Macular carotenoids and cognitive function

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Disclosures

• This presentation has been approved for Category “A” continuing education for eyecare professionals.
• These slides were developed solely by the speaker.
• Dr. Renzi Hammond has served as a consultant for the following eyecare businesses:
  – Johnson and Johnson Vision Care, Inc.
  – Alcon Laboratories
  – MacuHealth
  – Transitions Optical / Essilor
  – Abbott Laboratories
The natural history of vision
Other primates

Pan paniscus, (bonobos) in the DRC
Other primates

Mountain gorilla (*Gorilla beringei beringi*)

Image: African Wildlife Foundation
Other primates

Short-wave dominant sky

Mid-wave dominant vegetation

Image: World Wildlife Fund
Chromatic aberration

Extreme ends of the visible spectrum are more than 1 diopter out of focus
Distance vision

Image: Brittanica
Motion cues

Image: Harvard University
And post-Industrial Revolution?
The pandemic of myopia

Incidence of Myopia in the USA (12-54 yrs)

Vitale et al., 2009
Arch. Ophthalmol
Smoke caused massive haze

Sight distance extremely limited
PUBLIC HEALTH

Why Up to 90% of Asian Schoolchildren Are Nearsighted

Researchers say the culprit is academic ambition: spending too much time studying indoors and not enough hours in bright sunlight is ruining kids’ eyesight.

By Alice Park @aliceparkny | May 07, 2012 | 2 Comments

Scientists say an epidemic of myopia, or nearsightedness, is sweeping through Asian children, and is likely due to students’ spending too much time indoors studying and not enough time outside in the sunlight.

It has long been thought that nearsightedness is mostly a hereditary problem, but researchers led by Ian Morgan of Australian National University say the data suggest that environment has a lot more to do with it.
Myopia is, in part, an example of a mismatch between lifestyle and biology.

What about other lifestyle factors and disease?
Nutrition is linked to the concept of food. What is a food?
Nutrition is linked to the concept of food. What is a food?
Bioavailability: Vitamin C

What's in a Fresh Whole Clean Apple?

From "Handbook of Phytochemical Constituents of Generally Regarded as Safe (GRAS) Herbs"
Ideal diet?

Bolivian forager-horticulturalists: Tsimane

Diet:

- freshwater fish
- hunted game
- Plantains
- Rice
- Manioc (yuca)
- fruit

Martin et al. Maternal & Child Nutrition 2012;8:404-418
United States: The Revis family of North Carolina.
Mexico: The Casales family of Cuernavaca.
Ecuador: The Ayme family of Tingo.
60% FAT
The lasting impact of diet on biology

<table>
<thead>
<tr>
<th></th>
<th>Tsimane</th>
<th>US</th>
<th>Canada</th>
</tr>
</thead>
<tbody>
<tr>
<td>18:1n-9</td>
<td>27.5±4.56</td>
<td>30.2±3.44</td>
<td>34.6</td>
</tr>
<tr>
<td>18:2n-6</td>
<td>10.2±4.56</td>
<td>18.9±5.10</td>
<td>13.2</td>
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<tr>
<td>20:3n-6</td>
<td>0.47±0.12</td>
<td>0.33±0.88</td>
<td>0.38</td>
</tr>
<tr>
<td>20:4n-6</td>
<td>1.06±0.33</td>
<td>0.55±0.09</td>
<td>0.42</td>
</tr>
<tr>
<td>22:5n-6</td>
<td>0.21±0.07</td>
<td>0.05±0.03</td>
<td>0.05</td>
</tr>
<tr>
<td>18:3n-3</td>
<td>1.90±0.84</td>
<td>1.58±0.65</td>
<td>1.51</td>
</tr>
<tr>
<td>20:4n-3</td>
<td>0.25±0.18</td>
<td>0.06±0.03</td>
<td>0.05</td>
</tr>
<tr>
<td>20:5n-3</td>
<td>0.20±0.12</td>
<td>0.06±0.04</td>
<td>0.08</td>
</tr>
<tr>
<td>22:5n-3</td>
<td>0.40±0.14</td>
<td>0.14±0.04</td>
<td>0.14</td>
</tr>
<tr>
<td>22:6n-3</td>
<td>0.69±0.26</td>
<td>0.16±0.26</td>
<td>0.27</td>
</tr>
</tbody>
</table>

