It’s been said AREDS is “standard of care”, and one may even be ‘liable’ for not advising it to AMD patients. These statements are patently false. A definitive source of treatment recommendations, the AAO Preferred Practice Pattern Guidelines, defines AREDS product as “Discretionary” “...because of low quality evidence or because desirable and undesirable effects are closely balanced”. It only need be considered for category 3 or unilateral advanced disease.
U.S. Veterans Health Administration, with a huge stake in getting AREDS science right, is well aware of safety concerns, mediocre results and poor data analysis.

Criteria for Use of High Dose Vitamin Supplementation for Macular Degeneration
VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

The following recommendations are based on current medical evidence and expert opinion from clinicians. The content of the document is dynamic and will be revised as new clinical data becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardise and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient situation.

Introduction

Age related macular degeneration (ARMD) is a leading cause of blindness in the United States. It is estimated that 8 million people at least 55 years old have more advanced ARMD. The use of high dose vitamin supplementation for this population could have significant impact in quality of life and prevention of disease. Indeed, the AREDS Trial conducted by the National Institute for Health, high dose supplementation in patients with advanced AMD suggested an absolute risk reduction of 6% in progression to more advanced AMD or to further substantive visual acuity loss. This correlates to a NNT of 17. However, the result was based on a selective post-hoc analysis of data from the larger randomized control trial. In addition, use of high dose supplementation is not without risk, especially with the recent correlation of beta-carotene and lung cancers. Patients need to be appropriately screened prior to initiation of high dose supplementation, to insure optimal safety and efficacy of therapy.

Chew et al. assert Carl Awh used this poor scientific technique in developing the genetic test for zinc; in reality, he performed an FDA accepted and encouraged genetic retrospective review - http://www.fda.gov/AboutFDA/WhatWeDo/History/Overviews/ucm304485.htm (last paragraph)

AREDS Investigators Distort Findings - Daniel Seigel, ScD

In my opinion, the Age-Related Eye Disease Study (AREDS) investigators promoted a nonsignificant result into a conclusive recommendation.1 Here is how they did it.

The primary study outcomes for AREDS are explicitly stated in the “Participants and Methods” section of the article: (1) progression to advanced age-related macular degeneration (AMD) and (2) a 15-letter decrease in visual acuity. These outcomes were to be evaluated in all patients by independent tests of significance of the 2 primary treatments. This carefully specified primary analysis led to 4 tests, none of which was statistically significant. One, testing the effect of zinc on progression to advanced AMD, achieved a level of significance defined by the investigators as suggestive.

Despite these negative results, the investigators recommend combined treatment with antioxidants and zinc based on their secondary analysis. Two analytic approaches provided them with significant results. First, the authors restricted the analysis to a subgroup. The mainstream practice of clinical trials warns that unless the main overall comparison is significant, investigators should be conservative in their interpretation of significant subgroup results.2 Second, they featured the combined treatment group, which in secondary analysis broke the boundary of statistical significance, thereby disregarding the primary analysis in which neither treatment was significant.

In its discussion of relevant literature, the “Comment” section is as selective as the analysis. At a planning meeting, the AREDS chairman recounted his efforts to review retinal photographs from the first published study of zinc and AMD3 and his disappointment at learning they had been lost shortly after publication. By this criterion alone the relevance of that small clinical trial is depleted. Nevertheless, the AREDS investigators report its finding to support their recommendation. Some major epidemiological studies that are not supportive, glancingly mentioned in the introduction, have no voice in the “Comment” section.

Adverse effects reported by the investigators include an increase in hospitalizations for urinary tract problems among participants treated with zinc and yellowing of the skin among participants taking antioxidants. They modified the protocol for current and former smokers during the course of the study because of published reports of increased mortality among smokers supplementing with beta carotene. Furthermore, they caution that the health effects of long-term use of their proposed treatment are unknown.

