HHS Public Access

Author manuscript

Ann N Y Acad Sci. Author manuscript; available in PMC 2016 December 19.

Published in final edited form as:

Ann N Y Acad Sci. 2013 May ; 1287: 31–43. doi:10.1111/nyas.12138.

The paradox of overnutrition in aging and cognition

Roger A. Fielding[1], **John Gunstad**[2], **Deborah R. Gustafson**[3,4], **Steven B. Heymsfield**[5], **Lenore J. Launer**[6], **John G. Kral**[7], **Josef Penninger**[8], **David I.W. Phillips**[9], and **Nikolaos Scarmeas**[10,11]

[1]Nutrition, Exercise Physiology, and Sarcopenia Laboratory, Tufts University, Boston, Massachusetts [2]Department of Psychology, Kent State University, Kent, Ohio [3]Department of Neurology, SUNY Downstate Medical Center, Brooklyn, New York [4]Neuropsychiatric Eidemiology Research Unity, University of Gothenburg [5]Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, Louisiana [6]Laboratory of Epidemiology, Demography, and Biometry, Intramural Research Program, National Institute on Aging, Bethesda, Maryland [7]Departments of Surgery and Medicine, SUNY Downstate Medical Center, Brooklyn, New York [8]Institute of Molecular Biotechnology, Austrian Academy of Sciences, Vienna, Austria [9]Lifecourse Epidemiology Unit, University of Southampton, Southampton, United Kingdom [10]Department of Neurology, Columbia University College of Physicians and Surgeons, New York, New York [11]University of Athens, Athens, Greece

Abstract

Populations of many countries are becoming increasingly overweight and obese, driven largely by excessive calorie intake and reduced physical activity; greater body mass is accompanied by epidemic levels of comorbid metabolic diseases. At the same time individuals are living longer. The combination of aging and increased prevalence of metabolic disease is associated with increases in aging-related comorbid diseases such as Alzheimer's disease, cerebrovascular dementia, and sarcopenia. Here, correlative and causal links between diseases of overnutrition and diseases of aging and cognition are explored.

Keywords

overnutrition; obesity; cognitive decline; Alzheimer's disease; sarcopenia

Introduction

Over one billion people are estimated to be overweight, placing them at risk for diabetes, cardiovascular disease, and cancer. Type 2 diabetes (T2D) and related metabolic diseases have now become epidemic in resource-poor countries that have undergone rapid Westernization and where the consumption of energy-rich diets, coupled with reduced physical activity, has led to an increase in the incidence of obesity. The combination of T2D,

Author for correspondence: John G. Kral, Department of Surgery, SUNY Downstate Medical Center, 450 Clarkson Avenue, Box 40, Brooklyn NY 11203-2098. jkral@downstate.edu.

related metabolic diseases, and obesity, together with their greatly increased risk of cardiovascular disease, pose a major challenge to often poorly developed health services of resource-poor countries.

Indicators of overnutrition are linked to both clinical dementia and Alzheimer's disease (AD), as well as to overall mortality. AD and other dementias are the 5th leading US causes of death in people aged ≥65 years according to the Centers for Disease Control. One in 3 seniors currently dies from dementia. The risk of death in AD has steadily been increasing during the last 3 decades; it rose 39% from 2000 to 2010. Epidemiological studies in middle and later life have found that higher levels of body mass index (BMI) and waist circumference or waist-to-hip ratio (WHR), indicators of central adiposity, are associated with increased risk for dementia, whereas decline in body weight or BMI, and subsequent underweight in the years preceding and at the time of a dementia diagnosis, also relate to increased risk of dementia. The role of excess regional adipose tissue during different periods of life in relation to later and concurrent risk for cognitive decline and dementia as well as to overall aging is not understood. It has negative metabolic effects on peripheral and cerebral vasculature: adipose tissue (adipokines) and related hormones affect brain nuclei important for cognition, energy metabolism and influence genetic susceptibility.

On December 4, 2012, the Sackler Institute for Nutrition Science and the New York Academy of Sciences hosted the conference "The Paradox of Overnutrition in Aging and Cognition" to present cutting-edge research that links and investigates overnutrition, aging, and cognition. Various strategies, including the use of imaging and metabolic markers, and the identification of predictors of aging-related phenomena such as physical impairment, need to be employed to understand and affect the linkages between overnutrition and the aging process, especially its cognitive aspects. The meeting, which included students and scientists working on aging and nutrition research and its application to preventive and curative medicine, presented and discussed clinical and epidemiological aspects of the relationships between overnutrition, aging, and cognitive performance. The conference was structured as three sessions: (1) an exploration of genetics and body composition with regard to overnutrition and pathology, chaired by John G. Kral (SUNY Downstate Medical Center); (2) an examination of the links between cognition and aging and diabetes, chaired by Deborah R. Gustafson (SUNY Downstate Medical Center, and the University of Gothenburg, Sweden); and (3) a discussion of ways to measure and modify the risks of overnutrition, also chaired by Kral. The meeting concluded with a panel discussion including most of the participants and facilitated by Kral.

