AUTHOR COMMENTARIES - From Special Topics

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JoAnn Manson
From the Special Topic of Diabetes

According to our 2009 analysis of diabetes research, the work of Dr. JoAnn E. Manson ranks at #8 by total cites, based on 102 papers cited a total of 6,033 times between January 1, 1999 and February 28, 2009. In Essential Science Indicators℠ from Thomson Reuters, Dr. Manson's work can be found in the field of Clinical Medicine, where she is in the top 1% of authors. She has also been named a Highly Cited Researcher in this field.

Dr. Manson is the Chief of the Division of Preventive Medicine at Brigham and Women's Hospital, as well as Professor of Medicine and the Elizabeth Fay Brigham Professor of Women's Health at Harvard Medical School.

In this interview, ScienceWatch.com *talks with Dr. Manson about her highly cited work in diabetes.*

SW: Would you tell us a bit about your educational background and research experiences?

I'm a physician epidemiologist with training in Internal Medicine and Endocrinology. I've had a long-term clinical interest in the care of patients with diabetes, but it wasn't until my Endocrinology fellowship in the early 1980s that I became interested in doing research on the prevention and risk prediction of diabetes. Even at that time, type 2 diabetes seemed like a largely preventable disease through lifestyle modifications—and the evidence for that has only grown stronger over time.

As a result of this interest, I sought additional training in epidemiology and biostatistics in order to be able to do this research. I received an MPH in 1984 and a doctorate in epidemiology (DrPH) from the Harvard School of Public Health in 1987. Since that time, I've been actively involved in diabetes research, including the assessment of lifestyle factors and biomarker predictors, in several large-scale prospective cohorts including the Harvard Nurses' Health Study, the Women's Health Study, and the Women's Health Initiative. I've also been involved in several randomized clinical trials that have addressed diabetes prevention.

"...the burgeoning epidemic of obesity, especially among children and adolescents, raises enormous concern for a future pandemic of type 2

SW: How did you get involved in diabetes research, and what is your primary focus within the field?

As mentioned above, my interest was really sparked during my fellowship training in Endocrinology. I was seeing many patients with advanced complications of diabetes, both microvascular and macrovascular. It seemed important to be able to intervene earlier in the disease process, even before the development of glucose intolerance

and overt diabetes. Obesity was clearly a dominant risk factor but I was interested in studying other lifestyle factors as well, such as physical activity and dietary interventions, and I wanted to understand how to identify high-risk individuals who might benefit the most from lifestyle modifications and targeted interventions.

diabetes in the United States and around the world."

SW: Your most-cited paper in our analysis is the 2001 *JAMA* paper, "C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus" (Pradhan AD, *et al*., 286[3]: 327-34, 18 July 2001), which has been cited close to 1,000 times. Would you walk our readers through this paper and why you think it is so highly cited?

The inspiration for this paper was the emerging evidence that inflammation plays a crucial role in the pathogenesis of both cardiovascular disease and diabetes and may even serve as the link between these commonly co-existing conditions. Since the publication of our paper in *JAMA* in 2001, the evidence has just grown stronger that subclinical systemic inflammation is a risk factor for insulin resistance, glucose intolerance, and cardiovascular disease.

We assessed the predictive role of biomarkers of inflammation, including hsCRP and IL-6, in predicting risk of future diabetes and found that the prediagnostic plasma levels of these inflammatory markers were substantially higher in the women who were later diagnosed with diabetes than in the women who remained free of diabetes. For example, even after adjusting for other known risk factors for diabetes, the relative risk of type 2 diabetes was four-fold elevated for women in the highest vs. lowest quartile of hsCRP and about two-fold elevated for the highest vs. lowest quartile of IL-6.

We later published other articles confirming and extending these findings in other cohorts. These relationships help to explain the strong link between obesity and the risk of type 2 diabetes. Adipose tissue is now recognized as a dynamic endocrine organ that has systemic effects. In particular, abdominal and visceral fat secretes bioactive proteins (adipocytokines), including IL-6, adiponectin, resistin, and retinol binding protein, that influence insulin resistance as well as inflammation (including modulating the synthesis of CRP downstream) and may affect the risk of both diabetes and cardiovascular disease.

SW: Many of your papers appear to deal with the influence of lifestyle (smoking, diet, activity levels, etc.) on the risk of developing diabetes. Would you talk a little bit about this aspect of your work?

