FEATURE

Challenges in Advancing Knowledge in Energetics and Obesity Research

Written by Toni Rizzo

David B. Allison, PhD, University of Alabama at Birmingham, Birmingham, Alabama, USA, was selected as the Atwater Lecturer by the US Department of Agriculture and the American Society of Nutrition for his contributions toward improving worldwide nutrition. In his lecture, Dr. Allison discussed the challenges in advancing knowledge and making progress at the population level in energetics and obesity research.

HISTORY OF NUTRITION AND OBESITY RESEARCH

Obesity is a prevalent, serious, and complex problem that has been increasing for several hundred years, especially in the last third of the 20th century. According to Dr. Allison, Antoine Laurent Lavoisier (1743–1794) is considered the father of energetics for his pioneering work in the identification of the roles of oxygen, carbon dioxide, and energy in respiration and combustion. Wilbur Olin Atwater (1844–1907) used these ideas to make calorimeters and analyze the digestible and metabolizable contents of food. More recently, researchers such as Dale A. Schoeller and others have advanced and quantified energetics studies.

Albert Behnke used the principles of Archimedes to develop hydrodensitometry for measuring body composition. Subsequent advances led to the ability to make rigorous body composition measurements. Currently, Dr. Allison and his colleague Olivia Affuso are using electronic photographic methods that produce 3-dimensional reconstructions of the body to determine volume and estimate body composition.

The field of quantitative genetics led to an understanding of the genetic basis of obesity. More than 100 gene variants unequivocally associated with obesity in humans have been identified.

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FACTORS IMPEDING PROGRESS

Although progress has been made in the basic understanding of obesity and energetics, there has been little progress in reducing obesity at the population level. Additionally, much controversy exists about the progress, value, scientific quality, and integrity of obesity research. Dr. Allison identified factors and practices that impede progress in both understanding and reducing obesity levels.

The first factor is an overreliance on observational studies. A review of 12 clinical trials testing 52 observational claims about nutrition and obesity revealed that they did not confirm any of the observational claims [Young SS, Karr A. *Significance* 2011]. In fact, 5 claims were statistically significant in the clinical trials for the opposite result reported in the observational studies.

One might conjecture that eliminating confounding factors—such as measurement error, genetic variation, smoking, and socioeconomic status—might allow observational studies to recapitulate a randomized effect estimate. Dr. Allison eliminated such factors in a large ongoing observational study of life span as a function of caloric intake in genetically identical mice. The mice that were randomly assigned to stay obese had shortened life spans, while those randomly assigned to some weight loss lived a little longer and those randomly assigned to lose a large amount of weight lived the longest ($p = .003$ vs obese mice). However, among mice in an ad libitum group (essentially an observational epidemiologic study), self-selected average lifetime daily intake was positively correlated with life span ($r = 0.45$; $p = .0056$). Thus, mice that chose to consume more food energy lived longer, while mice assigned to consume more food energy had shorter life spans, suggesting some confounding factor between a mouse's selection and longevity. "[In this case] I cannot recapitulate with an observational epidemiologic study the results I can get in a randomized experiment," said Dr. Allison.

Short-term studies are insufficient to make long-term predictions, and they are used excessively for that purpose. They are appropriate when followed by a longer-term study, but conclusions should

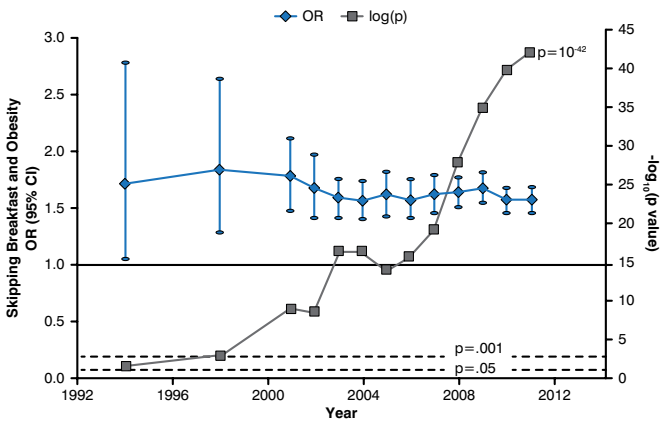
not be extrapolated from short-term studies alone. Short-term results can be misleading because people become obese over time, not from a brief exposure to food.