All C 20 & 22 n-6 & n-3 high, DHA is not the only variable
'Bad luck' mutations increase cancer risk more than behavior, study says

By Susan Scutti, CNN

Updated 2:00 PM ET, Thu March 23, 2017
The breast cancer risks for women in the study born after 1940 were significantly higher for those born in the same families before 1940.

Science 302, 643-646 (October 24, 2003).
Cancer is a disease of the Western Lifestyle
Breast cancer rates among Chinese women who moved to San Francisco compared to Chinese women who stayed in China

Waterhouse, Muir, et al., 2003
Many other diseases seem to be linked to Western lifestyle, rather like myopia.

At least we can treat myopia. What about AMD? Alzheimer’s disease?
Retina is one of the most metabolically active tissues in the body.

e.g., Cohen & Noell, 1965; Anderson & Satlzman, 1964; Ames, 1992.
Retina is one of the most neurologically dense tissues in the body

Optic nerve: 1,200,000 fibers.
Next most dense cranial nerve: 140,000 fibers (sensory root of trigeminal nerve)
2500 mm² area, 120 microns thick → 148.2 million receptors and ganglia
Dowling was right
Viewing the CNS

Image: Cho et al, 2014
Predicting the Outcome of Optic Neuritis

P. Nilsson MD, E. M. Larsson MD, PhD, P. Maly-Sundgren MD, PhD, R. Perfekt PhD, Magnhild Sandberg-Wollheim MD, PhD

Abstract

Background

Multiple sclerosis (MS) is a common disease with considerable risk for disability. Optic neuritis (ON) is a common first symptom of MS but it can also remain an isolated episode. Therefore, predicting the outcome of ON has gained in importance, particularly in light of current discussions of early disease modifying treatments in individuals at risk of developing MS. We reported previously on our cohort of 86 patients with acute monosymptomatic unilateral ON of whom 33 had progressed to MS after up to 18 years. Three patients had died. The present study extends the observation period to 31 years.
Retinal change as a predictor

Similarities:

Clinical pathological features
- Oxidative stress
- Inflammation

Molecular similarities between deposits
- Drusen and amyloid plaques

Decreased capacity to degrade damaged cellular proteins

Genetic risk factors
- APOE
- Complement factors

Lifestyle risk factors

Age-Related Macular Degeneration (AMD): Alzheimer’s Disease in the Eye?

Kai Kuurna et al.

Abstract. Age-related macular degeneration (AMD) is a late-onset, neurodegenerative retinal disease that shares several clinical and pathological features with Alzheimer’s disease (AD), including stress stimuli such as oxidative stress and inflammation. In both diseases, the detrimental intra- and extracellular deposits have many similarities. Aging, hypercholesterolemia, hypertension, obesity, arteriosclerosis, and smoking are risk factors to develop AMD and AD. Cellular aging processes have similar organ coke and signaling association in the retina and brain tissues. However, it seems that these diseases have a different genetic background. In this review, differences and similarities of AMD and AD are thoroughly discussed.

Keywords: Age-related macular degeneration (AMD), aggregation, aging, Alzheimer’s disease, autophagy, lysosome, oxidative stress, proteosome
For age-related retinal and brain diseases, prevention is key.
An apple a day keeps the heart doctor away

The 150-year-old proverb 'an apple a day keeps the doctor away' stands the test of time, say Oxford University researchers.

Writing in the more light-hearted Christmas edition of the BMJ medical journal, the scientists estimated how effective this Victorian health advice would be today in preventing heart disease among people over 50.