Analyses in clinical trials are complex endeavors. Austin Bradford Hill observed that the inferences we draw turn on our personalities.4 In an article in the New York Times, Gina Kolata spoke to public frustration at reports of clinical research that convert suggestive results to conclusive ones.5 A public that is concerned with AMD, physicians who need to advise and treat, and industry representatives who wish to provide us with products that are effective all depend on us to get it right in clinical research. In my opinion, the message that should have emerged from AREDS is that these treatments failed to demonstrate efficacy in preventing AMD and are not recommended for that use.
AREDS Misses on Safety - Bruce I. Gaynes, OD, PharmD Chicago, III

I have read with interest the article pertaining to the Age-Related Eye Disease Study (AREDS) in the October 2001 issue of the ARCHIVES. However, I believe that while the results are of clinical interest, the findings of the AREDS pertaining to age-related macular degeneration (AMD) should be interpreted with caution. Although inorganic trace elements and vitamins are essential nutrients required for health maintenance, it is erroneous to address the use of such entities as therapeutics without a clear understanding and appreciation of their relevant pharmacokinetic and pharmacodynamic properties. Furthermore, consideration of factors such as biological variability and dose-response, which express therapeutic action in terms of efficacy as well as toxicity, are in large part poorly defined within the AREDS study design. Characterization of the pharmacologic response to various high-dose vitamin and nutrient administration requires stringent assessment of population-, disease-, and formulation-specific variables that may influence the occurrence of adverse effects in ways not described in the AREDS. For example, changes in drug disposition with age are characterized by alterations in lean body mass, which influences the volume of distribution and partition coefficients pertinent to fat-soluble vitamins, particularly alpha-tocopherol. Furthermore, individuals who use vitamin A as a source of beta-carotene should be advised that absorption of vitamin A1 (retinol) varies considerably depending on the formulation of the preparation as well as the amount of dietary fat an individual typically ingests. In addition, febrile infections and stress may markedly decrease serum retinol, whereas chronic renal disease may result in significantly elevated serum retinol, requiring the need for an alteration in intake. Moreover, the AREDS neglects to discuss assignment of causality, as well as the temporal relationship and outcome of reported adverse events, particularly those noted as “circulatory.” Furthermore, discussion of additive or synergistic effects, either observed or potential, of the AREDS therapy with various prescription and nonprescription products is lacking. The AREDS also does not address the need for continuing surveillance of the safety of vitamin and nutrient therapy for AMD in terms of elucidation of unexpected idiosyncratic reactions, an important yet complex task because of the ease of accessibility of such agents. Additionally, and perhaps of greater significance, it is unknown how the results of ongoing prospective trials of vitamin and nutrient therapy for disorders other than AMD will affect those currently following AREDS recommendations. Vitamins and nutrients are not only ubiquitous in nature and easily obtained from nourishing diets, they are also aggressively marketed by pharmaceutical companies eager to promote perceived as well as validated claims of health benefit. In addition, the clever marketing strategies of pharmaceutical companies, such as those promoting doses that “exceed AREDS recommendations,” demonstrate the need for clinicians to closely monitor vitamin and nutrient intake. I believe that the AREDS findings are inadequate in the elucidation of clear and concise safety guidelines for entities that are largely unregulated and widely promoted with an array of ingredients, formulations, and equivalency provided for public interpretation.

Age-Related Eye Disease Study Caveats – Jayakrishna Ambati, MD & Balamurali K. Ambati, MD

It is wonderful to finally see the data from the Age-Related Eye Disease Study (AREDS)1 addressing the issue of nutritional supplements in age-related macular degeneration (AMD). Predictably, no sooner were the results released than a commercial preparation was also released. We are concerned about the misplaced enthusiasm that has met the study findings and would like to advise a more tempered response.