Genetics and body composition

Systems biology approaches to overnutrition and aging

Nearly all essential metabolic regulators (e.g., insulin or mTOR signaling) exert conserved functions across different phyla. Similar to mammals, *Drosophila melanogaster* and *Caenorhabditis elegans* utilize a variety of evolutionarily conserved metabolic networks to control the equilibrium of energy and nutritional states. In *C. elegans*, an RNAi feeding model has been used to classify novel regulators of fat storage.[1] Recently, a genome-wide

library of transgenic-RNAi lines of *D. melanogaster* has been developed in which the expression of any gene can be temporally and spatially controlled.[2]

Joseph Penninger (Austrian Academy of Sciences) described a genome-wide RNAi screen designed to genetically dissect essential pathways of adiposity in adult *D. melanogaster*. Using tissue-specific (e.g., muscle, oenocyte, fat body, and neuronal) gene expression technology (i.e., tissue-specific GAL4 promoters), Penninger and colleagues classified candidate obesity genes according to function.[3] Among multiple known and novel candidate pathways, hedgehog signaling was the most prominent fat body–specific obesity pathway. To translate these findings to mammals, tissue-specific mutant mice were generated to have constitutively active hedgehog signaling pathway in fat cells; the mice (aP2-*Sufu*) displayed near total loss of white, but not brown, adipose tissue. Mechanistic studies by Penninger's group revealed that activation of hedgehog signaling blocked differentiation of white adipocytes through dysregulation of early adipogenic factors. Activation of the hedgehog pathway did not, however, affect the differentiation of brown adipocytes in cell culture systems or in mutant mice.[3] This work identified a novel role for hedgehog signaling in the determination of white/brown adipocytes. Moreover, the genetic screen provided a proof-of-principle that results obtained via unbiased *in vivo* RNAi-based scanning of the *D. melanogaster* genome can be used to explore adipocyte cell fate in mammals.

On the basis of these initial findings, the Hedgehog signaling pathway was also evaluated in mature, differentiated adipocytes and *in vivo* in mice.[4] These experiments identified a novel Ca^{2+}/G protein–coupled Hedgehog–Smo–AMPK axis that triggers a rapid Warburg-like aerobic glycolysis state. Small molecule Smo modulators uncoupled the Hedgehog–Smo–AMPK axis from the classical Hedgehog activation cascade; also, induction of the novel Smo–AMPK axis resulted in rapid glucose clearance in muscle and brown adipose tissue *in vivo*, and activation of the pathway bypassed the requirement for insulin in type 1 diabetic mice. These data demonstrate that Hedgehog signaling can rewire cellular metabolism in the context of glucose dysregulation, and thus may provide a unique therapeutic avenue for obesity and type 1 diabetes.[4]

With the advance of new sequencing technology, thousands of candidate genes have been identified as being involved in the basic control of physiology and disease pathogenesis. In *D. melanogaster* and *C. elegans*, large scale screens have been performed examining pathologies related to adiposity. A key goal of functional disease genomics is to more rapidly translate the wealth of genetic associations found in model organisms to studies in mammals, especially as the data from experimental systems have used methodologies such as RNAi screens or time-consuming breeding of genetically altered mice.

Penninger and colleagues have introduced a novel technology with the potential to revolutionize functional genomics in mammalian cells: haploid mouse embryonic stem (ES) cells.[5] The types of haploid organisms—those carrying single copies of each chromosome—range from yeast to social insects and fish. There are also near-haploid human tumor cells. Insects, fish, and near-haploid tumor cells have proven to be very useful for carrying out genome wide mutagenesis studies and for analyzing recessive phenotypes.[6,7] Penninger reported the generation of the first haploid mouse ES cell lines, which carry 20

chromosomes, express *bona fide* stem cell markers, and maintain genome integrity. Functionally, the haploid ES cells can develop, *in vitro* and *in vivo*, into cell types of all germ layers; the haploid ES cells can be readily mutagenized, thus making it possible to perform whole-genome forward genetics.

Since all ES cells offer access to unlimited quantities of nearly every cell type, haploid ES cells may provide a tool to genetically assess fundamental developmental and biological processes in defined cell types found in adipocyte differentiation or clarify functions of mature white, brite and brown adipocytes.

Precursors and secular trends in metabolic disease

David Phillips (University of Southampton) discussed many of the factors driving global trends of increasing incidence of metabolic disease, and the mechanisms underlying the increased susceptibility of populations vulnerable to these health risks. Type 2 diabetes and related metabolic diseases have become epidemic in several resource-poor countries that have undergone rapid westernization.[8] Although this epidemic was precipitated by the abandonment of traditional lifestyles, consumption of energy-rich foods, reduced physical activity, and increased obesity, these are not the only factors involved in high disease rates in these countries. People with a history of poverty and undernutrition may be uniquely susceptible to these lifestyle changes. Recent research suggests that the process of developmental plasticity, also referred to as early life programming, may offer a cogent explanation of this susceptibility.

Developmental plasticity describes a process by which organisms (or populations) adapt to adverse environments by developing non-genetically determined phenotypic alterations in body composition and physiology to counteract the adversity. However, such changes can only be considered adaptive (and thus healthy) if the population continues to live in the conditions responsible for the adverse environment (e.g., poverty). The adaptations are (or can become) maladaptive (unhealthy), in contrast, when the environmental adversity is (externally) removed, such as when a poor country rapidly westernizes.[9]

Developmental plasticity is present in most animal species and has been well documented in animal experiments. In human studies, low birth weight and poor postnatal growth have been used as proxies for developmental adversity. Low birth weight, prevalent in many resource-poor countries, is associated with disturbed body composition — central obesity, low muscle, and poor bone mineralization — in later life. It is also linked to abnormalities of carbohydrate metabolism (insulin resistance and defective insulin secretion), vascular function (high blood pressure), and functions of major organs such as the liver and kidneys; these abnormalities raise the risk of type 2 diabetes, hypertension, and cardiovascular disease. Current studies of mechanisms underlying such phenotypic and physiological alterations imply that they are epigenetic. Some pathways have been defined. For example, early life stress is known to alter the epigenetic regulation of glucocorticoid receptors in target tissues; this results in lifelong changes in the hormonal systems that mediate the bio-behavioral response to stress, a known regulator of carbohydrate metabolism and vascular physiology.[10] It follows that improving the nutrition of pregnant women and infants—to

reduce the likelihood of unhealthy alterations in body composition later—may be an effective way to prevent these emerging health problems in some developing countries.

