# INTERACTIONS BETWEEN NUTRITION, OBESITY AND THE IMMUNE SYSTEM

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs Universitet kommer att försvaras offentligt i hörsal Arvid Carlsson, Academicum, Medicinaregatan 3, Göteborg, fredagen den 11 dec 2009, kl. 09:00.

av

**Louise Strandberg**

Fakultetsopponent: Professor Jan Wernerman, Institutionen för klinisk vetenskap, intervention och teknik, Karolinska Institutet, Stockholm, Sverige

Avhandlingen baseras på följande delarbeten:

**I** **Mice chronically fed high-fat diet have increased mortality and disturbed immune response in sepsis**
Strandberg L, Verdrengh M, Enge E, Andersson N, Amu S, Önnheim K, Benrick A, Brisslert M, Bylund J, Bokarewa M, Nilsson S, Jansson JO
*PLoS ONE 2009 Oct;4(10):e7605*

**II** **Septic mortality is lower in mice fed a diet rich in polyunsaturated compared with saturated fatty acids**
Strandberg L, Benrick A, Andersson N, Nilsson S, Jansson JO
*Manuscript*

**III** **Interleukin-1 system gene polymorphisms are associated with fat mass in young men**
Strandberg L, Lorentzon M, Hellqvist A, Nilsson S, Wallenius V, Ohlsson C, Jansson JO
*J Clin Endocrinol Metab 2006 Jul;91(7):2749-2754*

**IV** ***IL6*** **and** ***IL1B*** **polymorphisms are associated with fat mass in older men: the MrOS Study Sweden**
Strandberg L, Mellstrom D, Ljunggren O, Grundberg E, Karlsson MK, Holmberg AH, Orwoll ES, Eriksson AL, Svedberg J, Bengtsson M, Ohlsson C, Jansson JO
*Obesity (Silver Spring) 2008 Mar;16(3):710-713*

UNIVERSITY OF GOTHENBURG

# INTERACTIONS BETWEEN NUTRITION, OBESITY AND THE IMMUNE SYSTEM

Louise Strandberg

*Department of Physiology, Institute of Neuroscience and Physiology*
*The Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden, 2009*

## ABSTRACT

There are several links between body fat and the immune system. For example, mice lacking activity of the pro-inflammatory interleukin-(IL)-1 and IL-6 develop obesity. Conversely, obesity is associated with adipose tissue inflammation and increased risk of infection. The aims of this thesis were to investigate (1) the effect of Western diet on *Staphylococcus aureus* (*S. aureus*)–induced mortality in mice; (2) if dietary fat composition affects mortality in *S. aureus* inoculated mice; and if IL-6 and IL-1 system gene polymorphisms, associated with expression, are associated with fat mass in (3) young and (4) elderly men.

The *S. aureus*-induced mortality was investigate in mice fed a lard-based high-fat diet (HFD) rich in saturated and monounsaturated fatty acids (HFD/S) or a low fat diet (LFD). After 8 weeks on these diets, the mice were intravenously inoculated with *S. aureus*. The obese HFD/S-fed mice had increased *S. aureus*-induced mortality compared with the lean LFD-fed mice. The HFD/S-fed mice showed signs of immune suppression as evident by increased bacterial load and decreased capacity to phagocytose bacteria. We then added a group of mice fed a HFD rich in polyunsaturated fatty acids (HFD/P) from fish. The HFD/P-fed mice displayed a degree obesity and glucose intolerance that was milder than in the HFD/S-fed mice, but higher than in LFD mice. However, the *S. aureus*-induced mortality and the bacterial load of HFD/P-fed mice were comparable with that of LFD-fed mice, and markedly lower than that of mice fed HFD/S.

Gene polymorphisms were investigated in two well-characterized population-based cohorts of young and elderly Swedish men. In young but not elderly men, we found that carriers of the T variant of the +3953 C>T *IL1B* polymorphism had lower total fat mass, compared with CC carriers. In elderly but not young med, the *IL1B* -31T>C polymorphism was associated with total fat mass. In young but not elderly men, we found that *IL-1RN**2 carriers, with two repeats of the *IL1RN* 86 base pair variable number tandem repeat polymorphism, had increased total fat mass. Also, *IL1RN**2 was associated with increased IL-1Ra production *in vitro* and enhanced serum IL-1Ra *in vivo*. We also confirmed earlier findings that the C variant of the -174G>C *IL6* is associated with obesity in elderly men.

Thus, the present results indicate the *S. aureus*-induced mortality is associated with dietary fat consisting of saturated and monounsaturated fatty acids, but not polyunsaturated fatty acids. We also show that polymorphisms in the *IL1B*, *IL1RN*, and *IL6* genes are associated with obesity. In conclusion, this thesis emphasize that there are reciprocal interactions between the immune system on one hand and obesity and nutrition on the other.

**Keywords:** obesity, nutrition, infection, polymorphisms, interleukin, fatty acids, fat mass, neutrophils, innate immunity, mortality

ISBN 978-91-628-7954