We are beginning to understand the potential risk of high doses of beta carotene and zinc, which have previously not been consumed in high doses for long periods by many people. The supplements used in this study, particularly beta carotene and zinc, are not without risk. In addition, risks may be higher among some smokers, 2,3 and there is evidence from 1 epidemiologic study and 1 study of beta carotene supplementation in primates to suggest that the risks may be higher among those who drink alcohol.4

High levels of zinc, a synaptic neuromodulator, can under certain circumstances, be toxic to central neurons. Zinc damage worsens neurodegeneration in rats. 5 This may be important in human conditions, such as transient global ischemia, that are common among elderly persons. Consistent with this, elevated zinc levels in the cerebrospinal fluid are associated with poorer prognosis in patients following acute stroke.6 Elevated serum zinc is observed in patients with Alzheimer’s disease,7 and a causal role is postulated because it promotes aggregation of amyloid –beta peptide.8 Recent data reveal that high levels of zinc, which are uptaken from the choroidal circulation, can induce apoptotic cell death of retinal pigment epithelial cells in culture.9 High-dose zinc supplementation also elevates glycosylated hemoglobin levels in patients with type 1 diabetes mellitus10 and aggravates glucose intolerance in patients with type 2 diabetes mellitus.11

This raises the possibility of potential adverse health effects from high-dose supplements, a theory that needs further evaluation in long-term human studies. Until this evidence is available, a blanket recommendation for mega-dose supplements may be unwarranted.

Beyond potential risks, the very benefit of these supplements is questionable. The AREDS report continues the unfortunate trend of post-hoc touting of groups exhibiting statistically significant differences among treatments. Although the alpha-spending function approach to group-sequential testing adjusts for the repeated significance testing, it does not correct for post hoc analysis.12 It is contended that for patients in categories 3 and 4, the P value for the protective effect of antioxidants plus zinc on progression to advanced AMD is .001. But considering that this particular grouping (of categories 3 and 4) is only 1 of 16 possible a priori subsets, the actual P value is .016 (1-.001)16=.016, which is higher than the study’s threshold for statistical significance. The effect of the combination treatment on loss of visual acuity, the only endpoint that truly matters to patients, which was non-significant at P=0.02, is even less compelling at a similarly corrected P=.24.

Our anemic arsenal against AMD leads patients affected by this scourge to grasp at any straw. We owe them and their families candid advice and guidance on treatment options, even if it entails suggesting no therapy. We would recommend that the most prudent nutritional advice to offer patients with AMD is to advocate a diet rich in fruits and vegetables as opposed to any specific pharmacologic intervention, particularly a modular approach that disregards the mechanistic complexity of the disease.
By Cynthia J MacKay, MD
Clinical Professor of Ophthalmology, Columbia University College of Physicians and Surgeons

Q. What were the results of this study? (AREDS)
The results of the study were negative. The drug had no beneficial effect on vision, and it did not stop the progression of AMD, in any of these three groups of patients.

Q: Were there any financial conflicts of interest in this study?
The Principal Investigator and Study Chairman of the AREDS Study, Dr. Frederick Ferris, has the patent to this drug. The AREDS study was financed partly by Storz, which is now part of Bausch and Lomb, the company that manufactures these pills.

Q: So why does anybody think these drugs work?
After the study was completed, the researchers went back and changed their research design. They arbitrarily threw out all patients with mild AMD from the study. This is a strange decision. Patients with mild disease are the ones who should benefit the most from this drug. Then, they changed their definition of “success”, from: “preventing vision loss and progression”, to: “preventing AMD events”.

After these manipulations, the data seemed to show that the drug prevented what they called “AMD events”, but it did so for only in one group of patients, the one who had intermediate AMD in one eye, and advanced AMD in the other. The study did NOT show that these patients had any vision benefit from taking this drug.

Q. Is it standard scientific practice to change criteria after a study is over?
No. This manipulation has caused a storm of criticism in scientific meetings, and in the scientific literature. Scientists are not supposed to throw out a negative result, and then report on a small subgroup that seems to have a positive result. It does not conform to standard scientific practice. In short, the value of PreserVision has not been proven by accepted scientific methods.

