.
- [Dietrich M](#)¹, [Block G](#), [Benowitz NL](#), et al. **Vitamin C supplementation decreases oxidative stress biomarker f2-isoprostanes in plasma of nonsmokers exposed to environmental tobacco smoke.** Nutr Cancer 2003;45(2):176-84.

Secondhand smoke increases eye disease

Nutrient treatment improves disease

- Secondhand smoke has been shown to increase eye disease, such as age-related macular degeneration.
- The Age-Related Eye Disease Study from the National Eye Institute (NEI) is the first large clinical trial to test the effect of a high dose antioxidant vitamin combination plus **zinc** on preventing or delaying the progression of AMD and its associated vision loss.
- The antioxidant vitamins and **zinc** supplement reduced the risk of developing advanced AMD by about 25 % in the study subjects who were at high risk for developing the advanced stage of this disease. In the same high-risk group, the supplements also reduced vision loss by 19%.
- According to researchers, **this supplement combination is the first effective treatment to slow the progression of AMD.**

<http://www.news-medical.net/news/2005/12/22/15097.aspx>

Vitamin C may help protects nonsmokers from secondhand smoke oxidative stress

- **Vitamin C** helps reduce oxidative stress in passive smokers
- published Aug. 5 in the journal *Nutrition and Cancer*, “**provides hope for people who cannot escape secondhand smoke**”, said Gladys Block, professor of nutritional epidemiology at UC Berkeley's School of Public Health and principal investigator of the study.
- “there are few studies that have looked at the effects of **vitamin C** on oxidative stress in secondhand smokers the way we have.”
- Measured levels of F2-Isoprostanes.
- 67 adult nonsmokers who had been randomly assigned to one of three treatment groups in the double-blind trial. One group took daily doses of 500 milligrams of **vitamin C**, a second group took a daily mixture of **vitamin C** with **vitamin E** and the antioxidant alpha-lipoic acid, and a third group took daily placebo capsules.
- after two months of treatment, blood levels of F2-Isoprostanes dropped significantly - by 11.4 percent and 12.7 percent for those in the **vitamin C** and the mixture groups, respectively - compared with those taking the placebo. **The difference between the vitamin C-only group and the mixture group was not statistically significant.**
- “**These results are very encouraging,**” said Dietrich. “**They show that vitamin C may help protect nonsmokers from the oxidative damage caused by secondhand tobacco smoke.**”
- http://berkeley.edu/news/media/releases/2003/08/05_vitamin.shtml

Secondhand smoke and vitamin C in children

- 512 children aged 2-12 y; 50% of them were exposed to ETS in the home because their parents smoked.
- Plasma ascorbate concentrations were lower, by 3.2 micro mol/L on average, in ETS-exposed, highly significant difference ($P = 0.002$).
- Children exposed to ETS **should be encouraged to consume increased amounts of foods rich in vitamin C or should be given the equivalent amount of this vitamin as a supplement.**
- Alan M Preston, Cindy Rodriguez, Cynthia E. Rivera, et al. Influence of environmental tobacco smoke on vitamin C status in children. Am J Clin Nutr 2003 Jan;77(1):167-72.

Vitamin E and Selenium protective against tobacco smoke hazards and are depleted by tobacco smoke

- The protective effects of **vitamin E and Se (selenium)** against cigarette smoke hazards on second-hand smoker (passive smoker) male mice (Balb/c) were investigated.
- **Vitamin E and Se (selenium)**, when given to smoke-exposed mice together, had an additive protective effect against cigarette smoke hazards ($p < 0.05$).
- **Vitamin E and Se** had an additive protective effect against increasing MDA level.
- **Vitamin E** had a protective effect against formation of 8-OHdG amounts and COMT activity alterations.
- [Fiskin K¹](#), [Ozkan A](#), [Ayhan AG](#). Investigation of protective effects of selenium and vitamin E against DNA oxidation, membrane damage and alteration of COMT metabolism in smoke-exposed male mice (Mus musculus, Balb/c). [Acta Biol Hung](#). 2006 Dec;57(4):403-13.

