The Role of the Microbiome in Brain Health and Disease

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Faculty Disclosure

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After participating in this presentation, clinicians should be better able to:

- Understand the pivotal role of the microbiome in determining brain health and functionality
- Recognize the detrimental effects of common medications in terms of threatening microbial diversity
- Expand their tool boxes in terms of dealing with common degenerative conditions
mammalian cells

microbial cells
mammalian DNA

microbial DNA
Inflammation

- Alzheimer’s disease
- Parkinson’s disease
- Autism
- Multiple sclerosis
- Stroke
- Depression
- ADHD
Commensal flora and the regulation of inflammatory and autoimmune responses
Factors for Symbiosis
- high fiber diet
- natural birth
- breast feeding
- exposure to microbes
- consumption of probiotics
- favorable genetics

Effects of Symbiosis
- resolution of inflammation
- epithelial barrier integrity
- regulation of neutrophil activity
- reduced T-helper 17 cells
- increased Treg (suppressor)

Factors for Dysbiosis
- antibiotic use
- antibiotics in livestock
- obesity
- Western diet
- hygiene
- stress
- pathogenic bacteria

Effects of Dysbiosis
- inflammation
- cancer
- autoimmunity
Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa

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Gut microbiota composition depends on different dietary habits just as health depends on microbial metabolism, but the association of microbiota with different diets in human populations has not been shown. In this work, we compared the fecal microbiota of European children (EU) and that of children from a rural African village of Burkina Faso (BF), where the diet, high in fiber content, is similar to that of early human settlements at the time of the birth of agriculture. By using high-throughput 16S rDNA sequencing and biochemical analyses, we found significant differences in gut microbiota between the two groups. BF children showed a significant enrichment in Bacteroidetes and depletion in Firmicutes (P < 0.001), with a unique abundance of bacteria from the genus Prevotella and Xylanibacter, known to contain a set of bacterial genes for cellulose and xylan hydrolysis, completely lacking in the EU children. In addition, we found significantly more short-chain fatty acids (P < 0.05) in BF than in EU children. Also, Enterobacteriaceae (Shigella and Escherichia) were significantly underrepresented in BF than in EU children (P < 0.05). We hypothesize that gut microbiota coevolved with the poly saccharide-rich diet of BF individuals, allowing them to maximize energy intake from fibers while also protecting them from infections and noninfectious colonic diseases. This study investigates and compares human intestinal microbiota from children characterized by a modern western diet and a rural diet, indicating the importance of preserving this treasure of microbial diversity from ancient rural communities worldwide.

metagenomics | nutrigenomics | biodiversity | 454-pyrosequencing | short-chain fatty acids

The human gut “metagenome” is a complex consortium of trillions of microbes, whose collective genomes contain at least 100 times as many genes as our own eukaryote genome (1). This essential “organ,” the microbiome, provides the host with enhanced metabolic capabilities, protection against pathogens, education of the immune system, and modulation of gastrointestinal (GI) development (2).

We do not yet completely understand how the different environments and wide range of diets that modern humans around the world have affected the microbial ecology of the human gut.

Contemporary human beings are genetically adapted to the environment in which their ancestors survived and which conditioned their genetic makeup. In mammals, both diet and phylogeny influence the increase in bacterial diversity from carnivore to omnivore to herbivore (3). Dietary habits are considered one of the main factors contributing to the diversity of human gut microbiota (2). Profound changes in diet and lifestyle conditions began with the so-called “Neolithic revolution” with the introduction of agriculture and animal husbandry in10,000 years ago (4). After that time, food resources became more abundant and constant, the concentration of large populations in limited areas created selective pressure that favored pathogens specialized in colonizing human hosts and probably produced the first wave of emerging human diseases (5). It has been hypothesized that bacteria specialized in human-associated niches, including our gut commensal flora, underwent intense transformation during the social and demographic changes that took place with the first Neolithic settlements (6).

Western developed countries successfully controlled infectious diseases during the second half of the last century, by improving sanitation and using antibiotics and vaccines. At the same time, a rise in new diseases such as allergic, auto immune disorders, and inflammatory bowel disease (IBD) both in adults and in children has been observed (5), and it is hypothesized that improvements in hygiene together with decreased microbial exposure in childhood are considered responsible for this increase (7). The GI microflora plays a crucial role in the pathogenesis of IBD (8), and recent studies demonstrate that obesity is associated with imbalance in the normal gut microbiota (9, 10).