This practice is termed HARKing

HARKing: Hypothesizing After the Results are Known

Norbert L. Kerr
Department of Psychology
Michigan State University

This article considers a practice in scientific communication termed HARKing (Hypothesizing After the Results are Known). HARKing is defined as presenting a post hoc hypothesis (i.e., one based on or informed by one’s results) in one’s research report as if it were, in fact, an a priori hypotheses. Several forms of HARKing are identified and survey data are presented that suggests that at least some forms of HARKing are widely practiced and widely seen as inappropriate. I identify several reasons why scientists might HARK. Then I discuss several reasons why scientists ought not to HARK. It is conceded that the question of whether HARKing’s costs exceed its benefits is a complex one that ought to be addressed through research, open discussion, and debate. To help stimulate such discussion (and for those such as myself who suspect that HARKing’s costs do exceed its benefits), I conclude the article with some suggestions for deterring HARKing.

From AREDS Report#8 In the original study design, participants in Categories 2, 3, and 4 were pooled for data analysis and that remains the primary analysis. However, by 5 years there were only 15 AMD events in Category 2 distributed across all 4 treatment groups (3 in the placebo group). The low event rate makes it impossible to assess treatment effects in this category for the AMD outcome and less likely that any of the treatments would be recommended. Therefore, analyses are also presented for those participants most likely to benefit from an effective treatment (Categories 3 and 4).

Note the authors concede the study endpoint changed once results were known, specifically to a group “most likely to benefit”. Switching to a single AMD endpoint- progression to advanced disease- leaves a gap in our knowledge about actual disease progression from one stage to the next-Category 1 or 2, moving to Category 2 or 3, respectively. This is, arguably, of greater importance to the vast majority with AMD (80% cat. 1-2), hoping not to develop high risk for progression. A critical analysis of this unpublished data has been missing, particularly important considering statements by the former NEI associate director, a biostatistician who was privy to unpublished data; he indicated early AMD subjects suffered increased disease progression.
Benefits Are Not Plain to See

"For a Proven Product,blurry Claims" [April 23] suggested that Bausch & Lomb, which manufactures a dietary supplement called OcuVite, is prohibited from telling consumers about the product's proven ability to treat macular degeneration, a disease causing loss of vision in the elderly. In fact, there is nothing in the law that prevents Bausch & Lomb from making proven claims.

Under the Federal Food, Drug and Cosmetic Act, each manufacturer makes a choice about how much evidence it wants to submit to the Food and Drug Administration and the types of claims it wants to make about its product. A manufacturer who chooses to market a product as a dietary supplement is not required to submit proof of its claims, forgoes government review of the product's safety and effectiveness, and generally avoids requirements about product warnings and quality control. In exchange for this lenient treatment, the manufacturer can make only limited claims related to preserving health ("maintains healthy eyes").

Alternatively, the same manufacturer can choose to market the product as a drug and submit evidence of the product's safety and effectiveness, provide adequate directions for the product's use and adhere to quality control standards. In exchange, the manufacturer is entitled to make significant disease-treatment claims ("for the treatment of age-related macular degeneration"). In this case, Bausch & Lomb chose to avoid submission of data and other regulatory requirements and is now marketing its product with vague and misleading claims.

It makes sense that OcuVite should not be marketed for treatment of a serious disease when the risks of the product are not described on the label, who exactly can benefit from the product is misleadingly stated and the manufacturer is not held to the same quality control standards as for drugs.

Rep. Henry A. Waxman (D-Calif.)
Washington

The story presented only the perspective of Bausch & Lomb and the chairman of the AREDS study.

By contrast, in Lee Jampol's editorial accompanying the [published] study results, he asked whether there are "weaknesses in this trial that could cast doubt on its conclusion that the supplements were effective." He then described such weaknesses in detail and admitted to finding them troubling.

I wrote a letter published in the March issue of the Archives of Ophthalmology arguing that the investigators had distorted the study results. The treatments had in fact failed to demonstrate effectiveness. The analysis had violated several fundamental principles found in every textbook of clinical trials.