Sarcopenia and muscle power

Sarcopenia: normal versus pathologic

Steven B. Heymsfield (Louisiana State University) shifted the focus to examine aging-related diseases. A long-recognized age-related phenomenon, sarcopenia—the gradual aging-related loss of skeletal muscle mass with associated changes in muscle quality and function[11]— is a clinically important component of frailty and some metabolic disturbances. Sarcopenia is the focus of active research programs aimed at understanding underlying mechanisms in order to develop preventive and therapeutic measures. Gradual loss of skeletal muscle mass is a normal part of the aging process, related to increasing inactivity. It can also be caused by underlying catabolic illness, usually referred to as *cachexia*, which differs metabolically from classical sarcopenia.[11] Thus, sarcopenia is classified as primary or secondary (inactivity versus cachexia); primary sarcopenia appears in stages, beginning with pre-sarcopenia, advancing to clinically manifest sarcopenia, and finally to severe sarcopenia.[11]

Recently sarcopenia has been recognized in obese individuals, a comorbidity referred to as *sarcopenic obesity*. As might be expected from two conditions that individually pose increased risk, sarcopenic obesity is associated with greater morbidity risk than either condition alone.

Skeletal muscle mass reaches peak values during the late teen years and early twenties, and then begins to slowly decline in healthy adults at a rate of about 0.5–1% per year. Age-related rates of skeletal muscle mass loss vary; individuals with rapid muscle loss are at risk for sarcopenia, as are those with rapid bone loss and osteoporosis. Determinants of skeletal muscle mass include genetic susceptibility, height, activity level, race, adiposity and abnormal levels of key hormones.

Heritability estimates for human skeletal muscle (lean) mass is ~ 0.52, with similar corresponding estimates for leg extensor and grip strength.[12] Myostatin is a gene that regulates skeletal muscle mass; inactivation leads to significantly larger skeletal muscles in mammals. Taller adults have more skeletal muscle than their shorter counterparts. Skeletal muscle scales with the square of height, similar body weight.[13] Analogous to body mass index (BMI; weight/height^2), *skeletal muscle mass index* (SM/height^2) adjusts for individual differences in height, allowing definition of diagnostic criteria for sarcopenia. People who exercise regularly have greater skeletal muscle mass. A large percentage of Americans have suboptimal levels of leisure time physical activity, particularly the elderly. On average, African Americans have more skeletal muscle mass than Caucasians matched for weight, height, and age[14] through unknown mechanisms. Anabolic hormones, such as androgens, growth hormone and IGF-1 stimulate growth and maintenance of skeletal muscle mass, effects that decline with aging, particularly from the sixth decade onward. Finally, greater skeletal muscle mass develops with larger mechanical loads. Thus, obese people tend to have

a more skeletal muscle than age-matched counterparts; the proportion of fat free mass as skeletal muscle increases with greater adiposity.

While the classical approach to sarcopenia focuses on skeletal muscle mass, growing interest surrounds *dynapenia*, or loss in muscle strength.[11] Functional limitations, frailty, and other consequences of age-related changes in muscle strength are of central importance to the morbidity and mortality associated with sarcopenia. Beginning around the seventh decade and progressing beyond, rates of loss of skeletal muscle function exceed those of mass. Functional effects are very slow to return following periods of illness and lack of activity.

Obviously, sarcopenia results from multiple interacting factors, the mechanisms of which remain to be determined. Skeletal muscle does not develop in isolation; it grows during development and declines with senescence under the influence of neural and hormonal regulation. These factors influence skeletal muscle mass and function and contribute to the pathogenesis of sarcopenia. For example, an elderly person's fall with injury may be attributable to insufficient skeletal muscle mass with poor functional quality (poor leg strength and coordination), as well as to a series of neurocognitive and neuromuscular pathways functioning below optimal levels. Thus, it is only within a broader physiological context that a full understanding of sarcopenia and its clinical manifestations will evolve.

Skeletal muscle power: a determinant of physical functioning in older adults

Roger Fielding (Tufts University) discussed the importance of muscle power output as one of the variables that contribute to physical impairment associated with aging. Skeletal muscle, the largest organ mass in the body, comprising 40–50% of total body mass, is required for locomotion and is a determinant of oxygen consumption, whole body energy metabolism, and substrate turnover and storage. Advancing age is associated with the loss of skeletal muscle (sarcopenia), and can lead to declines in physical functioning. The causes of sarcopenia, like many complex geriatric syndromes, are multifactorial.[5] The loss of muscle mass and strength, and the concurrent increase in joint dysfunction and arthritis that occurs with aging, results in a decrease in physical function and an increased risk of disability. Disability is associated with limitations in performing regular activities of daily living, including rising from a chair, climbing flights of stairs, bathing, and preparing food. Studies have shown that the ability to perform these tasks decreases with age in both men and women.