Melatonin and Vitamin C on smoke-induced kidney damage

- **Melatonin** and **vitamin C** administration produced in some degree protection against smoke-induced damage (in the kidney).
- Ozan E, Sonmaz EF, Ozan S, et al. Effects of Melatonin and vitamin C on cigarette smoke-induced damage in the kidney. *Toxicol Ind Health* 2007 Sept; 23(8):479-85

Vitamin E and Selenium

- Cigarette smoking generates reactive oxidant species and contributes to systemic oxidative stress, which plays a role in the pathophysiology of chronic diseases.
- **Long-term Vitamin E supplementation decreases urine 8-iso-PGF2 α among male cigarette smokers.**
- K A Guertin, RK Grant, KB Arnold, et al. Effect of Long Term Vitamin E and Selenium Supplementation on Urinary F2-Isoprostanes, a Biomarker of Oxidative Stress.

Vitamin D replacement

- Hypovitaminosis D was frequent in children with asthma who lived in a Mediterranean country. In these children, lower levels of **vitamin D** were associated with reduced asthma control and **passive smoking exposure**.
- I Chinellato, M Piazza, M Sandri, et al. Correlation between Vitamin D serum levels and Passive Smoking Exposure in Children with Asthma. Allergy Asthma Proc 2018 May 1;39(3):8-14.

Secondhand smoke in workplace mitigated by antioxidant supplementation

- Environmental tobacco smoke (ETS) is a pervasive contaminant in the workplace.
- 8-Hydroxy-2-deoxyguanosine, a marker of oxidative DNA damage was 63% greater in the exposed group compared with controls.
- 60-day trial of over-the-counter antioxidant formulation consisting of 3000 microg of beta-carotene, 60 mg of vitamin C, 30 I.U. of alpha-tocopherol, 40 mg of zinc, 40 microg of selenium, and 2 mg of copper.
- A 62% decrease in 8-hydroxy-2-deoxyguanosine was observed after supplementation. Lipid peroxidation levels were also decreased, as were the antioxidant enzyme activities.
- The biochemical evidence suggests that **exposure to ETS in the workplace increases oxidative stress and that antioxidant supplementation may provide some protection.**
- DJ Howard, RB Ota, LA Briggs, et al. Oxidative stress induced by environmental tobacco smoke in the workplace is mitigated by antioxidant supplementation. Cancer Epidemiol Biomarkers Prev. 1998 Nov;7(11):981-8

Tobacco Smoking

- Tobacco Smoking and Replenishment of Antioxidants and Micronutrients.

Mechanisms of action of tobacco smoke damage and Vitamin C

- The current scientific opinion considers ROS-mediated pathways to contribute significantly to the pathogenesis of many neurological diseases. This hypothesis is strongly supported by *in vivo* and *in vitro* experiments where antioxidant supplementation prevents oxidative damage and inflammation induced by cigarette smoke.
- Even the Food and Nutrition Board of the National Academy of Sciences has established a higher recommended dietary allowance (RDA) of **vitamin C** for smokers (over 200 mg/day versus the recommended 90 mg/day for non-smokers).
- Recent observations suggest **antioxidant supplementation has proven to be beneficial in alleviating a loss of BBB integrity and a vascular inflammatory response in smoke-exposed *in vitro* BBB cultures**.
- Pun PB, Lu J, Moolchhala S. Involvement of ROS in BBB dysfunction. Free Radic Res. 2009;43:348–364. [\[PubMed\]](#)
- Hossain M, Mazzone P, Tierney W, Cucullo L. In vitro assessment of tobacco smoke toxicity at the BBB: do antioxidant supplements have a protective role? BMC Neurosci. 2011;12:92. [\[PMC free article\]](#) [\[PubMed\]](#)
- [Pooja Naik](#) and [Luca Cucullo](#). **Pathobiology of tobacco smoking and neurovascular disorders: untied strings and alternative products**. Fluids Barriers CNS. 2015; 12: 25.

Supplementation in Smokers

- Antioxidant supplementation prevented cardiac hypertrophy and attenuated indicators of atherosclerosis markers associated with cigarette smoke exposure.
- [Al Hariri M](#)¹, [Zibara K](#)², [Farhat W](#)³, et al. Cigarette Smoking-Induced Cardiac Hypertrophy, Vascular Inflammation and Injury Are Attenuated by Antioxidant Supplementation in an Animal Model. [Front Pharmacol](#). 2016 Nov 9;7:397.

Vitamin B-6 in smokers and lung cancer

In a multinational study in Europe
Greater than one half million participants:

Vitamin B6 levels were inversely associated with the risk of cancer.

Elevated serum **vitamin B-6** and methionine levels are associated with lower risk of lung cancer in tobacco smokers.

- Johansson M, et al. Serum B vitamin levels and risk of lung cancer. JAMA 2010 Jun16;303(23):2377-85

Vitamin B-6 is protective

- The higher **vitamin B-6** intakes were linked to protection against inflammation.