The aim of this study was to compare the gut microbiota of children aged 1–6 living in a rural village in an environment that still resembles that of Neolithic subsistence farmers with the gut microbiota of western European children of the same age, eating the diet and living in an environment typical of the developed world. These two childhood populations provided an attractive model for assessing the impact of many environmental variables on the gut microbiota.

In our study, we address three general questions regarding the geography and evolution of the human microbiota: (i) how is bacterial diversity partitioned within and between the two populations studied; (ii) is there a possible correlation between bacterial diversity and diet; and (iii) what is the distribution of well-known bacterial pathogens in the two populations, given the different hygienic and geographic conditions?

Results and Discussion

Characterization of Dietary Habits of Children from the Boupon Rural Village and from Florence, Italy. In this study, we characterized the fecal microbiota of 14 healthy children from the Moshi ethnic
Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa

Comparison of fecal microbiota:

- European children (EU)
- Rural African children Burkina Faso (BF)
- 16S rDNA sequencing and biochemical analysis
African
- Prevotella
- Xylanibacter
- Acetitomaculum
- Faecalibacterium
- Subdoligranulum
- Others

Bacteroidetes

European
- Alistipes
- Bacteroides
- Acetitomaculum
- Faecalibacterium
- Roseburia
- Subdoligranulum
- Others

Firmicutes

Bacteroidetes
Germ Free
↑ Fat
↑ Fermicutes
↓ Bacteriodites

Conventional
↓ Fat
↓ Fermicutes
↑ Bacteriodites
Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa

Increased gut microbial diversity and reduced quantities of potentially pathogenic strains in African flora would agree with the “old friend” hypothesis, indicating a role of microbiota in protecting children from pathogens as well as from gastrointestinal diseases.
Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa

Our results suggest that diet has a dominant role in shaping the gut microbiota. We can hypothesize that the reduction in richness we observe in EU compared with BF children, could indicate how the consumption of sugar, animal fat, and calorie-dense foods in industrialized countries is rapidly limiting the adaptive potential of the microbiota.
Ancient Human Microbiomes

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ABSTRACT

Very recently, we discovered a vast new microbial self: the human microbiome. Our native microbiota interface with our biology and culture to influence our health, behavior, and quality of life, and yet we know very little about their origin, evolution, or ecology. With the advent of industrialization, globalization, and modern sanitation, it is intuitive that we have changed our relationship with microbes, but we have little information about the ancestral state of our microbiome, and we therefore lack a foundation for characterizing this change. High-throughput sequencing has opened up new opportunities in the field of paleomicrobiology, allowing us to investigate the evolution of the complex microbial ecologies that inhabit our bodies. By focusing on recent coprolite and dental calculus research, we explore how emerging research on ancient human microbiomes is changing the way we think about ancient disease and how archaeological studies can contribute to a medical understanding of health and nutrition today.

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Introduction

Genetic sequencing has revolutionized our understanding of the tree of life and humans’ place within it. The development of the Sanger method of DNA sequencing in 1977 and the polymerase chain reaction (PCR) method of DNA amplification in 1983 ushered in an explosion of genetic data that determined the phylogeny of humans and the great apes (Buolala, 1997), rejected the biological concept of race in humans (Long and Kittles, 2003), and reconstructed the peopling of the world (Oppenheimer, 2012). The advent of next generation sequencing (NGS) in the late 1990s facilitated the sequencing of the first complete human genome (Venter et al., 2001), and the subsequent commercial release of this technology in the mid-2000s enabled the genome sequencing of archaic humans, including Neanderthals (Green et al., 2010; Prüfer et al., 2014), Denisovans (Krause et al., 2010; Reich et al., 2010; Meyer et al., 2012), and the mitochondrial genome of an archaic hominin classified as Homo heidelbergensis (Meyer et al., 2014), resulting in discoveries that have further reorganized and refined the human family tree. These studies have addressed fundamentally important aspects of human evolution. Nevertheless, the human genome encompasses only a fraction of the total genetic diversity found within humans. The collective microbial communities inhabiting the human body, known as the human microbiome, contain a vast amount of genetic and functional diversity far exceeding that of our own nuclear and mitochondrial genomes (Qin et al., 2010). A growing appreciation of the role of microbiomes in host essential life functions, the etiology of disease, and even speciation (Human Microbiome Project Consortium, 2012; Blaser et al., 2013; Brucker and Bordenstein, 2013; McFall-Negri et al., 2013) challenges conventional views of the biological species concept (Mayr, 1963; Brucker and Bordenstein, 2013) and raises the question of whether or not ancient human microbiomes should also be investigated in order to explore broader issues in human evolution. This paper will discuss the relationship between humans and their microbiomes and review new developments in the emerging field of ancient microbiome research. We argue that only by also exploring our microbiomes both today and in the past can we fully understand what it means to be human.