Despite the high prevalence and major health implications, sarcopenia still has no broadly accepted clinical definition or diagnostic criteria. The most current definition of sarcopenia includes gait speed < 1.0 m/s combined with a low ratio of appendicular lean mass (aLM) to height squared (≤ 7.23 kg/m^2 in males, ≤ 5.67 kg/m^2 in women), two standard deviations below the mean aLM of young healthy adults.

Skeletal muscle power output (the product of force and velocity) declines earlier and more precipitously with advancing age compared to muscle strength. In cross-sectional and longitudinal studies of older adults, Fielding and colleagues observed that declines in muscle mass could not fully explain the observed deficits in skeletal muscle power output, suggesting that factors related to deficits in neuromuscular activation may play a role.

Fielding reported significant reductions in neuromuscular activation patterns and deficits in rapid activation of voluntary lower extremity muscle groups in older adults with measured limitations in physical functioning. Peak muscle power has also emerged as an important predictor of functional limitations in older adults, and as an important outcome measure in clinical trials of resistance training of older adults. Fielding explained that his group's current working hypothesis is focused on examining lower extremity muscle power as a more critical variable in understanding the relationship between impairments, functional limitations, and resultant disability with aging.

Cognition and diabetes

Cognitive reserve and aging

Yaakov Stern (Columbia University College of Physicians and Surgeons) discussed the concept of *reserve*—a variable that refers to the discrepancy (or discordance) between brain pathology and clinically apparent symptoms. Stern explained that reserve refers to differences between two components: brain reserve is the number of neurons or synapses unaffected by pathology; cognitive reserve is the resilience or plasticity of cognitive networks compensating for loss of functional neurons. Stern's group studies cognitive reserve using neuroimaging.

Whatever the mechanism, reserve is malleable and can strengthen or weaken at every stage of life. In AD and other diseases of aging associated with cognitive decline, the initiating and promoting pathology can precede the onset of clinical symptoms by decades depending on reserve. Exercise and environmental factors stimulate brain plasticity and can remodel neuronal circuitry, which in turn increases vascularization and neurogenesis in the dentate, and thus brain volume, cortical thickness, neuronal survival, and resistance to progressive brain pathology.

The concept of reserve has been supported by epidemiological studies. After following a cohort of clinically asymptomatic elderly individuals to determine the time of onset of AD symptoms,[22] Stern and colleagues report that individuals grouped by education level have different outcomes; those with less formal education were twice as likely to develop AD as those with more. Similarly, individuals with less education in occupations with lower cognitive demands were at twice the risk of AD as those with high occupational attainment and greater demands. Among the same cohort, when controlled for education and occupational attainment individuals who engaged in high levels of physical activity had reduced risk of AD compared with those with low activity. In studies of elderly individuals without diagnosed AD, higher levels of literacy correlated with lower rates of memory decline.[23]

Reserve seems to offer significant but incomplete protection against AD and other brain pathologies: individuals with high reserve and little pathology may be free of dementia or other clinical signs, while individuals with moderate pathology may have less severe dementia than individuals with low reserve. This suggests that individuals with low reserve and mild severity likely have less pathology. In imaging studies controlled for clinical

disease severity, Stern has reported an inverse relationship between level of education and parieto-temporal perfusion deficit, a marker of AD.[24]

In more recent studies, Stern's group used imaging techniques (e.g., fMRI) to examine brain regions that may be involved in reserve. A letter-recognition test unveiled two active brain networks: one primary, used by both young and elderly subjects, and one exclusively used by the elderly. While this suggested a compensatory neural network, individuals who used the second network performed comparatively poorly on the letter recognition task, and the more atrophy present within an individual's primary network the more likely s/he would be to use the second network. However, Stern showed that, given a level of atrophy, individuals with higher cognitive performance (I.Q.) performed better on the letter recognition test, even among those who used the second network.[25]

To summarize, Stern reiterated how the concept of reserve is supported by epidemiological and imaging evidence, and how it appears malleable, even at later stages of life. Reserve may be useful in a range of conditions impacting brain function. Influencing reserve has the potential to delay or reverse aging and brain pathology.

Diabetes and the brain

Lenore Launer (National Institute on Aging) provided an overview of recent reports demonstrating greater cognitive impairment in type 2 diabetes (T2D), associated with underlying structural changes with functional consequences. Obesity has many comorbidities, the most prevalent being diabetes. The rise in the prevalence and incidence of T2D and obesity[267] is reaching epidemic proportions with both conditions occurring earlier in life. Another public health concern nearing epidemic levels is the logarithmic increase in the incidence of dementia after 65 years of age. There have been several reports of associations between obesity and dementia, and dementia and T2D in the past decade.[27] Although data linking BMI and dementia are inconsistent (see Gustafson, below), the relationship between T2D and dementia is fairly robust, partly explaining the association between obesity and dementia.

Diabetes is associated with both vascular disease and neurodegenerative processes associated with cognitive impairment. These oxidative, inflammatory, metabolic, protein misfolding, neuroendocrine processes connect diabetes with mixed brain pathology that includes large, small, and microinfarcts and AD lesions (neuritic plaques, neurofibrillary tangles, and cerebral amyloid angiopathy).