Rather than wring our hands over the policies of the FDA, we should be thankful that that regulatory agency has a professional understanding of clinical trial methodology and would not, I am confident, approve the marketing of these supplements for the prevention of vision loss. The claims for efficacy of this product start with the investigators, where they are not blurry, just unfounded.

Daniel Seigel, ScD
Cushing, Maine

Note: The author is a former associate director of the National Eye Institute and retired professor of biostatistics at Harvard University.
Three quarters of those taking ocular vitamins are not AREDS candidates, up from one in five noted by Charkoudian, 2008 in *Ophthalmology*. [https://www.ncbi.nlm.nih.gov/pubmed/18096234](https://www.ncbi.nlm.nih.gov/pubmed/18096234)

**Upper Access**
ARVO Annual Meeting Abstract  |  September 2016

**Appropriate use of AREDS vitamins in the ophthalmic population**

Clinton Ellingson; Jayakrishna Ambati

Purpose: The purpose of this study is to assess the appropriate use of eye vitamins based on AREDS recommendations

Methods: This is a random, prospective, cross-sectional clinic-based study. Patients presenting to the ophthalmology clinic at an academic medical center who had a diagnosis of AMD or were actively taking eye vitamins were enrolled.

Results: Of the 101 participants taking eye vitamins, **73.5 did not meet AREDS criteria**. ... The **number needed to treat** (NNT) was adjusted to account for participants taking eye vitamins that did not meet AREDS criteria...

...determined to be 220.

...the **direct cost utility** from inappropriate vitamin use ranged between **$218,000-$657,000** per quality adjusted life year (QALY).

Conclusions: An overwhelming proportion of eye vitamin users did not meet AREDS treatment criteria...

...and increases exposure to unnecessary adverse drug effects.

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**Progression From No AMD to Intermediate AMD as Influenced by Antioxidant Treatment and Genetic Risk: An Analysis of Data From the Age-Related Eye Disease Study Cataract Trial**

Carl C. Awh, MD, Brent Zanke, MD, PhD, and Rafal Kustra, PhD

+Our analysis of AREDS cataract trial data provides evidence that treatment with antioxidants may impact the de novo development of intermediate AMD as a function of CFH and ARMS2 genetic risk.

+Under a Cox model, the covariant of **CFH and ARMS2 total risk allele number (range, 0-4)** was a significant determinant of progression risk (HR= 2.41; P < .0001) and interacted with treatment group (antioxidant vs placebo) with an HR of 0.41 (P = .001), demonstrating a genotype-influenced heterogeneity in antioxidant treatment response.

+While the average progression risk for patients in this analysis was not impacted by antioxidant treatment, **this average outcome appears to be the net result of dramatically different responses to antioxidant treatment**; patients with low CFH or ARMS2 genetic risk had significantly increased progression to intermediate AMD, while those with high CFH and ARMS2 genetic risk had significantly decreased progression risk.

+Persons with **low genetic risk constitute the majority of the general population** (63% in this study set).

-Five percent of patients in this analysis had 3 or 4 total CFH and ARMS2 risk alleles.

+Given the absence of evidence of benefit and the possibility of a similar adverse treatment response, patients without AMD should refrain from taking the AREDS or AREDS2 formulation, consistent with generally accepted recommendations.
...results of AREDS to date demonstrate no benefit of the study formulations for persons in Categories 1 or 2. Approximately 80% fall in these low-risk groups.

...it seems reasonable to defer consideration of supplementation until the risk of progression is higher, especially because analyses to date do not show that treatment is effective in slowing the progression of AMD from Category 2 to Categories 3 or 4.

For those participants who initially had early AMD (Category Two), the antioxidants and zinc used by the AREDS researchers did not slow the progression to intermediate AMD. Consequently, there is no apparent need for those diagnosed with early AMD to take the combination.