- Morris MS, et al Vitamin B-6 intake is inversely related to, and the requirement is affected by, inflammation status. J Nutr 2010 Jan;140(1):103-10.

Vitamin B6 is protective

Circulating **vitamin B6** levels have been found to be inversely associated with lung cancer.

D Theofylaktopoulou, O Midttun, P Ueland. Impaired Functional Vitamin B6 Status is associated with increased risk of lung cancer. Int J Cancer 2018 Jun 15;142(12):2425-2434.

Loss of vitamin B6 associate with lung cancer

- Increased vitamin B6 catabolism related to inflammation has been positively associated with lung cancer risk in two prospective European studies.
- This study included 5,323 incident lung cancer cases and 5,323 controls individually matched by age, sex, and smoking status.
- Based on pre-diagnostic data from 20 cohorts across 4 continents, this study **confirms that increased vitamin B6 catabolism related to inflammation and immune activation is associated with a higher risk of developing lung cancer.**
- H Zuo, PM Ueland, O Midttun, et al. Vitamin B6 catabolism and lung cancer risk: results from the Lung Cancer Cohort Consortium (LC3). Ann Oncol 2019 Mar 1;30(3):478-485

Vitamin B6- smoking reduction

- The vitamin B-6 group had an approximate 25% reduction in tobacco smoking ($P < 0.0001$) greater than the control group over 10 days. Hassan also used 50mg in this study.
- This is preliminary clinical evidence and not definitive proof that vitamin B6 is a smoking-reduction treatment.
- Hassan, Jubran K. Potential Effect of Oral Pyridoxine Alone and in Combination with Meclizine on Cigarette Smoking During a 10 day trial. Int. J Pharmaceutical Sciences and Research, 2017;8(9):3966-3970.
- My observation among tobacco smokers has shown a change in the taste of tobacco smoke. One patient who drank a cola beverage that contained vitamins B6 and B12 said, “the cigarettes taste nasty” after imbibing that beverage. In other patients where the vitamin B12 was not included, also showed a diminution of tobacco smoking. This unpleasant sensory experience may contribute to smoking reduction. This is preliminary evidence.

Vitamin B-6 and Folate protective

- Circulating concentrations of B vitamins and factors related to one-carbon metabolism have been found to be strongly inversely associated with lung cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) study.
- Participants with higher circulating concentrations of **Vitamin B6 and Folate** had a modestly decreased risk of lung cancer risk overall.
- These study results are compatible with a small decrease in lung cancer risk in ever smokers who avoid low concentrations of circulating **Folate and vitamin B6**.
- [Fanidi A](#)¹, [Muller DC](#)¹, [Yuan JM](#)¹, et al. Circulating Folate, Vitamin B6, and Methionine in Relation to Lung Cancer Risk in the Lung Cancer Cohort Consortium (LC3). [J Natl Cancer Inst](#). 2018 Jan 1;110(1).

Vitamin C depletion

- **Vitamin C** has been shown to prevent cigarette smoke induced inflammation by a major inflammatory marker (NF-kB).
- **Vitamin C** could be used for the prevention of cigarette smoke –induced inflammatory diseases.

- Das B, Maity PC, Sil AK. Vitamin C forestalls cigarette smoke induced NF-kB activation in alveolar epithelial cells. Toxicol Lett 2013 Jun20;220(1):76-81

Magnesium replacement

- >26,556 Finnish male smokers
- high levels of **Magnesium** in male smokers
- primary prevention of cerebral infarction.

- Larsson SC, et al. Magnesium, calcium, potassium, and sodium intakes and risk of stroke in male smokers. Arch Intern Med 2008 Mar 10;168(5):459-65.

Magnesium replacement

- We followed the **Magnesium** effect with internal administration in 53 adult neurotic smoking patients (more than 10 cigarettes/day) of both genders admitted into psychiatric hospital.
- patients that received **Magnesium** therapy showed a **significant decrease in the number of cigarettes smoked.**
- The results suggest that **Magnesium** might be a useful **adjuvant in treatment of nicotine pharmacodependence.**
- M Nechifor, D Cherlarescu, I Mandreci, et al. Magnesium Influence on Nicotine Pharmacodependence and Smoking. Magnes Res. 2004 Sep;17(3):176-81.

Vitamin C supplement

Vitamin C markedly improves endothelium-dependent responses in chronic smokers.

- T Heitzer, H Just, T Munzel. Antioxidant Vitamin C Improves Endothelial Dysfunction in Chronic Smokers. Circulation 1996 Jul 1;94(1):6-9.