The human microbiome

Collectively, the microorganisms of the human body include an astounding number of bacteria. Since the late 1970s, it has been known that the number of bacterial cells (~10^{14}) in and on the human body exceeds the number of human cells (~10^{13}) by at least an order of magnitude (Savage, 1977; Peterson et al., 2009; Bianconi et al., 2013). In 2010, it was established that the estimated number of
Ancient Human Microbiomes

- Next Generation Sequencing
- Dental calculus (mineralized bacterial biofilm)
“There can be no doubt that modern behavior and dietary changes are altering the microbial ecology of humans. While some of these changes could be beneficial, others are disruptive and may be a driving force behind the rapidly increasing rates of chronic inflammatory diseases in developed countries. Common medical interventions, such as antibiotic therapy, have dramatically reduced infectious disease burdens worldwide. However, rather than being targeted strikes against harmful bacteria alone, such therapies can also act as weapons of mass microbial disruption.”
Hygiene and the world distribution of Alzheimer's Disease

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Abstract

**Background and objectives:** Alzheimer’s Disease (AD) shares certain etiological features with autoimmunity. Prevalence of autoimmunity varies between populations in accordance with variation in environmental microbial diversity. Exposure to microorganisms may improve individuals' immunoregulation in ways that protect against autoimmunity, and we suggest this may also be the case for AD. Here we investigate whether differences in microbial diversity can explain patterns of age-adjusted AD rates between countries.
Hygiene and the world distribution of Alzheimer’s Disease

• Epidemiological evidence for a relationship between microbial environment and age-adjusted disease burden

• Comparison to hygiene (parasite load) with Alzheimer’s incidence
parasite stress
Alzheimer’s incidence
Increasing Parasitic Stress
Increasing Alzheimer's Prevalence
Increasing Alzheimer’s Prevalence

Increasing Parasitic Stress
Conclusions: Variation in hygiene may partly explain global patterns in AD rates. Microorganism exposure may be inversely related to AD risk. These results may help predict AD burden in developing countries where microbial diversity is rapidly diminishing.
Obesity and Gut’s Dysbiosis Promote Neuroinflammation, Cognitive Impairment, and Vulnerability to Alzheimer’s disease: New Directions and Therapeutic Implications

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Abstract

Obesity, an epidemic problem in the world is associated with several health problems. An understanding of mechanisms/factors that predispose, delay or protect individuals from obesity and its associated metabolic disturbances and cognitive impairment would be invaluable. The human gut harbors a diverse population of microbial organisms which are symbiotic and important for well being. However, studies on conventional and germ-free animals have shown that alteration in normal commensal gut microbiota and an increase in pathogenic microbiome (termed “dysbiosis”) contribute to gut inflammation, generation of LPS and pro-inflammatory cytokines, gut leakage, and systemic- and neuro-inflammation. The immune mechanisms that are necessary for gut homeostasis may become dysfunctional and lead to bowel inflammation and gut-brain axis dysfunction. These factors are potentially involved in inducing obesity as well. It may be wise to consider the wider hypothesis that gut’s dysbiosis, commencing as a response to fatty food, modulates neuro-inflammation and cognitive dysfunction. This may be enhanced by concomitant noxious factors such as consumption of NSAIDS and alcohol in the elderly. The neurotoxic mechanisms when chronic may enhance vulnerability to dementia of Alzheimer’s type (AD), and perhaps contribute to other dementias as well. Therapeutic strategies for amelioration of cognitive decline and AD are desperately needed. It is pragmatic then that immunologically mediated gut dyshomeostasis is abrogated by available options including Prebiotics, Probiotics, and Symbiotics. Decreasing gut’s dysbiosis may thus attenuate neuroinflammation and provide a potential treatment for obesity-related cognitive impairment. Further, the ‘gut-brain axis’ or ‘brain-gut axis’ (depending on whether one considers bottom-up or top-down pathway) is a bi-directional communication system, comprised of neural pathways encompassing enteric nervous system and the vagus. Vagus nerve stimulation in conjunction with α7 nAChR agonists may be an important therapeutic modality in gut pathology to upregulate parasympathetic/vagal efferent function, ameliorate gut-brain axis dysfunction and neuroinflammation, and decrease vulnerability to AD.
Obesity and Gut’s Dysbiosis Promote Neuroinflammation, Cognitive Impairment, and Vulnerability to Alzheimer’s disease: New Directions and Therapeutic Implications