Using mathematical models, the researchers calculated that prescribing an apple a day to all adults aged 50 and over in the UK would prevent around 8,500 deaths from heart attacks and strokes every year.
Introduction to dietary carotenoids
Selective absorption of carotenoids
Macular Pigment (MP)

MP is comprised of lutein (L) and zeaxanthin (Z), and their isomer, meso-zeaxanthin (MZ).
MP screens central cones

Central Fovea

Cell nuclei (purple), LM cones (green), rods (red), lipofuscin (orange)
MP absorbs short-wave light

Image: D. Max Snodderly
Xanthophylls are antioxidants

Light

Photosensitizer + O₂

DHA

Lipid Peroxidation

1O₂ 3O₂

Heat

Lutein
Which foods are best for L and Z?

<table>
<thead>
<tr>
<th>FOOD</th>
<th>SERVING</th>
<th>mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kale (cooked)</td>
<td>1 cup</td>
<td>23.8</td>
</tr>
<tr>
<td>Spinach (cooked)</td>
<td>1 cup</td>
<td>20.4</td>
</tr>
<tr>
<td>Collards (cooked)</td>
<td>1 cup</td>
<td>14.6</td>
</tr>
<tr>
<td>Turnip greens (cooked)</td>
<td>1 cup</td>
<td>12.2</td>
</tr>
<tr>
<td>Spinach (raw)</td>
<td>1 cup</td>
<td>3.8</td>
</tr>
<tr>
<td>Corn (can or cooked)</td>
<td>1 cup</td>
<td>2.2</td>
</tr>
<tr>
<td>Green peas (canned)</td>
<td>1 cup</td>
<td>2.2</td>
</tr>
<tr>
<td>Broccoli (cooked)</td>
<td>1 cup</td>
<td>1.6</td>
</tr>
<tr>
<td>Romaine lettuce (raw)</td>
<td>1 cup</td>
<td>1.3</td>
</tr>
<tr>
<td>Green beans (cooked)</td>
<td>1 cup</td>
<td>0.8</td>
</tr>
<tr>
<td>Eggs</td>
<td>2 (large)</td>
<td>0.3</td>
</tr>
<tr>
<td>Orange</td>
<td>1 (medium)</td>
<td>0.2</td>
</tr>
</tbody>
</table>
How do North Americans stack up?

1.0 + log units

0.3 log units

0.0 log units

20+ mg / day

1.5 mg / day

Micrograms, if any

Hammond & Caruso-Avery, 2000;
Curran-Celentano et al, 2002
Carotenoids and visual function: the evidence
Pigments absorb short-wave light. Tungsten sources make bad test lights.
Testing visual function

Contrast enhancement

The yellow macular pigment absorbs the background (like the sky) more than the target (like the ball) and therefore creates a bigger difference between the two (i.e., enhances contrast).
Glare disability
Photostress recovery
Photostress recovery
Xanthophylls improve visual function.

Renzi & Hammond, 2010; Hammond et al, 2013
Lutein + Zeaxanthin and Omega-3 Fatty Acids for Age-Related Macular Degeneration
The Age-Related Eye Disease Study 2 (AREDS2) Randomized Clinical Trial

The Age-Related Eye Disease Study 2 (AREDS2) Research Group

Carotenoids and cognitive function: the evidence
The many ways that one can age

Betty White: current age, 93
The many ways that one can age

Marlon Brando: died age 80, liver failure, congestive heart failure, obesity, diabetes, pulmonary fibrosis
The many ways that one can age

Paul Newman: died age 83, lung cancer
Successful aging?

"You start to lose your memory, you start to lose your confidence, you start to lose your invention. So I think that's pretty much a closed book for me."

