Insulin/Insulin-Like Growth Factor-1 Signaling and Cognitive Function in Humans

Sjoerd M. Euser, 1,2 Diana van Heemst, 1 Peter van Vliet, 1 Monique M. B. Breteler, 2 and Rudi G. J. Westendorp 1

1Department of Gerontology and Geriatrics, Leiden University Medical Center, Leiden, the Netherlands. 2Department of Epidemiology, Erasmus MC, Rotterdam, the Netherlands.

An accumulating body of evidence suggests the involvement of an evolutionary conserved insulin/insulin-like growth factor-1 (IGF-1) signaling (IIS) pathway in the regulation of the life and health span in nematodes, flies, rodents, and humans. We studied the association between insulin/IGF-1 signaling and cognitive function among 1015 participants, 85 years old or older, of the population-based Leiden 85-Plus Study. A composite IIS6 score, based on expected effects (increased or decreased signaling) of selected variants in the IIS pathway, was calculated to estimate IIS pathway activity. Cognitive function was assessed at baseline and annually during a 5-year follow-up, using the Mini-Mental State Examination (MMSE). In women, but not in men, lower IIS6 scores (indicating decreased signaling) were associated with a lower risk of cognitive impairment (MMSE score ≤ 18) (p trend = .010). The IIS6 score was not associated with change in cognitive function. In addition to old age survival, genetically reduced IIS seems to be beneficial for cognitive function in women.

Key Words: Insulin/IGF-1 signaling—Cognitive function—Cohort study—Human.

THE involvement of the evolutionary conserved insulin (INS)/insulin-like growth factor-1 (IGF-1) signaling (IIS) pathway in the hormonal regulation of aging has been shown in a number of model organisms like nematodes, flies, rodents, and humans. Genetic variation that causes a reduced IIS activation was associated with an increased life span in these organisms, with a stronger effect seen in the female sex (6,9–11). In accordance with these data on model organisms, we previously showed an association between a genetically reduced IIS pathway and better survival in elderly women (12).

Moreover, in model organisms, the IIS pathway has not only been implicated in the determination of life span but also in that of health span. At old age, there is a high prevalence of cognitive impairment, which for many is one of the most frightening prospects of old age. An accumulating body of evidence suggests the involvement of INS and IGF-1 in the development of cognitive impairment (13–15). Suggested biological mechanisms that underlie this relationship are inhibition of the amyloid β breakdown (through the INS-degrading enzyme) and the involvement of INS and IGF-1 in τ phosphorylation (14,16,17). In humans, it is yet to be elucidated how the evolutionary conserved IIS pathway, which has been shown to be associated with better survival in old age, is related to cognitive function and decline.

Therefore, we studied the relationship between genetic variation in IIS pathway activation and cognitive function and decline in a prospective, population-based study among 1015 participants of the Leiden 85-Plus Study.

METHODS

Population

The Leiden 85-Plus Study is a prospective, population-based cohort study that consists of two cohorts of inhabitants of Leiden, the Netherlands (18,19). For cohort ’87, 977 inhabitants of Leiden, 85 years old or older, were enrolled between 1987 and 1989, and cognitive function was assessed at baseline. For cohort ’97, 599 inhabitants of Leiden, 85 years old, were enrolled between 1997 and 1999. Cognitive function was assessed at baseline and annually during home visits, from age 85 until age 90 years. Of the 1576 participants in the two cohorts of the Leiden 85-Plus Study, DNA was available for 1245 participants, and IIS scores could be calculated for 1037 participants (12). Twenty-two participants did not have cognitive data available at baseline, resulting in a study sample of 1015 participants.