Vitamin C supplement

- Waterpipe tobacco smoking (WTS) resulted in inducing memory impairment, **which was prevented by Vit C** administration.
 - WTS exposure impaired both short- and long-term memory ($p < .05$).
 - This could be related to preserving hippocampus antioxidant mechanisms by **vitamin C** during WTS exposure.
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- MAY Alqudah, KH Alzoubi, GM Ma'abrih, et al. Vitamin C Prevents Memory Impairment Induced by Waterpipe Smoke: Role of Oxidative Stress Inhal Toxicol. Mar-Apr 2018;30(4-5):141-148.

Vitamin C supplement modifies COPD in smokers

- **Vitamin C** has a protective role against the risk of obstructive airways disease.
- **Vitamin C** an **effective modifier** for the **adverse effects of smoking on the risk of obstructive airways disease.**
- LA Sargeant, A Jaekel, NJ Wareham. Interaction of vitamin C with the relation between smoking and obstructive airways disease in EPIC Norfolk. European Prospective Investigation into Cancer and Nutrition. Eur Respir J 2000Sept;16(3):397-403

Vitamin C supplement

- This study (108 patients)
- higher intake of **vitamin C** is associated with the decreased risk of non-fatal Ischemic Heart Disease (IHD) in a population with a high prevalence of smoking.
- CM Nam, KW Oh, KH Lee, et al. Vitamin C Intake and Risk of Ischemic Heart Disease in a Population With a High Prevalence of Smoking. J am Coll Nutr 2003 Oct;22(5):372-8.

Vitamin C and vitamin E more efficient in reducing the inflammatory process combined than alone

- The inflammatory process after cigarette exposures was reduced by **ascorbic acid (vitamin C)** , **alpha-tocopherol (vitamin E)** more efficiently by both vitamin supplementations.
- [Silva Bezerra F](#), [Valença SS](#), [Lanzetti M](#), et al. **Alpha-tocopherol and ascorbic acid supplementation reduced acute lung inflammatory response by cigarette smoke in mouse.** Nutrition. 2006 Nov-Dec;22(11-12):1192-201.

Vitamin C replenishment

- Cigarette smoking is one of the most critical risk factors for peripheral arterial disease (PAD) and inversely correlated **vitamin C**.
- In a study with 912 smokers and 207 diagnosed with peripheral arterial disease (PAD).
- As an anti-oxidant and anti-inflammatory, low serum **vitamin C** appears to associates with the risk of PAD in smokers. Modulating **vitamin C** in current smokers may help mitigate the risk of PAD ...
- [Guangzhi Cong](#),^a [Ru Yan](#),^b and [Ulka Sachdev](#)^a Low serum vitamin C correlates with an increased risk of peripheral arterial disease in current smokers: Results from NHANES 2003–2004
- [Int J Cardiol Hypertens.](#) 2020 Sep; 6: 100037.

Vitamin C cocktail replenishment in smokers

- In a double-blind, placebo-controlled design, the effect of a vitamin cocktail containing 272 mg **Vitamin C**, 31 mg **all-rac-alpha-tocopheryl acetate**, and 400 mcg **Folic acid** on plasma antioxidants was determined in a population of smokers (n = 37) and nonsmokers (n = 38).
- Only **ascorbic acid** was significantly depleted by smoking per se ($P < 0.01$).
- After the 3-mo supplementation period, **ascorbic acid** was efficiently replete in smokers ($P < 0.001$).
- Plasma **ascorbic acid** was depleted by smoking and replenished by moderate supplementation.
- [Lykkesfeldt J, Christen S, Wallock LM](#), et al. Ascorbate is depleted by smoking and repleted by moderate supplementation: a study in male smokers and nonsmokers with matched dietary antioxidant intakes. Am J Clin Nutr. 2000 Feb;71(2):530-6.

