Chapter 7

Serum insulin-like growth factor 1 and late-life depression: a population-based study

N. C. van Varsseveld | C. C. van Bunderen | E. Sohl | H. C. Comijs
B. W. J. H. Penninx | P. Lips | M. L. Drent

Psychoneuroendocrinology 2015; 54: 31-40

This is the peer reviewed accepted version of the following manuscript: Van Varsseveld NC, van Bunderen CC, Sohl E, Comijs HC, Penninx BWJH, Lips P, Drent ML. Serum insulin-like growth factor 1 and late-life depression: a population-based study. Psychoneuroendocrinology 2015; 54: 31-40. The formal publication may be accessed via http://dx.doi.org/10.1016/j.psyneuen.2015.01.014.

© 2015. This manuscript version is made available under the CC-BY-NC-ND 4.0 license http://creativecommons.org/licenses/by-nc-nd/4.0/.
Abstract

Objective
Serum insulin-like growth factor 1 (IGF-1) concentration decreases, while the prevalence of depressive symptoms increases with advancing age. Although basic research indicates a link between low IGF-1 concentration and depression, this has scarcely been investigated in humans. This study investigates whether lower IGF-1 concentrations are associated with prevalent and incident late-life depression over a three-year period.

Methods
The study included 1188 participants, aged ≥ 65 years, from the Longitudinal Aging Study Amsterdam (LASA), an ongoing, population-based cohort study. Depression was assessed at baseline and after three years, using the Center for Epidemiological Studies-Depression Scale (CES-D) and the Diagnostic Interview Schedule (DIS), and categorized into minor depression and major depression (MDD). Serum IGF-1 concentration was determined at baseline. Associations were adjusted for relevant confounders.

Results
Serum IGF-1 concentrations were within the normal range (mean 13.9 nmol/liter, standard deviation 5.3). At baseline, in men, as compared to high concentrations, mid concentrations decreased the probability of prevalent minor depression (odds ratio [OR] = 0.35, 95% confidence interval [CI], 0.15 - 0.82). In women, as compared to high concentrations, low concentrations tended to increase the probability of prevalent MDD (OR = 2.66, 95% CI, 0.89 - 7.89).

At three-year follow-up, in men, no significant prospective associations were detected. In women, as compared to high concentrations, mid concentrations decreased the probability of incident minor depression (OR = 0.43, 95% CI, 0.19 - 0.95).

Conclusions
Several associations, which differed across the genders, were observed between IGF-1 and depression. Cross-sectional findings were not supported by longitudinal findings, which suggests that IGF-1 may not play an important predictive role in the development of depression in older persons over time. However, a more acute role of IGF-1 in current depression, as indicated by the cross-sectional results, may be possible. Further studies are needed to elucidate the complex relation between IGF-1 and late-life depression.
Introduction

Depression is a common and burdensome disorder in older individuals\textsuperscript{1,2}. While the prevalence of major depression (MDD) is relatively low (1.8%), the prevalence of all clinically relevant depressive syndromes, some of which do not fully fulfill criteria for MDD, is high (13.5%) in community-dwelling elderly\textsuperscript{1}. Both may have detrimental consequences for the wellbeing and functioning of older persons, and are associated with increased mortality\textsuperscript{3-5}.

To date, the exact etiology and pathophysiology of depression are still unclear, but are presumed to be multifactorial\textsuperscript{5}. It is hypothesized that biological factors, such as insulin-like growth factor 1 (IGF-1) may play a role\textsuperscript{6}.