IIS Score

To determine the genetic variation that influences IIS, we selected six polymorphisms in five genes from the IIS pathway (growth hormone–releasing hormone receptor [GHRHR], growth hormone 1 [GH1], IGF-1, INS, and INS receptor substrate-1 [IRS1]) based on previous reports of their effects on gene expression or protein function. As the effect sizes of the six selected IIS polymorphisms were unknown, these were assumed to be equal, and a simple additive model (hereafter referred to as IIS6 score) was used to test for combined effects of the selected polymorphisms. Per individual, we calculated a composite IIS6 score by...
Cognitive Function

Cognitive function was assessed with the Mini-Mental State Examination (MMSE) (20), and was available for 1015 participants of both cohorts at baseline. The MMSE is a measure of global cognitive function and ranges from 0 to 30 points, with lower scores indicating worse cognitive function. Although the MMSE is a widely used test that was developed as a screening instrument for dementia and is a reliable measure of global cognitive function, it might lack reliability and validity in persons with severe cognitive impairment (21). Therefore, we dichotomized the cognitive test scores and defined cognitive impairment as an MMSE composite IIS6 score and the risk of cognitive impairment, adjusted for age. A higher IIS6 score was associated with a higher risk of cognitive impairment, but only for women (odds ratio [95% confidence interval] per 1-unit increase in IIS6 score was 1.28 [1.06–1.53], \( p = .010 \)). In men, a higher IIS6 score was, if anything, associated with a lower risk of cognitive impairment (odds ratio [95% confidence interval] per 1-unit increase in IIS6 score was 0.85 [0.60–1.19], \( p = .329 \)).

Statistical Analyses

The relationship between the IIS6 score and the risk of cognitive impairment was assessed with logistic regression models.

The relationship between the IIS6 score and the annual change in cognitive function during follow-up was assessed with analyses of covariance, with the annual change in cognitive function as the dependent variable, and the IIS6 score as the grouping variable. To assess the association between the IIS6 score and the risk of cognitive impairment, we used linear regression models with the annual change in MMSE score as the dependent variable and the IIS6 score as the independent variable.

All analyses were adjusted for age and carried out using the SPSS statistical package (release 12.0.1; SPSS, Inc., Chicago, IL).

RESULTS

Table 1 shows the baseline characteristics of the study participants. The mean age of the 1015 participants from the combined cohorts of the Leiden 85-Plus Study was 87.4 years, and 68% were women. Mean MMSE score at baseline was 23.9 points and ranged from 0 to 30 points.

Table 2 shows the sex-specific relationship between the IIS6 score and the risk of cognitive impairment. A higher IIS6 score was associated with a higher risk of cognitive impairment, but only for women (odds ratio [95% confidence interval] per 1-unit increase in IIS6 score was 1.28 [1.06–1.53], \( p = .010 \)). In men, a higher IIS6 score was, if anything, associated with a lower risk of cognitive impairment (odds ratio [95% confidence interval] per 1-unit increase in IIS6 score was 0.85 [0.60–1.19], \( p = .329 \)).

Note: Data are presented as mean (standard deviation [SD]), percentage, or median (interquartile range [IQR]).

MMSE = Mini-Mental State Examination; IIS6 score = insulin/insulin-like growth factor-1 signaling score.

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Combined Cohorts</th>
<th>Cohort ’87</th>
<th>Cohort ’97</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>1015</td>
<td>504</td>
<td>511</td>
</tr>
<tr>
<td>Age, y (SD)</td>
<td>87.4 (3.1)</td>
<td>89.8 (2.9)</td>
<td>85 (0)</td>
</tr>
<tr>
<td>No. of women</td>
<td>68</td>
<td>69</td>
<td>66</td>
</tr>
<tr>
<td>MMSE score, points (SD)</td>
<td>23.9 (6.4)</td>
<td>23.9 (6.4)</td>
<td>23.8 (6.5)</td>
</tr>
<tr>
<td>IIS6 score, points (IQR)</td>
<td>-2 (-3 to -1)</td>
<td>-2 (-3 to -1)</td>
<td>-2 (-2 to -1)</td>
</tr>
</tbody>
</table>

Notes: Data are presented as mean (standard deviation [SD]), percentage, or median (interquartile range [IQR]).

MMSE = Mini-Mental State Examination; IIS6 score = insulin/insulin-like growth factor-1 signaling score.