To the Editor: The review of age-related macular degeneration by Jager et al. (June 12 issue) does not refer to an editorial accompanying the report of the Age-Related Eye Disease Study (AREDS) in the Archives of Ophthalmology in 2001 and two subsequent letters, all of which criticized the study analysis for setting aside a negative result in which dietary supplementation with high doses of vitamins and minerals was ineffective and instead reporting on a subgroup in which the result was positive. The investigators argued that the excluded patients had too few end points to be eligible for treatment.

However, the group of patients who received the supplement had greater disease progression and provided valuable data regarding early intervention. Discarding prespecified negative analyses and reporting on positive subgroup analyses has been repeatedly discouraged. The omission of the above information perpetuates the myth that the supplement used in the AREDS was effective, at the price of a treatment that has no benefit and carries undetermined risks.


Prof. Seigel oversaw AREDS as Associate Director of the National Eye Institute. He's a retired Harvard professor of biostatistics and qualified epidemiologist.
Financial Gains Taint Debate About Nutritional Supplements

The National Institutes of Health (NIH), parent to the NEI, receives royalties as an institution for a patent on the AREDS formula. And Frederick Ferris III, MD, leader of AREDS and an NEI employee, receives royalties as an individual. Emily Chew, MD, the lead author of several AREDS studies, is a deputy director at the NEI.

Financial Disclosures

Ophthalmologists are accustomed to considering the investments — both financial and emotional — that their colleagues have in various devices and medications. But it might come as a surprise to some that the bank accounts of individual researchers at the NIH can be affected by the studies they publish.

The NIH has not released the amount of money it is earning from the patent for the AREDS supplements, which it has licensed to Bausch + Lomb. The law allows individuals to receive up to $150,000 per year.

But in response to a Freedom of Information Act request from ArcticDx, the agency provided a document entitled "Recipient: Ferris, Frederick III," with the figure $150,000 repeated on 12 lines. The agency declined to provide an interpretation of the document to Medscape Medical News, but Dr. Zanke said the NIH told him that it means that Dr. Ferris has so far received $1.8 million for his work on the supplements.

Although some of the AREDS publications have disclosed the royalties paid to Dr. Ferris and the NIH, others have not.

In a conversation with Medscape Medical News, Dr. Chew at first said she has no conflicts of interest to disclose.

And she said she is not influenced by the money paid to Dr. Ferris. "There is concern that my boss gets it, but I work independent of him. I'm working for the American people," she explained.

In response to a request for an interview with Dr. Ferris about his disclosures, an NEI spokesperson acknowledged that the NIH guidelines call on its scientists to disclose "all relevant financial interests" to journal editors.

The spokesman quoted Dr. Ferris as saying, "I believe I have a duty to report all conflicts and I believe I always do."

In a separate email, Dr. Ferris noted that two of the studies concerned cataracts rather than macular degeneration, apparently implying that the patent on the formula for the supplements is so specific to age-related macular degeneration that its potential use by people with cataracts is irrelevant.

Dr. Zanke pointed out that this seems to be in conflict with the disclosure policy at Ophthalmology. The journal uses a disclosure form provided by the International Committee of Medical Journal Editors, which asks authors to list "financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with any entity that could be considered broadly relevant to the work."

The form also asks, "Do you have any patents, whether planned, pending, or issued, broadly relevant to the work?"

Busted!
Meanwhile, through a Freedom of Information Act request... ...discovered that Dr. Frederick Ferris, a superior of Chew’s at the NEI, has personally earned US $1.8 million from the Bausch & Lomb patent.

Government scientists secretly on the take: lying about conflict of interest violates a fiduciary duty, appears to be scientific misconduct, and it’s potentially illegal.


Government scientists secretly on the take: lying about conflict of interest violates a fiduciary duty, appears to be scientific misconduct, and it’s potentially illegal.

http://biotech.law.lsu.edu/Books/lbb/x236.htm
The scandal of poor medical research

We need less research, better research, and research done for the right reasons

What should we think about a doctor who uses the wrong treatment, either willfully or through ignorance, or who uses the right treatment wrongly (such as by giving the wrong dose of a drug)? Most people would agree that such behaviour was unprofessional, arguably unethical, and certainly unacceptable.