Another issue is that biological organisms are adaptive systems. For example, in a meta-analysis recently submitted for publication [Dhurandhar E, Kaiser K, et al.], researchers analyzed studies where human subjects were randomly assigned to manipulations of their energy intake or expenditure in situations with very high compliance, and they found that weight change was significantly less than expected if no behavioral compensation had occurred. Subjects in overfeeding conditions typically gained about only one-third of the weight expected. Investigators need to take into account that people have compensatory responses, resulting in less-than-projected effects in most cases.

Studies are sometimes conducted beyond the point of providing new knowledge. Such repetitive studies tend to increase belief rather than knowledge. An analysis of studies from the 1990s of breakfast consumption found that people who skipped breakfast had ~1.7 odds of becoming obese. As subsequent studies were published, the investigators added them to the analysis and recalculated the meta-analytic point estimate, resulting in a stabilized odds ratio of ~1.5 and increasingly narrow confidence intervals as more data were added. Rather than conducting randomized trials after numerous observational studies, on the order of 100 observational studies have now been done until the p value equaled 10^{42} (Figure 1) [Brown AW et al. *Am J Clin Nutr* 2013].

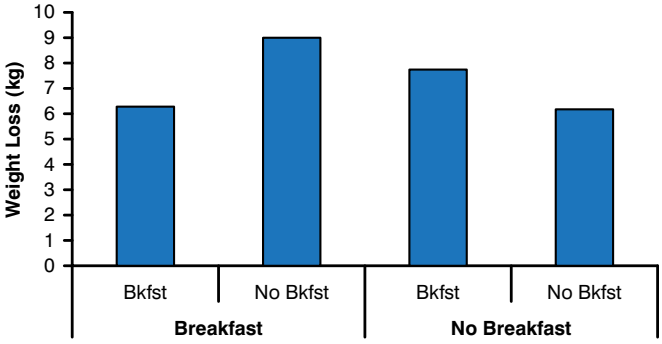
Dr. Allison identified only 1 randomized trial of breakfast consumption and obesity from 1992. Moderately obese women were stratified according to baseline breakfast eating habits and randomly assigned a weight-loss program. The results showed a treatment × strata × time interaction effect ($p < .06$), suggesting the possibility that women who had to make the most substantial changes in eating habits to comply with the program achieved better results (Figure 2).

Figure 1. Meta-analysis of Studies of Breakfast Consumption



Reproduced from Brown AW et al. Belief beyond the evidence: using the proposed effect of breakfast on obesity to show 2 practices that distort scientific evidence. *Am J Clin Nutr* 2013;98:1298–308. With permission from the American Society for Nutrition.

Figure 2. Treatment - Strata - Time Effect in Study of Breakfast Consumption and Weight Loss



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Dr. Allison also called for greater open-mindedness in pursuing less popular research, such as the effects of home temperature, sleep patterns, and antidepressant use on obesity, as was done by Keith et al. [*Int J Obes* 2006] and McAllister et al. [*Crit Rev Food Sci Nutr* 2009]. Other factors that negatively affect results of obesity studies include failure to take measurement as seriously as in other domains, difficulty and neglect in controlling for nonspecific effects, distorting statistical manipulations, and publication bias. Misleading press releases, conclusion spinning, and conflating one's moral position or beliefs with the empirical evidence also lead to confusion and distrust of results.

FUTURE DIRECTIONS

Dr. Allison concluded with several principles needed to improve progress in obesity research at the population level. Humans should be recognized as adaptive systems. Obesity research must be performed with the same rigor as in any other scientific field. Short-term studies, studies using intermediary endpoints, and observational studies have their place but should not be stopping points or bases for overreaching conclusions. "Meta-methods" that collectively buttress and ensure implementation of existing scientific methods need to be developed and implemented. Finally, "unfailingly pursuing truth through science is not a job but a discipline, a vocation, and a privilege," Dr. Allison said.