-- Paul Newman, 2007, on retiring from acting
Cognition?
Altered sensory input with age

Cognition?
Stroke risk: cognitive future

Aerobic Exercise Training Increases Brain Volume in Aging Humans

Stanley J. Colcombe, Kirk L. Erickson, Paige L. Scalf, Jenny S. Kim, Ruchika Prakash, Edward McAuley, Steriania Ilavsky, David X. Marquez, Liang Hu and Arthur F. Kramer

Abstract

Background. The present study examined whether aerobic fitness training of older humans can increase brain volume in regions associated with age-related decline in both brain structure and cognition.

Methods. Fifty-nine healthy but sedentary community-dwelling volunteers, aged 60-79 years, participated in the 6-month randomized clinical trial. Half of the older adults served in the aerobic training group, the other half of the older adults participated in the toning and stretching conditions.

Results. One-way ANCOVAs revealed that aerobic training resulted in significant increases in brain volume in regions associated with memory and executive function, with no significant differences in brain volume in regions associated with other cognitive functions.

Conclusions. These findings suggest that aerobic exercise training may be a promising method for preserving brain structure and function in older humans.
Cognition?

Altered sensory input with age

Raz et al, 2004

Peelle et al, 2013
Cognition?

- Altered sensory input with age
- Loss of cortical volume
- Alterations in processing strategy
- More or less successful execution of behavioral tasks
Cognition?

More or less successful execution of behavioral tasks
Measuring behavior

Category confusion: staging decline vs. direct measures of function vs. cognitive functional reductionism
What’s in a neuron?
What’s in a neuron?

Fatty acids (lipid bilayers)
What’s in a neuron?

Fatty acids (lipid bilayers)
Electrolytes (ion channels)
What’s in a neuron?

- Fatty acids (lipid bilayers)
- Electrolytes (ion channels)
- Vitamins (fat and water soluble)
What’s in a neuron?

- Fatty acids (lipid bilayers)
- Electrolytes (ion channels)
- Vitamins (fat and water soluble, aqueous and lipid compartments)
- Proteins and carbohydrates (cytoskeleton, receptors)

Carotenoids?
Retinal L and Z concentrations relate to cortical concentrations

Vishwanathan et al, 2013
How many rows of 50 would be needed to accommodate all 1,752 undergraduates?
And what if I read that out loud?

1. Hearing

2. Sensory processing

3. Working memory

4. Conversion to long-term storage

5. Permanence
Measuring processing speed

Processing speed is the pace at which a person takes in information from the world.
Lutein levels relate to processing speed

Critical Flicker Fusion Threshold (HZ)

n = 355

Low MP (0.0-0.20)  Medium MP (0.21-0.40)  High MP (0.41-0.81)

Hammond & Wooten, 2005
Renzi & Hammond, 2010
Supplementation with lutein and zeaxanthin improves CFF

When young people supplement lutein and zeaxanthin, CFF improves significantly.
As CFF improves, reaction times also improve.
CFF is the “gateway” to higher cognition

CFF is one of the best predictors of cognitive function young, healthy people and older adults. People who can process information quickly tend also to be better at other cognitively challenging tasks.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Relationship to CFF (r)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global cognition</td>
<td>0.377</td>
</tr>
<tr>
<td>Processing speed</td>
<td>0.344</td>
</tr>
<tr>
<td>Reasoning</td>
<td>0.386</td>
</tr>
<tr>
<td>Executive functioning</td>
<td>0.465</td>
</tr>
</tbody>
</table>
Early life influences on cognition


\[ N = 40 \]
\[ p = 0.007 \]
### Early life influences on cognition

<table>
<thead>
<tr>
<th></th>
<th>Children, aged 7-12 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relation to Macular Pigment (r)</td>
<td>Statistical Significance (p≤)</td>
</tr>
<tr>
<td><strong>Achievement</strong></td>
<td>0.40</td>
</tr>
<tr>
<td></td>
<td>0.01*</td>
</tr>
<tr>
<td><strong>Reading</strong></td>
<td>0.28</td>
</tr>
<tr>
<td></td>
<td>0.05*</td>
</tr>
<tr>
<td><strong>Math</strong></td>
<td>0.35</td>
</tr>
<tr>
<td><strong>Written Language</strong></td>
<td>0.41</td>
</tr>
<tr>
<td><strong>Reading fluency</strong></td>
<td>0.22</td>
</tr>
<tr>
<td></td>
<td>0.09†</td>
</tr>
</tbody>
</table>

Barnett et al, *in press*, *Nutritional Neuroscience*
Does it work?