Several epidemiologic studies comprising several ethnic groups have reported approximately twice the risk for dementia, including AD, in individuals with T2D compared to those without diabetes. Evidence for the link between diabetes and dementia is further drawn from studies of associations between T2D and intermediary measures of brain structure and function.[27–29] They suggest that individuals with T2D perform more poorly on tests of memory, processing speed, and executive function, and that performance worsens with duration of diabetes and poor glycemic control. Magnetic resonance imaging (MRI) demonstrates that patients with T2D have increased numbers of infarct-like lesions, hippocampal atrophy (reflecting neurodegeneration), or both. There is additional indirect

evidence that microvascular pathology is associated with poor performance on speed and executive function tests, and that diabetic patients have cerebral microvascular angiopathy, MRI-detected white matter damage and cerebral microbleeds. In addition patients with T2D have reduced total brain and gray matter volume, suggesting that, in addition to neurodegeneration, loss of gray matter microvasculature contributes to the brain atrophy seen in dementia.

Finally, genetic susceptibility factors seem to modulate the risk of cerebral pathology in individuals with T2D. Autopsy studies in the Honolulu Asia Aging Study suggest that those with diabetes and the apolipoprotein E ε4 allele, a genetic susceptibility factor for AD, have a much higher risk for cerebral amyloid angiopathy, infarcts, and neurotic plaques than those without diabetes and the ε4 allele. A similar association was found for clinical dementia.[27] With rapidly evolving genetic technology it is likely such links will be better understood in the next few years.

Although there is strong evidence that dysglycemia in itself can contribute directly and indirectly to vascular damage and neurodegeneration, T2D patients and those with the metabolic syndrome, including insulin resistance, hypertension, coronary disease, and dyslipidemia, often exhibit brain pathology.[28] Studies of the association of T2D with brain structure/function need to include models adjusted for these comorbidities and to test for compounding effects of these comorbidities to determine pathology.

Measuring and modifying risks

The effects of obesity on dementia

Deborah R. Gustafson (SUNY Downstate Medical Center, University of Gothenburg) discussed the relationship between body mass and risks for AD. Body weight and body mass index (BMI) are common, simple measures of overnutrition, commonly termed “overweight” and “obesity”. BMI and central obesity, measured as waist circumference (WC) or waist-to-hip ratio (WHR), are linked to manifest dementia and late-onset AD (LOAD) in epidemiological studies.[30–33] Overweight and obesity in middle and later life may increase risk for dementia, whereas decline in body weight or BMI and underweight in years preceding and at the time of LOAD diagnosis may also contribute to dementia and its clinical progression.

While mid-life (adult) and late-life (approximately 60 years and older) factors are associated with AD, the pathogenesis is more complex. On average BMI increases throughout life until age 60–70 years; higher mid-life BMI or central obesity decades before dementia onset are linked to higher risk of AD later in life.[34–38] Risk estimates for AD and all dementias associated with overweight and obesity are in the range of 1.5- to 3-fold higher than among normal-weight individuals. This level of risk is similar to that observed for hypertension and other cardiovascular risk factors. Levels of mid-life BMI and central obesity associated with AD are in overweight and obese ranges, based on traditional cutoffs used in majority Caucasian populations for assessing cardiovascular risk and predicting overall mortality (e.g., BMI ≥ 25 kg/m^2 or WHR ≥ 0.85 in women and ≥ 0.90 in men). Subsequently, BMI declines. Thus, while high levels of BMI during mid-life may increase risk for the chronic

neurodegenerative diseases of aging, the direction of the BMI–AD relationship appears to plateau and/or change in late life.[38,39] On average, in later life individuals with AD have a lower body weight or BMI than those without AD. This paradoxical combination of higher LOAD risk associated with mid-life overweight and obesity and decline in BMI and underweight in the years immediately preceding and at the time of LOAD diagnosis requires further investigation. Ongoing studies are evaluating adipose tissue hormones (adipokines), adipose tissue vascularity and angiogenesis, and regional differences between adipose depots in relation to clinical dementia and brain structure and function.

Nutrition and cognition: limitations, complexities and interpretations

Nikolaos Scarmeas (University of Athens and Columbia University) discussed the limitations of, and complexities in, our understanding of the links between nutrition and cognition. Studies have found that cognitive performance and risk for AD and other brain diseases associated with dementia vary with intake of micro- and macronutrients and with dietary pattern. And while this literature is extensive, studies are often not confirmed and associations are reported that are not always consistent.[40,41] As a result, few clear recommendations can be made regarding nutritional habits with the potential to improve cognitive performance or protect from dementia or cognitive impairment. This uncertainty might engender the idea that no definitive association exists between nutrition and cognition. Scarmeas urged, however, that methodological limitations are the root of the problem. For example, nutritional supplementation may only be effective in people with actual deficiencies, in contrast to those who participate in scientific studies and have a normal nutritional status, leaving little possibility of physiological improvement.[42]

Scarmeas also described difficulties in measuring cognitive outcomes, including the subjectivity of dementia diagnosis, a lack of reliable biomarker diagnosis, and the variability of neuropsychological evaluations. There are also significant inherent limitations in the assessment of nutritional exposure. For example, food frequency questionnaires probe for answers that require complex consideration or focus on a limited number of foods covering a proportion of overall diet. Nutrient biomarkers can be inaccurate, costly, and usually do not indicate central nervous system levels of nutrients; they are also limited to a relatively low number of nutritional elements, while a normal diet comprises thousands of chemicals many of which have cognitive effects. Furthermore, self-reporting is notoriously inaccurate. Analyses that follow from a reductionist consideration of a limited number of nutritional elements impose the significant constraint of ignoring both confounders and agents, while simultaneously failing to summarize dietary habits in a single measure. Scarmeas urged a more holistic approach to dietary patterns, which would partially remedy some of these problems and provide significant public health information, even though not elucidating mechanisms explaining interactions between diet and cognition.[43]