- Obesity is associated with inflammation
- Obesity is associated with hippocampal atrophy
- Obesity is associated with cognitive decline
Central Obesity and the Aging Brain

William Jagust, MD; Danielle Harvey, PhD; Dan Mungas, PhD; Mary Haan, DrPH

**Background:** Central adiposity as an indicator of visceral fat is linked to vascular and metabolic factors that in turn are related to cognitive decline and dementia.

**Objective:** To determine whether larger waist-hip ratio (WHR) is associated with structural brain changes that underlie cognitive decline and dementia.

**Design:** Cross-sectional analysis of an epidemiologic cohort study of cognitive and functional decline (Sacramento Area Latino Study on Aging).

**Setting:** California Central Valley.

**Participants:** A total of 112 individuals selected from an ongoing cohort study of 1789 older Latino individuals. Baseline anthropomorphic measures (WHR) and measurements of fasting blood glucose, cholesterol, and insulin levels and blood pressure were obtained.

**Main Outcome Measures:** Baseline magnetic resonance images were analyzed quantitatively to determine the hippocampal volumes in the right and left hemispheres and rated for the percentage of white matter hyperintensities.

**Results:** Greater WHR ($P=.02$) and older age ($P<.001$) were negatively related to hippocampal volumes. The WHR and age were positively related to white matter hyperintensities ($P=.02$ and $P=.001$, respectively). A 1-SD increase in WHR was associated with a 0.2-SD decrease in hippocampal volume and a 27% increase in white matter hyperintensities. These relationships were not affected by adjustment for body mass index, total cholesterol, fasting blood glucose, and insulin levels or systolic blood pressure in the models.

**Conclusion:** A larger WHR may be related to neurodegenerative, vascular, or metabolic processes that affect brain structures underlying cognitive decline and dementia.

*Arch Neurol.* 2005;62:1545-1548
Central Obesity and the Aging Brain

Jagust. W., et al., Arch Neurol 62: 1545-48; October, 2005

- 112 older Latinos
- Waist to Hip Ratio
- Volumetric MRI of hippocampus
Plot of waist-hip ratio vs age-adjusted hippocampal volume

Obesity and Gut’s Dysbiosis Promote Neuroinflammation, Cognitive Impairment, and Vulnerability to Alzheimer’s disease: New Directions and Therapeutic Implications

- Obesity is associated with dysbiosis
“This may be enhanced by concomitant noxious factors such as consumption of NSAIDS.”

dysbiosis

- gut inflammation
- increased gut permeability
- translocation of LPS
- pro-inflammatory cytokines
- neuro-inflammation
dysbiosis

gut inflammation
increased gut permeability
translocation of LPS
pro-inflammatory cytokines
neuro-inflammation
Chronic intestinal inflammation alters hippocampal neurogenesis

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Abstract

Background: Adult neurogenesis in the subgranular zone of the hippocampus is involved in learning, memory, and mood control. Decreased hippocampal neurogenesis elicits significant behavioral changes, including cognitive impairment and depression. Inflammatory bowel disease (IBD) is a group of chronic inflammatory conditions of the intestinal tract, and cognitive dysfunction and depression frequently occur in patients suffering from this disorder. We therefore tested the effects of chronic intestinal inflammation on hippocampal neurogenesis.

Methods: The dextran sodium sulfate (DSS) mouse model of IBD was used. Mice were treated with multiple-cycle administration of 3% wt/vol DSS in drinking water on days 1 to 5, 8 to 12, 15 to 19, and 22 to 26. Mice were sacrificed on day 7 (acute phase of inflammation) or day 29 (chronic phase of inflammation) after the beginning of the treatment.