In healthy adults, the secretion of growth hormone (GH) and IGF-1 decreases with advancing age, a process also known as the ‘somatopause’\textsuperscript{7,8}. Decreased functioning of the GH-IGF-1 axis is also found in adult patients with growth hormone deficiency (GHD). Adult GHD is, amongst others, associated with decreased cognitive functioning, impaired quality of life and psychiatric symptoms\textsuperscript{9-11}. GH supplementation has been shown to improve these symptoms\textsuperscript{11,12}. Since features of normal aging resemble those of GHD, it has been suggested that the ‘somatopause’ contributes to age-associated changes and disorders\textsuperscript{7,8,11,13}. For instance, lower IGF-1 concentrations are related to impaired cognitive functioning, which frequently coincides with late-life depression, in healthy elderly\textsuperscript{14}. In addition, IGF-1 receptors have been localized within many brain structures that are associated with mood, such as the hippocampus and the amygdala\textsuperscript{15}. Also, there is evidence that IGF-1 has direct effects on the central nervous system through blood-brain barrier passage and local autocrine and paracrine mechanisms\textsuperscript{16}. Moreover, basic research has shown that the expression of neurotrophic and growth factors, such as IGF-1, is decreased by chronic stress and depression in brain regions associated with depression, and increased by antidepressant treatment\textsuperscript{6,13}. Recently, an animal study demonstrated that adult onset long-term IGF-1 deficiency is able to induce depressive behavior in normally developed mice\textsuperscript{13}. Nevertheless, only few studies with limited sample sizes and no or short follow-up time have addressed the relation between IGF-1 and depression in humans\textsuperscript{17-23}. So far, only one epidemiological study has been reported, in which lower IGF-1 concentrations were associated with any depressive disorder in women, while higher IGF-1 concentrations were associated with any depressive disorder in men\textsuperscript{24}. However, in this study only a screening self-report questionnaire was used for the assessment of any depressive disorder, which complicates interpretation of the results. Moreover, the relation between IGF-1 and depression has not yet been specifically studied in older individuals.
Therefore, we aimed to investigate the association between IGF-1 and depression cross-sectionally as well as prospectively in a large, representative cohort of community-dwelling elderly, using both a depression symptoms rating scale and a diagnostic psychiatric evaluation. We hypothesized that persons with lower IGF-1 concentrations would be more likely to have current minor depression or MDD and would be more likely to develop minor depression or MDD in the future than persons with higher IGF-1 concentrations.

**Material and methods**

**Study design and sample**

The data for this study were collected within the framework of the Longitudinal Aging Study Amsterdam (LASA). LASA is an ongoing, prospective, multidisciplinary Dutch cohort study on predictors and consequences of changes in physical, cognitive, emotional and social functioning in community-dwelling elderly. The data collection and sampling procedures have previously been described in detail elsewhere. Briefly, a nationally representative random sample of older men and women aged 55-85 years, stratified by age, sex, urbanization and expected five-year mortality rate, was drawn from the population registers of 11 municipalities in three geographical regions in the Netherlands. At the LASA baseline (1992/1993), 3107 subjects, 99% Caucasian, were enrolled. Examinations were performed in the participants’ homes at baseline and every three years thereafter by trained and intensively supervised interviewers. Informed consent was obtained from all participants. The study was approved by the Medical Ethics Committee of the VU University Medical Center (VUmc).

For the present study, respondents who participated in the second LASA data collection cycle (1995/1996) and who were aged 65 year or older as of January 1st 1996 (n = 1509) were selected, because in these participants blood samples for IGF-1 measurements were collected (n = 1319). Respondents in whom IGF-1 concentration was not measured (n = 190) were older (p < 0.001) and had more often clinically relevant depressive symptoms (p = 0.03) than respondents in whom IGF-1 concentration was measured. Participants with no or incomplete data on the Center for Epidemiological Studies Depression Scale (CES-D) were excluded (n = 38). Additionally, subjects using recombinant GH (n = 1) or with clinical hypothyroidism (n = 5) were excluded. Respondents free of clinically relevant depressive symptoms (CES-D score < 16) at baseline of the present study, but with clinically relevant depressive symptoms in the first LASA data collection cycle (1992/1993) were excluded (n = 87) in order to
obtain a not recently depressed control group. As a result, 1188 participants were included in the cross-sectional analyses.

For the prospective analyses on incident depression over a three year follow-up period, participants with complete CES-D data in the following data collection cycle (1998/1999) were included, while participants with clinically relevant depressive symptoms (CES-D score ≥ 16) at baseline of this study were excluded, resulting in a sample of 855 subjects. Respondents not included in the prospective analyses were older (p < 0.001), more often female (p = 0.03), had lower baseline IGF-1 concentrations (p = 0.01) and poorer cognitive function (p < 0.001) than those included in the prospective analyses.

**Measurements**

**Serum IGF-1**

Blood samples were drawn in the morning and centrifuged within 60 minutes after withdrawal. Participants were allowed to take tea and toast, but no dairy products beforehand. Samples were kept frozen until determination in 1999. IGF-1 concentrations were determined by an immunoradiometric assay after extraction (Diagnostic Systems Laboratories, Webster, TX, USA) at the Endocrine Laboratory of the VUmc. The detection limit was 1 nmol/liter, the intra-assay coefficient of variation (CV) less than 4% and the inter-assay CV less than 14%. For the method used, the reference range values (P5-P95) of serum IGF-1 in persons aged > 60 were 11 - 19 nmol/l, for both men and women.