Finally, cognition is an extremely complex activity influenced by a multiplicity of cerebral biological mechanisms (including vascular, inflammatory, metabolic, oxidative, and β-amyloid-, τ-, and α-synuclein-related). Consequently, there are likely multiple nutritional effects with interacting, and even opposing, directionality.[44]

A series of attempts to partially address some of the above issues includes consideration of baseline levels of nutrients, measurements of nutrient biomarkers and examination of their relationship with neurodegeneration-related (and other mechanism-related) biomarkers,[44] estimates of dietary patterns,[42] and the use of brain imaging biomarkers of various types. Although such attempts have emerged only relatively recently, they may soon increase in number and frequency enhancing the current limited understanding of the relation between nutrition and cognition.

Bariatric surgery, cognitive function, and Alzheimer's disease

Further discussing the links between obesity and cognitive dysfunction, John Gunstad (Kent State University) presented an analysis of the beneficial metabolic effects of bariatric surgery on cognitive function and AD. Gunstad emphasized that while obesity has been recognized as an independent risk factor for adverse neurocognitive outcomes, including AD, vascular dementia, stroke, and accelerated cognitive decline, it is also associated with cognitive dysfunction long before onset of these conditions. Deficits in attention, executive function, memory, and psychomotor speed are commonly found on neuropsychological tests done before the occurrence of overt symptoms of neurodegenerative disease. Such deficits accord with neuroimaging findings in the obese population including global and specific atrophy, reduced frontal lobe metabolism, and white matter abnormalities (reviewed in Ref. 45). In the absence of evidence that these types of neuropathology might be reversible, it was tempting to study whether obesity-related cognitive dysfunction could be reversed through significant weight loss.

Obesity is associated with many conditions exhibiting reversible cognitive deficits, including hypertension, type 2 diabetes, sleep apnea, and depression, which support the hypothesis that weight loss may improve cognitive function and ultimately reduce risk of adverse neurocognitive outcomes in obese patients.[45] An ongoing project is examining this possibility by prospectively assessing cognitive function in patients that undergo various forms of bariatric surgery. Bariatric operations are safe and effective for metabolic obesity, and gastric bypass patients can lose more than 60% of their excess weight at nadir.[46] If weight loss were to produce improvements in cognitive function, it would most likely appear in severely obese or dysmetabolic individuals who maintain a medically significant amount of weight loss.

Gunstad described a prospective assessment[47] of 125 patients undergoing either Roux-en-Y gastric bypass or gastric banding from the Longitudinal Assessment of Bariatric Surgery (LABS) parent project, as well as 125 demographically similar obese control patients. As predicted, cognitive impairment was prevalent in bariatric surgery candidates, with nearly 25% exhibiting clinically significant levels of dysfunction (> 1.5 SD below normative performance) prior to surgery; up to 40% exhibited milder deficits (1 SD below normative performance). Nearly all patients underwent Roux-en-Y gastric bypass procedures and those without surgical complications did not exhibit cognitive decline at 12 weeks postoperative. While past studies show that a small number of patients experience neurological complications due to nutritional deficiencies over the long term after surgery,[48] often owing

to failure to adhere to supplementation, the absence of widespread cognitive dysfunction on testing in this ongoing project suggests these complications are fairly rare.

More interesting were findings that surgical patients exhibited significant improvements compared to baseline on multiple cognitive tests as early as 12 weeks postoperative. Most notably, performance improved on multiple memory indices (e.g., learning, recall, recognition) in surgery patients, whereas memory declined in obese controls during the same relatively short period of time.[47] *Post hoc* analyses showed that magnitude of weight loss and improvement in comorbid medical conditions contributed very little to this effect.

Continued assessment of these patients reveals that the cognitive benefits of bariatric surgery persist over time. A series of submitted papers describe that bariatric surgery patients show further cognitive improvement 1 year postoperative and maintenance of the gains at 2 years. Further studies are needed to determine whether cognitive benefits persist for longer periods (e.g., 60 months) when weight regain is common among patients undergoing any form of weight loss surgery, and the degree to which these procedures may reduce risk for AD or other neurological disorders later in life.

Conclusions

The material presented here summarize the current understanding of the risks posed by overnutrition for cognitive decline, Alzheimer's disease, dementia, sarcopenia, and other diseases associated with aging. Crucially, the risks of overnutrition are potentially modifiable; this is especially significant if addressing overnutrition can minimize or mitigate the development of dementia, for which no effective treatments exist and monetary cost to the U.S. alone reach over $150 billion per year.[49] Effectively reducing these risks will require further exploration of appropriate and optimal temporal targets for intervention—whether the obese brain is entrained very early in life or whether the potential for exercise and neural plasticity to reduce risks of cognitive decline persist throughout life. Improvements in epidemiological methods will be necessary to fully examine the relationship between obesity and cognitive decline, including technological advances in tele-medicine that can standardize and reduce the irregular intervals at which epidemiological data are collected. Large cohorts of patients tracked from birth are now reaching ages relevant to the study of these conditions, and data from these studies may be essential to understanding the contribution of childhood factors to diseases of aging. Developing work linking exploring more sophisticated measures of body composition, hormones, and metabolic markers to specific subpopulations with genetic polymorphisms may yield more definitive results than past work correlating outdated measures like BMI with clinical outcomes.