Results: During the acute phase of inflammation, we found increased plasma levels of IL-6 and TNF-α and increased expression of Iba1, a marker of activated microglia, accompanied by induced IL-6 and IL-1β, and the cyclin-dependent kinase inhibitor p21Cip1 (p21) in hippocampus. During the chronic phase of inflammation, plasma levels of IL-6 were elevated. In the hippocampus, p21 protein levels were continued to be induced. Furthermore, markers of stem/early progenitor cells, including nestin and brain lipid binding protein (BLBP), and neuronal marker doublecortin (DCX) were all down-regulated, whereas glial fibrillary acidic protein (GFAP), a marker for astroglia, was induced. In addition, the number of proliferating precursors of neuronal lineage assessed by double Ki67 and DCX staining was significantly diminished in the hippocampus of DSS-treated animals, indicating decreased production of new neurons.

Conclusions: We show for the first time that chronic intestinal inflammation alters hippocampal neurogenesis. As p21 arrests early neuronal progenitor proliferation, it is likely that p21 induction during acute phase of inflammation resulted in the reduction of hippocampal neurogenesis observed later, on day 29, after the beginning of DSS treatment. The reduction in hippocampal neurogenesis might underlie the behavioral manifestations that occur in patients with IBD.

Keywords: Inflammatory bowel disease, Chronic peripheral inflammation, Hippocampus, Adult neurogenesis, p21
Chronic intestinal inflammation alters hippocampal neurogenesis

Adult neurogenesis in the hippocampus is involved in learning, memory, and mood control. Decreased hippocampal neurogenesis elicits significant behavioral changes, including cognitive impairment and depression.
Chronic intestinal inflammation alters hippocampal neurogenesis

Dextran sodium sulfate (DSS) added to drinking water. Animals sacrificed day 7 and 29 (acute and chronic phases of inflammation)
Day 29 after DSS administration
Day 29 after DSS administration
Day 29 after DSS administration

**Graph:**

- **Y-axis:** TNF-α (pg/ml)
- **X-axis:**
  - Control
  - DSS

**Comparison:**
- Control: 0 pg/ml
- DSS: 18 pg/ml

*Journal of Neuroinflammation (2015) 12:65*
Day 29 after DSS administration
Day 29 after DSS administration

Ki-67 + cells

neurogenesis

control

DSS

In vitro IL-6 administration (50ng/ml)

neuronal differentiation

TUJ-1 + cells

control

IL-6
Chronic intestinal inflammation alters hippocampal neurogenesis.

Chronic intestinal inflammation suppresses hippocampal neurogenesis. Increased levels of proinflammatory cytokines have detrimental effects on proliferation of progenitors of neuronal lineage. Deficient hippocampal neurogenesis may underlie increased rate of mood disorder and cognitive impairment observed in IBD patients.
• Antibiotics
• Method of delivery
• Medications
• Water treatment
• Diet
• Hormone therapy
• GMO
Global Glyphosate Market to Reach 1.35 Million Metric Tons by 2017, According to a New Report by Global Industry Analysts, Inc.

... growing adoption/planting of glyphosate-ready Genetically Modified crops,
Glyphosate, pathways to modern diseases II: Celiac sprue and gluten intolerance

- Changes in microbiome
- Impairment of cytochrome P450 enzymes (detoxification)
- Compromises D3 activation, maintaining bile acid
- Chelation of iron, cobalt, molybdenum and copper
- Depletion of tryptophan, tyrosine, methionine and selenomethionine
Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate

In March, 2015, 17 experts from 11 countries met at the International Agency for Research on Cancer (IARC, Lyon, France) to assess the carcinogenicity of the organophosphate pesticides tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate (Table). These assessments will be published as volume 112 of the IARC Monographs.1

The insecticides tetrachlorvinphos and parathion were classified as “possibly carcinogenic to humans” (Group 2B). The evidence from human studies was scarce and considered inadequate. Tetrachlorvinphos induced hepatocellular tumours (benign or malignant) in mice, renal tubule tumours (benign or malignant) in male mice, and spleen haemangio ma in male rats. Tetrachlorvinphos is a reactive oxon with affinity for esterases. In experimental animals, tetrachlorvinphos was systemically distributed, metabolised, and eliminated in urine. Although bacterial mutagenicity tests were negative, tetrachlorvinphos induced genotoxicity in some assays (chromosomal damage in rats and in vitro) and increased cell proliferation (hyperplasia in rodents). Tetrachlorvinphos is banned in the European Union. In the USA, it continues to be used on animals, including in pet flea collars.