NAC

- Human smokers treated with **N-acetylcysteine** reported a **reduction in cigarettes smoked**.
- For the smoking reduction study in humans, nicotine-dependent smokers were treated for 4 weeks with **N-acetylcysteine** (2,400 mg daily)
- cystine-glutamate exchanger and the glial glutamate transporter are downregulated after nicotine self-administration, and augmenting exchanger activity with **N-acetylcysteine** **reduced the number of cigarettes smoked in nicotine-dependent individuals**.
- [Knackstedt LA¹](#), [LaRowe S](#), [Mardikian P](#), et al. **The role of cystine-glutamate exchange in nicotine dependence in rats and humans.** [Biol Psychiatry](#). 2009 May 15;65(10):841-5

NAC

- **NAC** treatment (3gm/day) **significantly reduced the daily number of cigarettes smoked, versus placebo.**
- **NAC** treatment also significantly reduced the Hamilton Depression Rating Scale score in patients with tobacco use disorder.
- [Prado E](#), [Maes M](#), [Piccoli LG](#), et al. N-acetylcysteine for therapy-resistant tobacco use disorder: a pilot study. [Redox Rep](#). 2015 Sep;20(5):215-22.

Vitamin C and vitamin E helps protect against smoke induced inflammation and helps protect the blood brain barrier

- Smokers often have significant decreases in plasma **alpha-tocopherol (vitamin E)** and **ascorbic acid (vitamin C)** levels due to increased anti-oxidative mobilization in response to oxidative stress evoked by TS (tobacco smoke).
- Pre-treatment with antioxidant **vitamins (C and/or E)** effectively reduced the pro-inflammatory activity associated with TS, protecting the viability and functions of the BBB (blood brain barrier).
- Loss of endothelial viability as well as BBB function and integrity caused by TS exposure **can be prevented or at least reduced by normal physiologic concentrations of antioxidant vitamins in vitro.**
- [Hossain M¹, Mazzone P, Tierney W, Cucullo L.](#) In vitro assessment of tobacco smoke toxicity at the BBB: do antioxidant supplements have a protective role? [BMC Neurosci.](#) 2011 Sep 24;12:92. doi: 10.1186/1471-2202-12-92.

Vitamin D replacement

- **Vitamin D3** is reduced by exposure to tobacco smoke.
- Exposure to Cigarette Smoke (CS) is associated with **reduced 25VD3 levels** and an impaired ability of human sino-nasal epithelial cell (HSNECs) to convert 25VD3 to 1,25VD3.
- **supplementation with 1,25VD3 (1, 25 Vitamin D3) will reverse smoke-induced inflammatory responses by HSNECs.**
- [Mulligan JK](#)¹, [Nagel W](#)², [O'Connell BP](#)², et al. Cigarette smoke exposure is associated with vitamin D3 deficiencies in patients with chronic rhinosinusitis. [J Allergy Clin Immunol](#). 2014 Aug;134(2):342-9.

Vitamin D and risk of tobacco-related cancers

- vitamin D is decreased in smokers.
- **vitamin D may be protective against tobacco-related cancers through the inhibition of the formation of tumors induced by tobacco carcinogens.**
- high vitamin D status [25(OH)D concentration ≥ 30 ng/mL] was associated with decreased risk of tobacco-related cancers, especially in smokers.
- These results, which are supported by mechanistic plausibility, suggest that **vitamin D may contribute to the prevention of tobacco-induced cancers in smokers** and deserve additional investigation.
- Melanie Deschasaux, Jean-Claude Souberbielle, Paule Latino-Martel, et al. Prospective associations between vitamin D status, vitamin D-related gene polymorphisms, and risk of tobacco-related disease. Am J Clin Nutr 2015 Nov;102(5):1207-15.

Vitamin E and Vitamin C depletion

- **Vitamin E** disappearance is accelerated in cigarette smokers due to their increased oxidative stress and is normalized by **vitamin C** supplementation.
- [Bruno RS¹](#), [Leonard SW](#), [Atkinson J](#), et al. **Faster plasma vitamin E disappearance in smokers is normalized by vitamin C supplementation.** [Free Radic Biol Med](#). 2006 Feb 15;40(4):689-97.

In case of a heart attack, N-Acetylcysteine (NAC) shown to protect heart

- **N-acetylcysteine (NAC)** treatment significantly reduced tobacco-exposed induced infarct size.
- These findings identify a novel post-infarction therapy for amelioration of the adverse effects of tobacco exposure on the infarcted myocardium and **advocate the use of dietary supplement antioxidants for habitual smokers to prevent and reverse cardiovascular adverse effects in the absence of successful achievement of cessation of smoking.**
- [Khanna AK¹](#), [Xu J](#), [Mehra MR](#). Antioxidant N-acetyl cysteine reverses cigarette smoke-induced myocardial infarction by inhibiting inflammation and oxidative stress in a rat model. [Lab Invest](#). 2012 Feb;92(2):224-35

NAC protects lungs from tobacco smoke

- **NAC** administration exhibited a **significant and considerable protective effect towards the cigarette smoke-induced alterations** of BAL (broncho-alveolar lavage) cellularity, and bone marrow cytotoxicity.
- [Balansky RB](#)¹, [D'Agostini F](#), [Zanacchi P](#), et al. Protection by N-acetylcysteine of the histopathological and cytogenetical damage produced by exposure of rats to cigarette smoke. [Cancer Lett.](#) 1992 Jun 15;64(2):123-31.