Ultimately, however, the greater challenge in addressing the relationship between nutrition and lifestyle and aging lies in translating and implementing what is already known into interventions and preventive measures in the population. The relationships between overnutrition and diseases like diabetes and cardiovascular disease are known; however, this knowledge has not reduced the trends toward increasing overweight and obesity in the United States and many other countries. Still, a reasonable approach to address the risks for

cognitive decline and sarcopenia, as well as other diseases of obesity, is education at the public, academic, and political levels in order to ignite dynamic changes in the priorities of public policy, the paradigms of research funding, and the messaging and communications of motives to both physicians and patients.

Acknowledgments

The conference “The Paradox of Overnutrition in Aging and Cognition” was supported by the Sackler Institute of Nutrition Science at the New York Academy of Sciences.

References

1. Ashrafi K, Chang FY, Watts JL, Fraser AG, et al. Genome-wide RNAi analysis of Caenorhabditis elegans fat regulatory genes. Nature. 2003; 421:268–272. [PubMed: 12529643]
2. Dietzl G, Chen D, Schnorrer F, Su KC, et al. A genome-wide transgenic RNAi library for conditional gene inactivation in *Drosophila*. Nature. 2007; 448:151–156. [PubMed: 17625558]
3. Pospisilik JA, Schramek D, Schnider H, et al. *Drosophila* genome-wide obesity screen reveals Hedgehog as a determinant of brown versus white adipose cell fate. Cell. 2010; 140:148–160. [PubMed: 20074523]
4. Teperino R, Amann S, Bayer M, McGee SL, et al. Hedgehog partial agonism drives Warburg-like metabolism in muscle and brown fat. Cell. 2012; 151:414–426. [PubMed: 23063129]
5. Elling U, Taubenschmid J, Wirnsberger G, et al. Forward and Reverse Genetics through Derivation of Haploid Mouse Embryonic Stem Cells. Cell Stem Cells. 2011; 9:563–574.
6. Carette JE, Guimaraes CP, Varadarajan M, Park AS, et al. Haploid genetic screens in human cells identify host factors used by pathogens. Science. 2009; 326:1231–1235. [PubMed: 19965467]
7. Streisinger G, Walker C, Dower N, Knauber D, Singer F. Production of clones of homozygous diploid zebra fish (Brachydanio rerio). Nature. 1981; 291:293–296. [PubMed: 7248006]
8. Fall CH. Fetal Programming and the Risk of Noncommunicable Disease. Indian J Pediatr. 2004; S1:13–20.
9. Bateson P, Barker D, Clutton-Brock T, Deb D, et al. Developmental plasticity and human health. Nature. 2004; 430:419–421. [PubMed: 15269759]
10. Phillips DI. Programming of the stress response: a fundamental mechanism underlying the long-term effects of the fetal environment? J Intern Med. 2007; 261:453–460. [PubMed: 17444884]
11. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010; 39:412–23. [PubMed: 20392703]
12. Arden NK, Spector TD. Genetic influences on muscle strength, lean body mass, and bone mineral density: a twin study. J Bone Miner Res. 1997; 12:2076–2081. [PubMed: 9421240]
13. Heymsfield SB, Heo M, Thomas D, Pietrobelli A. Scaling of body composition to height: relevance to height-normalized indexes. Am J Clin Nutr. 2011; 93:736–740. [PubMed: 21248190]
14. Heymsfield SB, Scherzer R, Pietrobelli A, Lewis CE, Grunfeld C. Body mass index as a phenotypic expression of adiposity: quantitative contribution of muscularity in a population-based sample. Int J Obes. 2009; 33:1363–73.
15. Morley JE, Baumgartner RN, Roubenoff R, Mayer J, Nair KS. Sarcopenia. J Lab Clin Med. 2001; 137:231–243. [PubMed: 11283518]
16. Jette AM, Assmann SF, Rooks D, Harris BA, Crawford S. Interrelationships among disablement concepts. J Gerontol. 1998; 53A:M395–M404.
17. Jette AM, Branch LG. The Framingham Disability Study: II. Physical disability among the aging. Am J Public Health. 1981; 71:1211–1216. [PubMed: 7294262]
18. Fielding RA, Vellas B, Evans WJ, et al. Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International working group on sarcopenia. JAMDA. 2011; 12:249–256. [PubMed: 21527165]