For parathion, associations with cancers in several tissues were observed in occupational studies, but the evidence in humans remains sparse. In mice, parathion increased bronchiolo-alveolar adenoma and/or carcinoma in males, and lymphoma in females. In rats, parathion induced adrenal cortical adenoma or carcinoma (combined), malignant pancreatic tumours, and thyroid follicular cell adenoma in males, and mammary gland adenocarcinoma (after subcutaneous injection in females). Parathion is rapidly absorbed and distributed. Parathion metabolism to the bioactive metabolite, paraoxon, is similar across species. Although bacterial mutagenicity tests were negative, parathion induced DNA and chromosomal damage in human cells in vitro. Parathion markedly increased rat mammary gland terminal end bud density.2 Parathion use has been severely restricted since the 1980s.

The insecticides malathion and diazinon were classified as “probably carcinogenic to humans” (Group 2A). Malathion is used in agriculture, public health, and residential insect control. It continues to be produced in substantial volumes throughout the world. There is limited evidence in humans for the carcinogenicity of malathion. Case-control studies of occupational exposures reported positive associations with non-Hodgkin lymphoma in the USA,1 Canada,3 and Sweden,4 although no increased risk of non-Hodgkin lymphoma was observed in the large Agricultural Health Study cohort (AHS). Occupational use was associated with an increased risk of prostate cancer in a Canadian case-control study5 and in the AHS, which reported a significant trend for prostate cancers after adjustment for other pesticides.6 In mice, malathion increased hepatocellular adenoma or carcinoma (combined)7. In rats, it increased thyroid carcinoma in males, hepatocellular adenoma or carcinoma (combined) in females, and mammary gland adenocarcinoma after subcutaneous injection in females.8 Malathion is rapidly absorbed and distributed. Metabolism to the bioactive metabolite, malaoxon, is similar across species. Malaoxon strongly inhibits esterases; atropine reduced carcinogenesis-related effects in one study.9 Malathion induced DNA and chromosomal damage in humans, corroborated by studies in animals and in vitro. Bacterial mutagenicity tests were negative. Compelling evidence supported disruption of hormone pathways. Hormonal effects probably mediate rodent thyroid and mammary gland proliferation.

Diazinon has been applied in agriculture and for control of home and garden insects. There was limited evidence for diazinon carcinogenicity in humans. Positive associations for non-Hodgkin lymphoma, with
Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate
Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate

“Glyphosate is a broad-spectrum herbicide, currently with the highest production volumes of all herbicides. It is used in more than 750 different products for agriculture, forestry, urban, and home applications.”
Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate

The Working Group classified glyphosate as “probably carcinogenic to humans.”
It is an antibiotic.
Threaten microbial diversity

- Antibiotics
- Method of delivery
- Medications
- Water treatment
- Diet
- Hormone therapy
- GMO

leading to increased gut permeability
Inflammation

- Alzheimer’s disease
- Parkinson’s disease
- Autism
- Multiple sclerosis
- Stroke
- Depression
- ADHD
Cardiorespiratory fitness as a predictor of intestinal microbial diversity and distinct metagenomic functions

- Reduced diversity - autoimmune, metabolic, and inflammatory diseases
Cardiorespiratory fitness as a predictor of intestinal microbial diversity and distinct metagenomic functions

- Diabetes (types 1 and 2), obesity, Alzheimer’s, MS, autism, colorectal cancer, inflammatory bowel disease.
Cardiorespiratory fitness as a predictor of intestinal microbial diversity and distinct metagenomic functions

- Analysis of fecal microbiota of 39 healthy participants with similar age, BMI, and diets but with varying cardiorespiratory fitness levels.