**Depression**

Depression status was assessed by a two-stage screening design. First, the CES-D was administered to all respondents. This is a 20-item self-report scale designed to measure depressive symptoms in the general population. Total scores range from 0 to 60, with a higher score indicating more depressive symptoms. The generally accepted cut-off score of ≥ 16 was used to identify respondents with clinically relevant depressive symptoms. The CES-D has been widely used in elderly population-based samples in which it has favorable psychometric properties.

Second, respondents with clinically relevant symptoms (CES-D score ≥ 16) were approached for a diagnostic psychiatric evaluation. In these respondents the National Institute of Mental Health (NIHM)-Diagnostic Interview Schedule (DIS) was used to obtain a diagnosis of MDD in the past month according to the Diagnostic and Statistical Manual of Mental Disorders, Third-Edition (DSM-III). Respondents with a CES-D score ≥ 16 not fulfilling the criteria for MDD were defined as having minor depression.
Chapter 7

**Potential confounders**

Various sociodemographic, lifestyle and health status variables were measured at baseline and included in the analyses as putative confounders. Potentially confounding sociodemographic factors included age and sex. Lifestyle variables included smoking status (never, former and current), alcohol consumption (based on the Garretsen index: none, light, moderate and (very) excessive 29), assessed by self-report, and physical activity. Physical activity was measured with the LASA Physical Activity Questionnaire, a validated interviewer-administered questionnaire that evaluates duration and frequency of activities such as walking outdoors, bicycling, light and heavy household activities and a maximum of two sport activities in the previous two weeks 30.

Health status variables included body mass index (BMI; weight (kg) / height (m)²), serum albumin concentration and number of chronic diseases. Body weight was measured without shoes and clothes using a calibrated balance scale. Height was measured with a stadiometer. Serum albumin concentrations were analyzed in three different Dutch laboratories (one in each region). For comparison, the results were converted with a validated formula 31. The number of chronic diseases was assessed by self-report, which included questions regarding the following seven major diseases: pulmonary disease, cardiac disease, peripheral arterial diseases, diabetes mellitus, stroke, osteoarthritis/rheumatoid arthritis, and malignancies.

**Other variables**

Other variables to describe the study sample, not included as confounders in the analyses, were also measured at baseline. Cognition was assessed with the Mini-Mental State Examination, a frequently used 20-item screening test for global cognitive functioning. Scores range from 0 to 30, with a higher score indicating better performance 32. The level of education was assessed by asking respondents for the highest educational level completed. Thyroid hormones were determined in frozen samples at the Endocrine Laboratory of the VUmc in 2001. If thyrotrophin, measured by a radio-immunometric assay, was not within the reference range, free thyroxine (fT4) was determined by a competitive immunoassay and if fT4 was normal, free triiodothyronine was also measured. A Hitachi 747 analyzer was used to measure serum creatinine concentration, as an indicator for renal function. The use of antidepressants, benzodiazepines, systemic corticosteroids or recombinant GH was assessed by self-report, combined with inspection of medication containers at the respondents’ homes.
Statistical analysis

Differences in baseline characteristics were analyzed by analysis of variance for normally distributed continuous variables, Kruskal-Wallis test for skewed continuous variables and Chi-square test for categorical variables. Spearman correlation coefficients (r) were calculated to examine the correlation between baseline IGF-1 concentration and continuous CES-D score at baseline and after three years of follow-up, respectively.

Multinomial logistic regression analyses were used to study the cross-sectional and longitudinal associations between baseline IGF-1 concentration and depression.

The outcome variables, depression at baseline and after three years of follow-up in respondents free of depression at baseline, respectively, were categorized into no depression, minor depression and MDD. No depression was set as the reference category in all analyses.

All continuous independent variables were individually checked for linearity with the outcome variables. Since the relations between IGF-1 concentration and the outcome variables were nonlinear, IGF-1 was divided into tertiles, with the last tertile representing the highest IGF-1 concentrations. For clarity, analyses were also performed with IGF-1 concentration as a continuous variable. These results are also presented in the tables.

In order to examine relevant confounding, all potential confounders were added separately to the age- and gender-adjusted models. Variables that gave a change in the regression coefficient of > 10% were included in the model as a relevant confounder. Potential effect modification by gender was examined by adding interaction terms (IGF-1 x gender) to the fully adjusted models. In case of a p-value < 0.10, analyses were presented in stratified groups. Three models were created for each of the outcome variables: a crude model, a model adjusted for age, and a model further adjusted for all other relevant confounders.