Financial and salutary effects of NAC in smokers and ex-smokers

- **N-acetylcysteine (NAC) 600 mg twice daily** is a well-tolerated oral antioxidant mucolytic that reduces the risk of moderate to severe chronic obstructive pulmonary disease (COPD) exacerbations
- Compared with placebo (N = 482), **NAC** (N = 482) **reduced the rate of healthcare resource utilization (HCU) events by 20%** ($p = 0.0027$), **with a larger effect in current/ex-smokers (23%; $p < 0.01$).**
- **NAC reduces the rate of COPD exacerbations**, particularly in patients with COPD who have a **significant smoking history...**
- [Papi A](#)¹, [Zheng J](#)², [Criner GJ](#)³, et al. Impact of smoking status and concomitant medications on the effect of high-dose N-acetylcysteine on chronic obstructive pulmonary disease exacerbations: A post-hoc analysis of the PANTHEON study. [Respir Med](#). 2019 Feb;147:37-43.
- [Zheng JP](#)¹, [Wen FQ](#), [Bai CX](#). High-dose N-acetylcysteine in the prevention of COPD exacerbations: rationale and design of the PANTHEON Study. [COPD](#). 2013 Apr;10(2):164-71.

NAC prevents genotoxic damage to lung cells

- This study demonstrates that Cigarette Smoke is clearly clastogenic (causing breaks in chromosomes, which results in sections of a chromosome being deleted, added, or rearranged) to alveolar macrophages and that **NAC** can efficiently prevent this cytogenetic damage.

- [D'Agostini F¹](#), [Scatolini L](#), [Maggiani M](#), et al. [Chemoprevention of genotoxic damage in lung cells of rats exposed to cigarette smoke]. [Boll Soc Ital Biol Sper](#). 1992 Feb;68(2):137-42.

Pregnant Smokers

Pregnant Smokers and Supplementation

Vitamin C and Vitamin E supplement in Pregnant Smokers

- **Vitamin C and E supplementation was protective of placental abruption and preterm birth in smokers.**
- A Abramovici, R Gandle, R Clifton, et al. Prenatal Vitamin C and Vitamin E Supplementation in Smokers is Associated with Reduced Placental Abruption and Preterm Birth: A Secondary Analysis. BJOG.2015;122(13):1740-1747.
- R Gandle, A Abramovici, et al. Prenatal vitamin C and E supplementation is associated with a reduction in placental abruption and preterm birth in smokers. Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Pregnancy Hypertens. 2012 Jul;2(3):331-2.
- **Vitamin C supplementation to pregnant smokers can lessen the impact of maternal smoking on offspring pulmonary function and decrease the incidence of wheeze at 1 year of age.**
- LE Shorey-Kendrick, CT McEvoy, B Ferguson, et al. Vitamin C Prevents Offspring DNA Methylation Changes Associated With Maternal Smoking in Pregnancy. Am J Respir Crit Care Med 2017 Sep 15;196(6):745-755.
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Vitamin C in Pregnant Smokers

- **Supplemental vitamin C to pregnant smokers significantly improved newborn pulmonary function tests.**
- CT McEvoy, LS Shore-Kendrick, K Milner, et al. Oral Vitamin C (500mg/d) to Pregnant Smokers Improves Infant Airway Function at 3 Months (VCSIP). A Randomized Trial. Am J Respir Crit Care Med 2019 May 1;199(9):1139-1147.
- **Smokers with Adequate vitamin C intake show a preferable Pulmonary Function Test.**
- JY Shin, JY Shim, DC Lee, et al. Smokers with Adequate Vitamin C intake show a preferable Pulmonary Function Test. J AM Coll Nutr 2015;34(5):385-90

Vitamin C in Pregnant Smokers

- **Vitamin C** supplementation (500mg/day) in pregnant smokers is a safe and inexpensive intervention that may **reduce the economic burden of pediatric asthma.**
- L Yieh, CT McEvoy, SW Hoffman, et al. Cost effectiveness of Vitamin C Supplementation for Pregnant Smokers to Improve Offspring Lung Function at Birth and Reduce Childhood wheeze/asthma. J Perinatol.2018 Jul;38(7):820-827.