- Correlated with peak oxygen uptake (VO2 peak), the gold standard measure of cardiorespiratory fitness.
Cardiorespiratory fitness as a predictor of intestinal microbial diversity and distinct metagenomic functions

• Our regression model showed that ~20% of variation in gut bacterial alpha diversity could be explained by VO$_2$ peak alone; in fact, VO$_2$ peak stood as the only variable that significantly contributed to increased alpha diversity. The primary findings from this study suggest that cardiorespiratory fitness is a good predictor of gut microbial diversity in healthy humans, outperforming several other variables including sex, age, BMI, and dietary components.
Cardiorespiratory fitness as a predictor of intestinal microbial diversity and distinct metagenomic functions

- The microbiome in high cardiorespiratory fitness individuals seems to favor a decreased LPS biosynthetic pathways. In addition, a strong positive correlation was observed between VO$_2$ peak and fecal butyric acid, a SCFA associated with gut health.
Threaten microbial diversity

- Antibiotics
- Method of delivery
- Medications
- Water treatment
- Diet
- Hormone therapy
- GMO

leading to increased gut permeability
Intestinal epithelium - absorption pathways

Transcellular

Paracellular

Tight Junction
• stress
• infection
• drugs
• xenobiotics
• gliadin
• AGEs
entry of LPS and food antigens into circulation

inflammation
LPS

Lipopolysaccharide (endotoxin) on cell membrane of gram (-) bacteria
Zhang, R., et al., J. Neuroimmunol. 2009; (206): 121-4,
Plasma LPS (pg/ml)

Healthy controls  Sporadic ALS

Zhang, R., et al., J. Neuroimmunol. 2009; (206): 121-4,
Zhang, R., et al., J. Neuroimmunol. 2009; (206): 121-4,
Plasma LPS (pg/ml)

Healthy controls  Alzheimer's

Zhang, R., et al., J. Neuroimmunol. 2009; (206): 121-4,
Endotoxin units/ml

Healthy controls  
Autism

Gut permeability and the microbiome

**Systemic** IgM-mediated response against LPS suggests bacterial translocation - “leaky gut”
• Antibiotics
• Method of delivery
• **Medications**
• Water treatment
• Diet
• Hormone therapy
• GMO
Potential Adverse Effects of Proton Pump Inhibitors in the Elderly

Thu, 08/19/10 - 11:48

Authors:
Ami Kapadia, MD, Daisy Wynn, MD, and Brooke Salzman, MD

Introduction
Since the introduction of omeprazole in 1989, proton pump inhibitors (PPIs) have become one of the most commonly prescribed classes of medications in the world. In 2007, PPI sales in the United States were in excess of $11 billion. 

Overall, with their high safety profile and demonstrated efficacy, PPIs represent a major advance in the treatment of acid-related disorders ranging from peptic ulcer disease to erosive esophagitis. However, it has been shown that PPIs are often misused and overused, which may have significant implications. With the widespread and frequent long-term use of PPIs, several adverse effects have come to light that may call for more selective prescribing practices, particularly in older adults who may be more vulnerable and likely to suffer the consequences of such adverse effects. With an estimated 8% of males and 15% of females age 65 years and older experiencing reflux and potentially using acid-suppressive therapy, understanding the risks for potential adverse effects associated with PPIs is critical in this population.

In this article, we review the current data on selected negative outcomes that may result from PPI use. Specifically, increasing evidence demonstrates that PPI therapy may be associated with the development of Clostridium difficile infections, hip fractures, community-acquired pneumonia, vitamin B12 deficiency, and possibly immunoglobulin E-mediated allergic reactions. The implications of such adverse outcomes, along with the evidence of the inappropriate use of PPIs, underscore the need for more judicious use of this class of medications.
Potential Adverse Effects of Proton Pump Inhibitors in the Elderly

Specifically, increasing evidence demonstrates that PPI therapy may be associated with the development of:

- *Clostridium difficile* infections
- hip fractures
- community acquired pneumonia
- vitamin B12 deficiency
- allergic reactions
Potential Adverse Effects of Proton Pump Inhibitors in the Elderly

The etiology of these side effects, particularly diarrhea, may be related to alterations in gut flora caused by acid suppression.
Proton Pump Inhibitor Usage and the Risk of Myocardial Infarction in the General Population

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Abstract

Background and Aims
Proton pump inhibitors (PPIs) have been associated with adverse clinical outcomes amongst clopidogrel users after an acute coronary syndrome. Recent pre-clinical results suggest that this risk might extend to subjects without any prior history of cardiovascular disease. We explore this potential risk in the general population via data-mining approaches.

Methods
Using a novel approach for mining clinical data for pharmacovigilance, we queried over 16 million clinical documents on 2.9 million individuals to examine whether PPI usage was associated with cardiovascular risk in the general population.

