

Human insulin/IGF-1 and familial longevity at middle age

Maarten P. Rozing¹, Rudi G.J. Westendorp^{1,2}, Marijke Frölich³, Anton J.M. de Craen¹, Marian Beekman⁴, Bastiaan T. Heijmans⁴, Simon P. Mooijaart¹, Gerard-Jan Blauw¹, P. Eline Slagboom⁴ and Diana van Heemst¹, on behalf of the Leiden Longevity Study (LLS) Group

¹ Department of Gerontology and Geriatrics, Leiden University Medical Center, 2300 RC, Leiden, the Netherlands

² Netherlands Consortium for Healthy Ageing (NCHA)

³ Department of Clinical Chemistry, Leiden University Medical Center, 2300 RC, Leiden, the Netherlands

⁴ Department of Molecular Epidemiology, Leiden University Medical Center, 2300 RC Leiden, The Netherlands

Running title: Insulin/IGF-1 and familial longevity

Key words: familial longevity, height, glucose handling, IGF-1, IGFBP3

Correspondence: Diana van Heemst, PhD, Department of Gerontology and Geriatrics, Leiden University Medical Center, PO Box 9600, 2300 RC, Leiden, the Netherlands

Received: 05/20/09; **accepted:** 07/22/09; **published on line:** 07/24/09

E-mail: D.van_Heemst@lumc.nl

Abstract: Recently, we have shown that compared to controls, long-lived familial nonagenarians (mean age: 93.4 years) from the Leiden Longevity Study displayed a lower mortality rate, and their middle-aged offspring displayed a lower prevalence of cardio-metabolic diseases, including diabetes mellitus. The evolutionarily conserved insulin/IGF-1 signaling (IIS) pathway has been implicated in longevity in model organisms, but its relevance for human longevity has generated much controversy. Here, we show that compared to their partners, the offspring of familial nonagenarians displayed similar non-fasted serum levels of IGF-1, IGFBP3 and insulin but lower non-fasted serum levels of glucose, indicating that familial longevity is associated with differences in insulin sensitivity.

INTRODUCTION

In Western societies, life expectancy has increased dramatically over the last century, but striking inter-individual differences in life expectancy remain [1]. Ample evidence has shown that healthy longevity is determined by a mix of genetic, environmental and chance elements. Because the odds of exceptional longevity runs in families, we designed the Leiden Longevity Study [2]. Recently, we have shown that the nonagenarian siblings included in the Leiden Longevity Study displayed a 41% lower risk of mortality compared to sporadic nonagenarians [3]. Moreover, compared to their partners, the offspring of nonagenarian siblings displayed a significantly lower prevalence of myocardial infarction, hypertension and

diabetes mellitus [3]. The differences in clinical phenotype observed after selection for familial longevity are in line with the lower prevalence of cardio-metabolic disease previously detected when offspring from sporadic centenarians were compared to offspring of parents who had died at average age [4] and when offspring from sporadic centenarians were compared to their partners [5]. Moreover, the observed lower mortality rate at high ages and better preservation of health at middle age indicates that resilience against disease and death may have similar underlying biological mechanisms that are influenced by genetic or familial factors.

Of the genetically determined pathways that have been implicated in longevity in a variety of different model organisms, the evolutionarily conserved insulin/IGF-1