19. Baumgartner RN, Koehler KM, Gallagher D, et al. Epidemiology of Sarcopenia among the elderly in New Mexico. Am J Epidemiol. 1998; 147:755–763. [PubMed: 9554417]
20. Clark DJ, Fielding RA. Neuromuscular contributions to age-related weakness. J Gerontol A Biol Sci Med Sci. 2012; 67:41–47. [PubMed: 21415261]
21. Reid KF, Fielding RA. Skeletal muscle power: a critical determinant of physical functioning in older adults. Exercise Sport Sci R. 2012; 40:4–12.
22. Stern Y, Gurland B, Tatemichi TK, Tang M, et al. Influence of Education and Occupation on the Incidence of Alzheimer's Disease. JAMA. 1994; 271:1004–1010. [PubMed: 8139057]
23. Manly JJ, Touradji P, Tang MX, Stern Y. Literacy and memory decline among ethnically diverse elders. J Clin Exp Neuropsychol. 2003; 25:680–90. [PubMed: 12815505]
24. Stern Y, Alexander GE, Prohovnik I, Mayeux R. Inverse relationship between education and parietotemporal perfusion deficit in Alzheimer's disease. Ann Neurol. 1992; 32:371–3765. [PubMed: 1416806]
25. Steffener J, Stern Y. Exploring the neural basis of cognitive reserve in aging. Biochim Biophys Acta. 2012; 1822:467–73. [PubMed: 21982946]
26. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999–2010. JAMA. 2012; 307:491–497. [PubMed: 22253363]
27. Launer LJ. Diabetes: vascular or neurodegenerative: an epidemiologic perspective. Stroke. 2009; 40:S53–55. [PubMed: 19064803]
28. Gorelick PB, Scuteri A, Black SE, et al. American Heart Association Stroke Council, Council on Epidemiology and Prevention, Council on Cardiovascular Nursing, Council on Cardiovascular Radiology and Intervention, and Council on Cardiovascular Surgery and Anesthesia. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/american stroke association. Stroke. 2011; 42:2672–2713. [PubMed: 21778438]
29. Saczynski JS, Siggurdsson S, Jonsson PV, et al. Glycemic status and brain injury in older individuals: the age gene/environment susceptibility-Reykjavik study. Diabetes Care. 2009; 32:1608–1613. [PubMed: 19509008]
30. Gustafson DR. Adiposity indices and dementia. Lancet Neurol. 2006; 5:713–720. [PubMed: 16857578]
31. Gustafson DR, Rothenberg E, Blennow K, Steen B, Skoog I. An 18-year follow up of overweight and risk for Alzheimer's disease. Arch Intern Med. 2003; 163:1524–1528. [PubMed: 12860573]
32. Gustafson D. A life course of adiposity and dementia. Eur J Pharmacol. 2008; 585:163–175. [PubMed: 18423446]
33. Anstey KJ, Cherbuin N, Budge M, Young J. Body mass index in midlife and late-life as a risk factor for dementia: a meta-analysis of prospective studies. Obes Rev. 2011; 12:e426–437. [PubMed: 21348917]
34. Whitmer RA, Gunderson EP, Quesenberry CP Jr, Zhou J, Yaffe K. Body mass index in midlife and risk of Alzheimer disease and vascular dementia. Curr Alzheimer Res. 2007; 4:103–109. [PubMed: 17430231]
35. Whitmer RA, Gustafson DR, Barrett-Connor E, Haan MN, Gunderson EP, Yaffe K. Central obesity and increased risk of dementia more than three decades later. Neurology. 2008; 71:1057–1064. [PubMed: 18367704]
36. Fitzpatrick AL, Kuller LH, Lopez OL, et al. Midlife and late-life obesity and the risk of dementia: cardiovascular health study. Arch Neurol. 2009; 66:336–342. [PubMed: 19273752]
37. Kivipelto M, Ngandu T, Fratiglioni L, et al. Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. Arch Neurol. 2005; 62:1556–1560. [PubMed: 16216938]
38. Gustafson DR, Bäckman K, Waern M, et al. Adiposity indicators and dementia over 32 years in Sweden. Neurology. 2009; 73:1559–1566. [PubMed: 19901247]
39. Gustafson D, Bäckman K, Joas E, et al. A 37-year longitudinal follow-up of body mass index and dementia in women. J Alzheimers Dis. 2012; 28:162–171.
40. Daviglus ML, et al. Risk factors and preventive interventions for Alzheimer disease: state of the science Arch Neurol. 2011; 68:1185–1190.

41. Plassman BL, et al. Systematic review: factors associated with risk for and possible prevention of cognitive decline in later life. Ann Int Med. 2010; 153:182–193. [PubMed: 20547887]
42. Morris MC, Tangney CC. A potential design flaw of randomized trials of vitamin supplements. JAMA. 2011; 305:1348–1349. [PubMed: 21467288]
43. Gu Y, Scarmeas N. Dietary patterns in Alzheimer's disease and cognitive aging. Curr Alzheimer Res. 2011; 8:510–519. [PubMed: 21605048]
44. Galasko DR, et al. Antioxidants for Alzheimer disease: a randomized clinical trial with cerebrospinal fluid biomarker measures. Arch Neurol. 2012; 69:836–441. [PubMed: 22431837]
45. Stanek K, Gunstad J. Can bariatric surgery reduce risk of Alzheimer's disease? Prog Neuropsychopharmacol Biol Psychiatry. 2012 online July 2012.
46. Buchwald H, Avidor Y, Braunwald E, et al. Bariatric surgery: a systematic review and meta-analysis. JAMA. 2004; 292:1724–1737. [PubMed: 15479938]
47. Gunstad J, Strain G, Devlin MJ, Wing R, et al. Improved memory function 12 weeks after bariatric surgery. Surg Obes Relat Dis. 2011; 7:465–472. [PubMed: 21145295]
48. Becker D, Balcer L, Galetta S. The neurological complications of nutritional deficiency following bariatric surgery. J Obes. 2012; 608534
49. Hurd MD, Martorell P, Delavande A, et al. Monetary costs of dementia in the United States. N Eng J Med. 2013; 368:1326–1334.