Saint, Renzi-Hammond, Hammond et al, in preparation
Measuring cognition at multiple levels of analysis, in multiple populations

• Randomized, double masked placebo-controlled trial
• N = 102 completers
  – n = 51 young, healthy adults
  – n = 51 community dwelling elders
• 12 mg L+Z vs. placebo
Measuring “cognition” at multiple levels of analysis, in multiple populations

**Level 1:** anthropo-, metrics, diet, serum, MPOD

**Level 2:** sensory input level

**Level 3:** structural integrity of the nervous system

**Level 4:** processing strategy, passive and active processing

**Level 5:** functional behavioral tasks

**Level 6:** functionally reductionist and diagnostic tasks

Baseline 4-mo 8-mo 12-mo
Level 1

- Basic anthropometrics
- Health screen
- MPOD
- Presence of / degree of cognitive impairment (clinical interview)
- Family Hx
- Serum carotenoids

Level 2

- Visual acuity
- Temporal contrast sensitivity
- Critical Flicker Fusion Frequency (CFF)

Level 3

- Structural magnetic resonance imaging (MRI)
- Voxel based morphometry

Level 4

- Resting state electro-encephalography (EEG)
- EEG in visual attention / target detection task
- EEG in simple flicker paradigm
- Functional MRI (fMRI) in operation span and memory tasks
- Diffusion tensor imaging (DTI)

Level 5

- Short physical performance battery (SPPB)
- Reaction time and coincidence anticipation testing

Level 6

- Attention
- Visual Memory
- Verbal Memory
- Processing Speed
- Psychomotor Speed
- Reasoning
- Executive Function
- Mood
- Social Function

Baseline 4-months 8-months 12-months
Testing cognitive function

Visual Memory

Remember this image

Press the SPACE BAR if you were asked to remember this image

Press the SPACE BAR if you were asked to remember this image

Remember this image
Testing cognitive function

Complex Attention

<table>
<thead>
<tr>
<th>Green</th>
<th>Red</th>
<th>Blue</th>
<th>Yellow</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Stroop Task

- Green
- Red
- Blue
- Yellow

Match to shape

- Press LEFT shift key

Match to color

- Press RIGHT shift key

Shifting Attention Task
Testing cognitive function

Complex Attention

Press the SPACE bar when you see the letter “B.”

Continuous Performance Task
Testing cognitive function

Reasoning ability: choose the option that best completes the pattern.
Lutein levels relate to processing speed

Critical Flicker Fusion Threshold (HZ)

n = 355

Low MP (0.0-0.20)  Medium MP (0.21-0.40)  High MP (0.41-0.81)

Hammond & Wooten, 2005
Renzi & Hammond, 2010
Lutein levels relate to reaction time

Renzi et al, 2013
Younger adults, by supplement
Younger adults, by improvement
Younger adults, by improvement
Older adults, by supplement
Older adults, by supplement
Older adults, by supplement
Brain activation, at rest

High MPOD = 0.69 average

Low MPOD = 0.28 average

12-15 Hz, $p = 0.031$

Thorne et al, 2015
Brain activation, with noise

High MPOD = 0.69 average

Low MPOD = 0.28 average

Oliver et al, 2015
Low levels of macular xanthophylls relate to increased utilization of compensatory processing mechanisms.