Table 2. Association Between Insulin/IGF-1 Signaling Score and the Risk of Cognitive Impairment in the Leiden 85-Plus Study

<table>
<thead>
<tr>
<th>IIS6 Score</th>
<th>Women</th>
<th></th>
<th></th>
<th>Men</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>MMSE Score</td>
<td>OR (95% CI)</td>
<td>( p_{\text{trend}} )</td>
<td>N</td>
</tr>
<tr>
<td>-4 and -5</td>
<td>33</td>
<td>24.6 (1.2)</td>
<td>1 (Ref)</td>
<td>.010</td>
<td>13</td>
</tr>
<tr>
<td>-3</td>
<td>139</td>
<td>24.0 (0.6)</td>
<td>0.80 (0.29–2.17)</td>
<td></td>
<td>73</td>
</tr>
<tr>
<td>-2</td>
<td>259</td>
<td>23.8 (0.4)</td>
<td>1.09 (0.42–2.78)</td>
<td></td>
<td>120</td>
</tr>
<tr>
<td>-1</td>
<td>193</td>
<td>22.5 (0.5)</td>
<td>1.65 (0.64–4.24)</td>
<td></td>
<td>89</td>
</tr>
<tr>
<td>0 and +1</td>
<td>65</td>
<td>22.3 (0.8)</td>
<td>1.61 (0.56–4.57)</td>
<td></td>
<td>31</td>
</tr>
<tr>
<td>Per IIS6 score</td>
<td>689</td>
<td>1.28 (1.06–1.53)</td>
<td></td>
<td></td>
<td>326</td>
</tr>
</tbody>
</table>

Notes: Insulin/insulin-like growth factor-1 (IGF-1) signaling IIS6 scores were calculated for each participant by assigning a score of +1 for carriership of a gene variant causing increased signaling and a score of −1 for carriership of a gene variant causing decreased signaling. Because of the limited number of participants with an IIS6 score of −5 (n = 3) or an IIS6 score of +1 (n = 6), we combined these, respectively, with the IIS6 score −4 and IIS6 score 0 categories. Mini-Mental State Examination (MMSE) scores (standard error [SE]) are presented per IIS6 score category. Odds ratios (OR) represent the risk of cognitive impairment per IIS6 score category. In women, 146 cases of cognitive impairment were present, in men, 38 cases were present. Values of \( p_{\text{trend}} \) represent the linear trend for the risk of cognitive impairment per increase in IIS6 score. All analyses were adjusted for age.

CI = confidence interval.
The longitudinal analyses, which were performed of 455 participants of cohort '97 only, showed no clear relationship between the IIS6 score and the annual change in cognitive function during follow-up. In both women (annual change in MMSE score [standard error {SE}]) per 1-unit increase in IIS6 score was −0.06 [0.12] points, $p = .612$ and men (annual change in MMSE-score [SE] per 1-unit increase in IIS6 score was −0.16 [0.15] points, $p = .311$) a higher IIS6 score was not associated with an accelerated or decelerated rate of decline in cognitive function during follow-up.

**DISCUSSION**

Our study showed that, in humans, a genetically reduced IIS pathway was associated with a lower risk of cognitive impairment in women, but not in men. There was no association between the IIS pathway and a change in cognitive function over time.

Together with our previous finding that showed an association between a genetically reduced IIS pathway with improved old age survival in women (12), our current findings are in accordance with the available data from model organisms that showed favorable effects of genetically induced lower IIS activity on both life span and health span. In model organisms, such as *Caenorhabditis elegans*, down-regulation of the IIS pathway occurs in response to adverse environmental conditions, such as food shortage. Its main function is to coordinate various aspects of the organism’s physiology, so that priorities are changed from growth and reproduction to mere survival until conditions become more favorable. In *C. elegans*, environmentally, as well as genetically induced down-regulation of the IIS pathway can dramatically increase life span, with concurrent maintenance of functional abilities (22). Furthermore, it was shown that the mutations in the IIS pathway are associated with associative learning behavior in *C. elegans* (23).