Vitamin C and fetal smoke exposure

- We previously demonstrated that prenatal nicotine exposure decreases neonatal pulmonary function in non-human primates (NHP) and maternal **vitamin C** supplementation attenuates these deleterious effects.
- **Vitamin C** supplementation mitigated the harmful effects of prenatal nicotine exposure on placental hemodynamics and development suggesting its use may limit some of the adverse effects associated with smoking during pregnancy.
- [Jamie O. Lo](#), MD,¹ [Matthias C. Schabel](#), PhD,² [Victoria H.J. Roberts](#), et al. Vitamin C Supplementation Ameliorates the Adverse Effects of Nicotine on Placental Hemodynamics and Histology in Non-Human Primates. [Am J Obstet Gynecol. 2015 Mar; 212\(3\): 370.e1–370.e8](#)

Prenatal smoking and effect modification with folate during pregnancy

- 701 mother child pairs studied
- Increased **folate** intake during pregnancy (from foods and/or supplements) may mitigate the risk of fetal growth restriction (small for gestational age, SGA) among those who are unable to quit smoking or cannot avoid secondhand smoke during pregnancy.
- Adrienne T Hoyt, Anna V Wilkinson, Peter H Langlois, et al. Prenatal exposure to tobacco and adverse birth outcomes: effect modification by folate intake during pregnancy. Matern Health Neonatol Perinatol 2022 Sept 12;8(1):6

NAC chemoprevention prevents lung tumors from tobacco smoke

- We recently demonstrated that mainstream cigarette smoke (MCS) induces a potent carcinogenic response in mice when exposure starts soon after birth.
- We also showed that the antioxidant **N-acetylcysteine (NAC)** prevents the extensive nucleotide and gene expression alterations that occur 'physiologically' at birth in mouse lung.
- Treatment with **NAC during pregnancy strikingly inhibited the formation of benign lung tumors and totally prevented occurrence of carcinomas.**
- These findings demonstrate for the **first time that treatment during pregnancy with an antioxidant chemo-preventive agent can affect the induction of tumors consequent to exposure to a carcinogen after birth.**
- [Balansky R¹](#), [Ganchev G](#), [Iltcheva M](#), et al. Prenatal N-acetylcysteine prevents cigarette smoke-induced lung cancer in neonatal mice. [Carcinogenesis](#). 2009 Aug;30(8):1398-401.

Relapse Prevention among Just Quit Smokers

Relapse Prevention Among Just Quit Smokers

NAC

- Evidence has emerged that glutamate transmission plays an important role in relapse.
- **N-acetylcysteine (NAC)**(3,600mg/day), restores glutamate homeostasis and appears to be a potential new treatment for substance dependence. (N=22)
- **NAC** might be a promising new treatment option for relapse prevention in nicotine dependence.
- [Schmaal L](#)¹, [Berk L](#), [Hulstijn KP](#), et al. Efficacy of N-acetylcysteine in the treatment of nicotine dependence: a double-blind placebo-controlled pilot study. . [Eur Addict Res](#). 2011;17(4):211-6.

NAC

- Smokers in the **N-Acetylcysteine** (1,200mg bid), group (n=8) maintained abstinence, reported less craving and higher positive affect ($p < 0.01$, each group).
- NAC maintained abstinence, reported less craving and positive affect (all P 's < 0.01) for 3 ½ days.
- **NAC may positively affect dysregulated cortico-striatal connectivity, restructure reward processing and help to maintain abstinence immediately following a quit attempt.**
- **NAC** might be a promising new treatment option for relapse prevention in nicotine dependence.
- [Froeliger B](#)¹, [McConnell PA](#)², [Stankeviciute N](#), et al. The effects of N-Acetylcysteine on frontostriatal resting-state functional connectivity, withdrawal symptoms and smoking abstinence: A double-blind, placebo-controlled fMRI pilot study. [Drug Alcohol Depend.](#) 2015 Nov 1;156:234-42.

NAC

This randomized controlled trial examined the efficacy and safety of **N-acetylcysteine** as an adjunctive treatment for smoking cessation.

First-line treatment for smoking cessation plus adjunctive N-acetylcysteine or placebo significantly reduced exhaled carbon monoxide (Coexh) ($p < 0.01$) $N=34$.

These findings **highlight the need to associate N-acetylcysteine** with first-line treatment for smoking cessation, since combined treatment may affect inflammation and metabolism components.