Terry et al, 2014
Left middle frontal gyrus and right superior parietal lobe show activation differences in adults with high macular xanthophylls.
## Cognitively impaired older adults

<table>
<thead>
<tr>
<th>Cognitive Status</th>
<th>RBANS Cognitive Domain</th>
<th>Relation to MPOD $(r$ value$)$</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants</td>
<td>Attentional</td>
<td>0.024</td>
<td>0.441</td>
</tr>
<tr>
<td></td>
<td>Visuospatial</td>
<td>0.251</td>
<td>0.057</td>
</tr>
<tr>
<td>Unimpaired participants</td>
<td>Attentional</td>
<td>-0.088</td>
<td>0.334</td>
</tr>
<tr>
<td></td>
<td>Visuospatial</td>
<td>0.091</td>
<td>0.329</td>
</tr>
<tr>
<td>Impaired participants</td>
<td>Attentional</td>
<td>0.466</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>Visuospatial</td>
<td>0.429</td>
<td>0.056</td>
</tr>
</tbody>
</table>

Renzi et al, 2013
Conclusions and recommendations for patient care
Having the hard conversation

- Asking about diet is awkward
- Patients have selective memories
- Modeling good behavior
- Track lifestyle
- Practice expansion / value add
  - OD is the new GP
- Nutrition is (needlessly) confusing
Eggs are good, eggs are bad… might as well eat a donut

Importance: Observational data have suggested that high dietary intake of saturated fat and low intake of vegetables may be associated with increased risk of Alzheimer disease.

Objective: To test the effects of oral supplementation with nutrients on cognitive function.

Design, Setting, and Participants: In a double-masked randomized clinical trial (the Age-Related Eye Disease Study 2 [AREDS2]), retinal specialists in 82 US academic and community medical centers enrolled and observed participants who were at risk for developing late age-related macular degeneration (AMD) from October 2006 to December 2012. In addition to annual eye examinations, several validated cognitive function tests were administered via telephone by trained personnel at baseline and every 2 years during the 5-year study.

Interventions: Long-chain polyunsaturated fatty acids (LCPUFAs) (1 g) and/or lutein (10 mg)/zeaxanthin (2 mg) vs placebo were tested in a factorial design. All participants were also given varying combinations of vitamins C, E, beta carotene, and zinc.

Main Outcomes and Measures: The main outcome was the yearly change in composite scores determined from a battery of cognitive function tests from baseline. The analyses, which were adjusted for baseline age, sex, race, history of hypertension, education, cognitive score, and depression score, evaluated the differences in the composite score between the treated vs untreated groups. The composite score provided an overall score for the battery, ranging from -22 to 17, with higher scores representing better function.

Results: A total of 89% (3741/4203) of AREDS2 participants consented to the ancillary cognitive function study and 93.6% (3501/3741) underwent cognitive function testing. The mean (SD) age of the participants was 72.7 (7.7) years and 57.5% were women. There were no statistically significant differences in change of scores for participants randomized to receive supplements vs those who were not. The yearly change in the composite cognitive function score was -0.19 (99% CI, -0.25 to -0.13) for participants randomized to receive LCPUFAs vs -0.18 (99% CI, -0.24 to -0.12) for those randomized to no LCPUFAs (difference in yearly change, -0.03 [99% CI, -0.02 to 0.13]; P = .63). Similarly, the yearly change in the composite cognitive function score was -0.18 (99% CI, -0.24 to -0.11) for participants randomized to receive lutein/zeaxanthin vs -0.19 (99% CI, -0.25 to -0.13) for those randomized to not receive lutein/zeaxanthin (difference in yearly change, 0.03 [99% CI, -0.14 to 0.19]; P = .66). Analyses were also conducted to assess for potential interactions between LCPUFAs and lutein/zeaxanthin and none were found to be significant.

Conclusions and Relevance: Among older persons with AMD, oral supplementation with LCPUFAs or lutein/zeaxanthin had no statistically significant effect on cognitive function.
Understanding null results, and consequences of category confusion

- Test, function, population all align.
- Appropriate level of analysis for the question.
- There is power in “nothing happening.”

TED: Brain Power: From Neurons to Networks
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