What, then, should we think about researchers who use the wrong techniques (either willfully or in ignorance), use the right techniques wrongly, misinterpret their results, report their results selectively, cite the literature selectively, and draw unjustified conclusions? We should be appalled. Yet numerous studies of the medical literature, in both general and specialist journals, have shown that all of the above phenomena are common.1-7 This is surely a scandal.

When I tell friends outside medicine that many papers published in medical journals are misleading because of methodological weaknesses they are rightly shocked. Huge sums of money are spent annually on research that is seriously flawed through the use of inappropriate designs, unrepresentative samples, small samples, incorrect methods of analysis, and faulty interpretation. Errors are so varied that a whole book on the topic,7 valuable as it is, is not comprehensive; in any case, many of those who make the errors are unlikely to read it.

Why are errors so common? Put simply, much poor research arises because researchers feel compelled for career reasons to carry out research that they are ill equipped to perform, and nobody stops them. Regardless of whether a doctor intends to pursue a career in research, he or she is usually expected to carry out some research with the aim of publishing several papers. The length of a list of publications is a dubious indicator of ability to do good research; its relevance to the ability to be a good doctor is even more obscure. A common argument in favour of every doctor doing some research is that it provides useful experience and may help doctors to interpret the published research of others. Carrying out a sensible study, even on a small scale, is indeed useful, but carrying out an ill designed study in ignorance of scientific principles and getting it published surely teaches several undesirable lessons.

In many countries a research ethics committee has to approve all research involving patients. Although the Royal College of Physicians has recommended that scientific criteria are an important part of the evaluation of research proposals,8 few ethics committees in Britain include a statistician. Indeed, many ethics committees explicitly take a view of ethics that excludes scientific issues. Consequently, poor or useless studies pass such review even though they can reasonably be considered to be unethical.9

The effects of the pressure to publish may be seen most clearly in the increase in scientific fraud,10 much of which is relatively minor and is likely to escape detection. There is nothing new about the "massage" of data or of "data torture", as it has recently been called.11 Charles Babbage described its different forms as long ago as 1830.12 The temptation to behave dishonestly is surely far greater now, when, all too often the main reason for a piece of research seems to be to lengthen a researcher's curriculum vitae. Bailar suggested that "there may be greater danger to the public welfare from statistical dishonesty than from almost any other form of dishonesty."13

Evaluation of the scientific quality of research papers often falls to statisticians. Responsible medical journals invest considerable effort in getting papers refereed by statisticians; however, few papers are rejected solely on statistical grounds.14 Unfortunately, many journals use little or no statistical refereeing—bad papers are easy to publish.

Statistical refereeing is a form of fire fighting. The time spent refereeing medical papers (often for little or no reward) would be much better spent in education and in direct participation in research as a member of the research team. There is, though, a serious shortage of statisticians to teach and, especially, to participate in research.15 Many people think that all you need to "do" statistics is a computer and appropriate software. This view is wrong even for analysis, but it certainly ignores the essential consideration of study design, the foundations on which research is built. Doctors need not be experts in statistics, but they should understand the principles of sound methods of research. If they can also analyse their own data, so much the better. Amazingly, it is widely considered acceptable for medical researchers to be ignorant of statistics. Many are not ashamed (and some seem proud) to admit that they "don't know anything about statistics."

The poor quality of much medical research is widely acknowledged, yet disturbingly the leaders of the medical profession seem only minimally concerned about the problem and make no apparent efforts to find a solution. Manufacturing industry has come to recognise, albeit gradually, that quality control needs to be built in from the start rather than the failures being discarded, and the same principles should inform medical research. The issue here is not one of statistics as such. Rather it is a more general failure to appreciate the basic principles underlying scientific research, coupled with the "publish or perish" climate.