Results
In multiple data sources, we found gastroesophageal reflux disease (GERD) patients exposed to PPIs to have a 1.16 fold increased association (95% CI 1.09–1.24) with myocardial infarction (MI). Survival analysis in a prospective cohort found a two-fold (HR = 2.00; 95% CI 1.07–3.78; P = 0.031) increase in association with cardiovascular mortality. We found that this association exists regardless of clopidogrel use. We also found that H2 blockers, an alternate treatment for GERD, were not associated with increased cardiovascular risk; had they been in place, such pharmacovigilance algorithms could have flagged this risk as early as the year 2000.

Conclusions
Consistent with our pre-clinical findings that PPIs may adversely impact vascular function, our data-mining study supports the association of PPI exposure with risk for MI in the
Proton Pump Inhibitor Usage and the Risk of Myocardial Infarction in the General Population

Review of 16 million clinical documents of 2.9 million individuals

PLOS ONE, June 10, 2015

Stanford University
Proton Pump Inhibitor Usage and the Risk of Myocardial Infarction in the General Population

Association with PPIs:

• Myocardial infarction - increased 16%

• Death from myocardial infarction - risk is doubled
Association of Proton Pump Inhibitors With Risk of Dementia

A Pharmacoeptiological Claims Data Analysis

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IMPORTANCE Medications that influence the risk of dementia in the elderly can be relevant for dementia prevention. Proton pump inhibitors (PPIs) are widely used for the treatment of gastrointestinal diseases but have also been shown to be potentially involved in cognitive decline.

OBJECTIVE To examine the association between the use of PPIs and the risk of incident dementia in the elderly.

DESIGN, SETTING, AND PARTICIPANTS We conducted a prospective cohort study using observational data from 2004 to 2011, derived from the largest German statutory health insurer, Allgemeine Ortskrankenassurance (AOK). Data on inpatient and outpatient diagnoses (coded by the German modification of the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision) and drug prescriptions (categorized according to the Anatomical Therapeutic Chemical Classification System) were available on a quarterly basis. Data analysis was performed from August to November 2015.

EXPOSURES Prescription of omeprazole, pantoprazole, lansoprazole, esomeprazole, or rabeprazole.

MAIN OUTCOMES AND MEASURES The main outcome was a diagnosis of incident dementia coded by the German modification of the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision. The association between PPI use and dementia was analyzed using time-dependent Cox regression. The model was adjusted for potential confounding factors, including age, sex, comorbidities, and polypharmacy.

RESULTS A total of 73,679 participants 75 years of age or older and free of dementia at baseline were analyzed. The patients receiving regular PPI medication (n = 2,950; mean [SD] age, 83.8 [5.4] years; 77.9% female) had a significantly increased risk of incident dementia compared with the patients not receiving PPI medication (n = 70,729; mean [SD] age, 83.0 [5.6] years; 73.6% female) (hazard ratio, 1.44 [95% CI, 1.36-1.52]; P < .001).

CONCLUSIONS AND RELEVANCE The avoidance of PPI medication may prevent the development of dementia. This finding is supported by recent pharmacoepidemiological analyses on primary data and is in line with mouse models in which the use of PPIs increased the levels of β-amyloid in the brains of mice. Randomized, prospective clinical trials are needed to examine this connection in more detail.

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Association of Proton Pump Inhibitors With Risk of Dementia

- 73,679 dementia free adults
- aged ≥ 75 years
- followed for 5.4 - 5.6 years
Risk of dementia in regular users of PPI drugs was increased by 44%.
Association of Proton Pump Inhibitors With Risk of Dementia

“Thus, the avoidance of PPI medication may contribute to the prevention of dementia.”
Probiotic foods

- kimchi
- sauerkraut
- yogurt
- kefir
- kombucha

Prebiotic foods

- jicama
- dandelion greens
- garlic
- chickory root
- Jerusalem artichoke
Probiotic foods and supplements
Prebiotic foods and supplements
Lower carbohydrates
More healthy fat
Magnesium
Aerobic exercise
DHA
After participating in this presentation, clinicians should be better able to:

• Utilize innovative laboratory studies to both recognize as well as remediate gut permeability issues

• Apply the knowledge gained in this presentation to cultivate lifestyle recommendations for patients/clients to change their brain’s health destiny