At first glance, the beneficial effects of genetically induced down-regulation of the IIS pathway seem to conflict with the available data on the association of IGF-1 serum levels with the human health span. In humans, the activity of the hypothalamic–GH–IGF-1 axis declines with age, and several aspects of functional decline, including cognitive decline, have been attributed to the somatopause. In several studies, higher levels of total circulating IGF-1 were associated with better cognitive function and less cognitive decline in elderly persons (24,25), although in at least one study, free IGF-1 levels were not associated with cognitive decline (25). The a priori prediction based on the genetic data from long-lived worms would have predicted an association between low serum IGF-1 levels (instead of high levels) and improved survival and better maintenance of functional abilities (22). Recently, a similar paradox was observed in mice: Decreased IGF-1 levels are not only a key feature of the serum profile of long-lived mice, such as calorically restricted wild-type mice, but also of mice that are short-lived due to mutations in DNA repair (26,27). The picture that now emerges is that down-regulation of IIS is an ancient survival response that can occur both in response to sudden external stresses (such as food shortage) as well as in response to chronic internal stresses (such as the accumulation of damage with aging) (28). Likewise, in humans, the decline in GH/IGF-1 levels with age may be an adaptive response aimed to prolong survival. According to this hypothesis, higher serum IGF-1 levels in old age might be indicative of a lower degree of (age-associated) accumulated damage.

The observed sex-specific involvement of IIS pathway activity in the development of cognitive impairment that is presented here is supported by previous findings. In the first discovered long-lived *C. elegans* mutant that mapped to the IIS pathway, both male and hermaphrodite worms were shown to be affected by age (1). Moreover, in female but not in male rats, heightened cognition, in addition to increased motor activity and reproductive shutdown, was observed as an important aspect of the survival response to caloric restriction (29). Improved learning and memory may play important roles in the success of seeking food elsewhere, which is especially important for the female sex, as females must obtain sufficient energy to support the survival and development of their offspring as well as themselves. The possible, not mutually exclusive, mechanisms by which reduced IIS pathway activity may contribute to heightened cognition in elderly women, include increased stress resistance and reduced amyloid β-induced autophagosome accumulation. Recent data obtained in a *C. elegans* model suggest that reduced IIS activity promotes the maturation of autophagosomes into degradative autolysosomes, whereas amyloid β impairs this process (30). Another study showed the involvement of IIS pathway mediation in the aggregation-mediated amyloid-β toxicity in *C. elegans* (31).

The observed association between a lower IIS6 score and better cognitive function was not seen in the longitudinal analyses. A lower IIS6 score was not associated with an accelerated or decelerated rate of decline in cognitive function during follow-up. A possible explanation could be that there were only longitudinal data on cognitive function available for the participants of cohort ’97, which reduced our sample size and concurrently the statistical power of our analyses. Furthermore, it has been suggested that in situations with substantial dropout during follow-up, cross-sectional analyses may provide the better estimates (32,33). Therefore, cross-sectional estimates might have been the preferred choice here to study the relationship between IIS and cognition as we were testing the consequence of genetic variants that have accumulated over a lifetime. Alternatively, genetically determined lifelong lower IIS activity may mainly have an effect on the onset of cognitive decline (postponing it to a later age) and not on the rate of the decline.

**Conclusion**

We showed that genetically reduced IIS seems to be beneficial for cognitive function in women but not in men. These results are in line with our previous findings that showed associations between reduced IIS signaling and increased longevity in women, and further indicates the involvement of the IIS pathway in the regulation of health span.
ACKNOWLEDGMENT

This study was supported by The Netherlands Organization for Scientific Research (NWO), Research Institute for Diseases in the Elderly (RIDE) grants 948-00-009 and 948-00-921, and by the International Foundation Alzheimer’s Research.

CORRESPONDENCE

Address correspondence to Sjoerd M. Euser, MSc, Department of Gerontology and Geriatrics, Leiden University Medical Center, PO Box 9600, 2300 RC, Leiden, the Netherlands (E-mail: s.euser@lumc.nl) or Department of Epidemiology, Erasmus University Medical Center, PO Box 2040, 3000 CA Rotterdam, the Netherlands (E-mail: s.euser@erasumsmc.nl)

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Received March 6, 2008
Accepted June 22, 2008
Decision Editor: Huber R. Warner, PhD