- [Regina C B R Machado¹²](#), [Heber O Vargas¹³](#), Marcela M Baracat, et al. N-acetylcysteine as an adjunctive treatment for smoking cessation: a randomized clinical trial. Braz J Psychiatry. Sept-Oct 2020;42(5):519-526

NAC

- Oral **N-acetylcysteine (NAC)** (100 mg/kg) was administered daily to the animals to determine its effect on both chronic voluntary EtOH and nicotine intake, on EtOH relapse and nicotine-conditioned place preference (CPP) reinstatement.
- Oral **NAC** administration...markedly inhibited (90%) voluntary nicotine intake and fully suppressed nicotine-conditioned place preference reinstatement.
- Data indicate... **the oral chronic administration of NAC may be of value in the concomitant treatment of alcohol and nicotine use disorders.**
- ME Quintinella, P Morales, F Ezquer, et al. **Commonality of Ethanol and Nicotine Reinforcement and Relapse in Wistar-Derived UChB Rats: Inhibition by N-Acetylcysteine.** Alcohol Clin Exp Res 2018 October;42(10):1988-1999

NAC

- Study evaluating NAC for end of treatment abstinence in adult smokers as a **monotherapy at 8 weeks** showed **no difference between placebo and NAC 1,200mg bid (N=59), placebo (N=55).**
- Authors state that **NAC may potentially be more useful in a younger population, as a combination pharmacotherapy, or in the presence of more intensive psychosocial treatment.**
- E A McClure, A E Wahlquist, R L Tomko, et al. Evaluating N-Acetylcysteine for early and end-of-treatment abstinence in adult cigarette smokers. Drug Alcohol Depend. 2021 Aug 1;225:108815

Smokeless Tobacco

- Smokeless tobacco use among adolescents remains a public health concern worldwide.
- The prevalence of smokeless tobacco use decreased in 57 of 100 countries, increased in 32 countries, and remained unchanged in 11 countries.
- [Hui Yang](#), [Chuanwei Ma](#), [Min Zhao](#), et al. Prevalence and trend of smokeless tobacco use and its associated factors among adolescents aged 12-16 years in 138 countries/territories, 1999-2019.

Smokeless Tobacco

- Although the primary form of **tobacco** use **worldwide** is cigarette smoking, the large majority of users in **India** consume **smokeless** forms of **tobacco**.
- There is a positive association between former smoking and current smokeless use may point to temporal substitutability at the individual level

- Kostova D, Dave D. [Smokeless tobacco use in India: Role of prices and advertising](#). Soc Sci Med. 2015 Aug;138:82-90.

Smokeless tobacco

- **Homocysteine concentrations in smokeless tobacco users (chewing and sniffing) were 11 times higher compared to non-user group. $P < 0.001$.**
- M Iqbal, M Yakub. Smokeless tobacco use: a risk factor for hyperhomocysteinemia in a Pakistani population. PLoS One. 2013 Dec 23;8(12)e83826.
- B Stegmayr, I Johnsson, F Huhtasarri, et al. Use of smokeless tobacco and cigarettes-effects on plasma levels of antioxidant vitamins. Int J Vitam Nurt Res 1993; 63(3): 195-200.

Homocysteine

- Elevated homocysteine is a secondary risk factor for:
 - Heart Disease
 - Stroke
 - Dementia

- 2016 May;1862(5):1008-17.
- 2016 May;1862(5):1008-17.
- 2016 May;1862(5):1008-17.

Lowering Elevated Homocysteine

Lowering of elevated homocysteine levels is well validated:

vitamin B6

vitamin B12

folate

- Hainsworth AH, Yeo NE, Weekman EM, et al. **Homocysteine, hyperhomocysteinemia and vascular contributions to cognitive impairment and dementia.** *Biochim Biophys Acta* 2016 May; 1862(5): 1008-17.

Summary

1. Tobacco smoking and secondhand smoke exposure cause drug-induced nutrient depletion, by unwittingly depleting antioxidants, micronutrients, and other substances.
2. Replenishment of some of these depleted substances:
 - reduces morbidity & mortality.
 - Improves biomarkers.

Summary

3. N-Acetylcysteine (NAC) has been shown to **improve relapse prevention** among former (just-quit) smokers.
4. NAC has as salutary effects for tobacco smokers.

Summary

5. Smokeless tobacco is another area where health benefits can be seen by replenishment of B-vitamins.

6. Replenishment of some of these depleted substances gives people a fighting chance of better health, and increased longevity.

Thank you for your kind attention.

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