I believe that lifestyle factors are powerful determinants of most chronic diseases, including type 2 diabetes and cardiovascular disease. We published a paper from the Nurses' Health Study in 2001 indicating that at least 90% of cases of type 2 diabetes could be prevented by lifestyle modifications, including exercising regularly, maintaining a healthy weight, avoiding tobacco, and following a diet low in refined carbohydrates and trans fats. We were fortunate to be one of the first research groups to document the benefits of physical activity in preventing type 2 diabetes, even after accounting for effects on adiposity.

"...type 2 diabetes seemed like a largely preventable disease through lifestyle modifications—and the evidence for that has only grown stronger over time"

We've had a wonderful group of colleagues working on diabetes in our research group, trying to learn as much as possible about diabetes prevention in these large-scale cohorts. In particular, I'd like to thank and acknowledge the enormous contributions of Drs. Frank Hu, Walter Willett, James Meigs, and Aruna Pradhan. As Chief of the Division of Preventive Medicine at our hospital, I believe strongly in the power of prevention and am committed to disseminating knowledge and research in this area. What we need now is a better understanding of how to best implement and translate this knowledge, how to effect sustained behavior changes at the individual and population levels. Some of this translation/implementation can best be achieved through changes in the built environment, food industry practices, and public policy initiatives.

SW: One of your more recent papers is the February 2009 *Diabetes Care* paper, "Circulating levels of resistin and risk of type 2 diabetes in men and women: Results from two prospective cohorts" (Chen BH, *et al*., 32[2]: 329-34, February 2009). What exactly is resistin and what sort of role did this paper discover it plays in diabetes?

Resistin is another one of the adipocytokines, or the bioactive proteins produced in adipose tissue, which has links to both inflammation and insulin resistance. It's a polypeptide and its exact role in humans has been controversial. In mice, resistin is secreted primarily by adipocytes and has potent effects on insulin resistance and sensitivity. In humans, resistin is produced

by both adipocyte and mononuclear cells. Although resistin levels tend to be higher among obese individuals in most studies, the link with insulin resistance has been weaker than for some of the other adipocytokines.

SW: What are your hopes for progress in diabetes research over the next decade?

My hope is for a cure for diabetes and the identification of powerful prevention tools. Of course, the burgeoning epidemic of obesity, especially among children and adolescents, raises enormous concern for a future pandemic of type 2 diabetes in the United States and around the world. One area that is of great interest to me is the potential role of vitamin D supplementation in reducing the risks of diabetes and cardiovascular disease. We plan a large-scale randomized trial of vitamin D in 20,000 Americans and hope to begin recruitment for the trial soon. Vitamin D may even have a role in reducing health disparities, as vitamin D deficiency is a particularly major problem among African Americans.

SW: What would you like the "take-away lesson" about your research to be?

That type 2 diabetes is a largely preventable disease and that lifestyle factors really do matter. We are very excited about the potential role of vitamin D and hope that this research will lead to new interventions to curb the diabetes epidemic and to close the gap in health disparities by race and ethnicity. And we hope that, with additional research on biochemical and genomic biomarkers, it will be possible to improve risk prediction of diabetes and target intervention to those who are most likely to benefit.

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JoAnn Manson 's current most-cited papers

- **In *Essential Science Indicators*, with 1,266 cites:** Anderson GL, *et al.*, "Effects of conjugated, equine estrogen in postmenopausal women with hysterectomy—the Women's Health Initiative randomized controlled trial," *JAMA-J. Am. Med. Assn*. 291(14): 1701-12, 14 April 2004.
- **In this special topic with 939 cites:** Pradhan AD, *et al*., "C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus," *JAMA-J. Am. Med. Assn.* 286(3): 327-34, 18 July 2001. 939 cites.

Source: *Essential Science Indicators* from Thomson Reuters.

Additional Information:

- JoAnn Manson is featured in ISIHighlyCited.com
- New Hot Paper comment in the field of Clinical Medicine (Nov. 2008).
- Fast Breaking Paper comment in the field of Clinical Medicine (Nov. 2008).

KEYWORDS: DIABETES MELLITUS, TYPE 2 DIABETES, LIFESTYLE MODIFICATIONS, BIOMARKER PREDICTORS, MICROVASCULAR COMPLICATIONS, MACROVASCULAR COMPLICATIONS, OBESITY, GLUCOSE INTOLERANCE, C-REACTIVE PROTEIN, INTERLEUKIN 6, ADIPOSE TISSUE, ADIPOCYTOKINES, RESISTIN, VITAMIN D
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