As the system encourages poor research it is the system that should be changed. We need less research, better research, and research done for the right reasons. Abandoning using the number of publications as a measure of ability would be a start.

DOUGLAS G ALTMAN
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Numerous trials and studies of pharmacologic doses of traditional antioxidants and mineral supplements demonstrate harm in terms of cardiovascular risks, lung, and prostate cancer. Zinc imbalance and beta-amyloid deposition in brain & retina should also be considered for those at risk of developing Alzheimer’s.

**Vitamin E and the Risk of Prostate Cancer: Updated Results of The Selenium and Vitamin E Cancer Prevention Trial (SELECT)**

n= 35,533  
**Conclusions** Dietary supplementation with Vitamin E significantly increases the risk of prostate cancer among healthy men. (HR, 1.17; 99% CI 1.004–1.36, p=.008)

**Zinc Supplement Use and Risk of Prostate Cancer**

n= 46,974  
...men who consumed more than 100 mg/day of supplemental zinc had a relative risk of advanced prostate cancer of 2.29 (95% confidence interval = 1.06 to 4.95; P=.003), and men who took supplemental zinc for 10 or more years had a relative risk of 2.37 (95% confidence interval = 1.42 to 3.95; P trend <.001).

**Vitamins E and C in the Prevention of Cardiovascular Disease in Men: The Physicians’ Health Study II Randomized Trial**

n= 14,641  
**Conclusions** vitamin E was associated with an increased risk of hemorrhagic stroke (HR, 1.74; 95% CI, 1.04–2.91; P=0.036)

**Long-Term Use of Supplemental Multivitamins, Vitamin C, Vitamin E, and Folate Does Not Reduce the Risk of Lung Cancer (VITAL Study)**

n=77,721  
Supplemental vitamin E was associated with a small increased risk of lung cancer (HR, 1.05 for every 100-mg/d (150IU/d) increase in dose; 95% confidence interval [CI], 1.00–1.09; P = 0.033). This risk of supplemental vitamin E was largely confined to current smokers (HR, 1.11 for every 100-mg/d increase; 95% CI, 1.03–1.19; P < 0.01) and was greatest for non–small cell lung cancer (HR, 1.07 for every 100-mg/d increase; 95% CI, 1.02–1.12; P = 0.004).

**Risk Factors for Lung Cancer and for Intervention Effects in CARET, the Beta-Carotene and Retinol Efficacy Trial**

n=18,314  
According to CARET’s pre-specified analysis, there was an RR of 1.36 (95% confidence interval [CI] = 1.07-1.73; P = .01) for weighted lung cancer incidence for the active intervention group compared with the placebo group, and RR = 1.59 (95% CI = 1.13-2.23; P = .01) for weighted lung cancer mortality

**Alpha-Tocopherol and Beta-Carotene Supplements and Lung Cancer Incidence in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study: Effects of Base-line Characteristics and Study Compliance**

n=29,133  
Beta-Carotene supplementation at pharmacologic levels may modestly increase lung cancer incidence in cigarette smokers, and this effect may be associated with heavier smoking and higher alcohol intake. (RR = 1.16; 95% CI = 1.02-1.33; P = .02, logrank test)

**Effects of long-term vitamin E supplementation on cardiovascular events and cancer (HOPE-TOO): a randomized controlled trial.**

n= 9,541  
In patients with vascular disease or diabetes mellitus, long-term vitamin E supplementation does not prevent cancer or major cardiovascular events and may increase the risk for heart failure. (RR, 1.13; 95% CI, 1.01-1.26; P = .03) & (RR, 1.21; 95% CI, 1.00-1.47; P = .045)

**The Women’s Angiographic Vitamin and Estrogen (WAVE) Trial**

n= 423  
In postmenopausal women with coronary disease... a potential for harm was suggested with each treatment. (HR, 1.5; 95% CI, 0.80-2.9)