Sensitivity analyses were performed in all fully adjusted models, for the cross-sectional as well as the longitudinal associations, by excluding respondents using antidepressants, systemic corticosteroids, or benzodiazepines or respondents with a decreased renal function (creatinine > 200 µmol/l) separately. In addition, sensitivity analyses were also performed for the longitudinal associations by including those participants who had missing CES-D data at three-year follow-up, but who were included in the cross-sectional analysis. Using the multivariate imputation by chained equations procedure, a regression-based method, missing values were estimated and imputed by using an imputation model including information from other complete
variables in the data set. According to the percentage of missing cases, 16 different imputed data sets were created. Results of the analyses in these different sets were pooled.

All statistical analyses were performed using the statistical software package IBM SPSS Statistics version 20. Two-sided p-values of ≤ 0.05 were considered significant.

**Results**

**Baseline characteristics**
The study cohort included 1188 participants, mean age 75.4 (6.5) years, of whom 161 (13.6%) had minor depression and 32 (2.7%) had MDD at baseline. The mean serum IGF-1 concentration was 13.9 (5.3) nmol/liter. Table 1 describes the baseline characteristics according to tertiles of IGF-1 concentration.

**Cross-sectional associations**
The Spearman correlation coefficient between baseline IGF-1 concentration and baseline continuous CES-D score, which measures depressive symptoms, was -0.11 (p < 0.001).

Multinomial logistic regression analysis was used to further examine the cross-sectional association of IGF-1 concentration with prevalent minor depression and MDD (table 2). The analyses were stratified for gender, since a significant interaction between IGF-1 and gender was observed (p = 0.02).

In men, both the unadjusted and the adjusted models (age, alcohol consumption, albumin, smoking status, number of chronic diseases, BMI, and physical activity) demonstrated significantly lower odds for minor depression for IGF-1 concentrations in the middle tertile compared to IGF-1 concentrations in the highest tertile.

In women, the odds for MDD were higher for IGF-1 concentrations in the lowest tertile compared to IGF-1 concentrations in the highest tertile in the unadjusted model. However, after adjustment for relevant confounders this association did not remain statistically significant. No other statistically significant associations were observed.

Separate exclusion of specific subgroups (users of antidepressants, systemic corticosteroids, benzodiazepines, and subjects with a decreased renal function) from the analyses, did not substantially influence the results.
Table 1 | Baseline characteristics of the study population according to tertiles of IGF-1 concentration

<table>
<thead>
<tr>
<th>Tertile I</th>
<th>Tertile II</th>
<th>Tertile III</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 11.5 nmol/l</td>
<td>&gt; 11.5 to ≤ 15.5 nmol/l</td>
<td>&gt; 15.5 nmol/l</td>
<td></td>
</tr>
</tbody>
</table>

- **No. of subjects**: 393 | 393 | 402 |  |
- **IGF-1, nmol/l (mean, SD)**: 8.6 (2.1) | 13.5 (1.1) | 19.5 (4.1) | <0.001 |
- **Depression status (n, %)**:  |
  - No depression: 314 (79.9) | 338 (86.0) | 343 (85.3) | 0.02 |
  - Minor depression: 60 (15.3) | 49 (12.5) | 52 (12.9) |  |
  - Major depression: 19 (4.8) | 6 (1.5) | 7 (1.7) |  |
- **Age at baseline, years (mean, SD)**: 77.5 (6.5) | 75.5 (6.6) | 73.4 (5.8) | <0.001 |
- **Female sex (n, %)**: 233 (59.3) | 188 (47.8) | 177 (44.0) | 0.001 |
- **Smoking (n, %)**:  |
  - Never: 172 (43.8) | 131 (33.3) | 119 (29.6) |  |
  - Former: 159 (40.5) | 191 (48.6) | 212 (52.7) |  |
  - Current: 62 (15.8) | 71 (18.1) | 71 (17.7) |  |
- **Alcohol consumption (n, %)**: 0.22 |
  - None: 103 (26.2) | 94 (23.9) | 92 (22.9) |  |
  - Light: 201 (51.1) | 183 (46.6) | 203 (50.5) |  |
  - Moderate: 71 (18.1) | 92 (23.4) | 76 (18.9) |  |
  - (Very) excessive: 18 (4.6) | 24 (6.1) | 31 (7.7) |  |
- **BMI, kg/m² (mean, SD)**: 26.8 (4.5) | 26.8 (4.1) | 27.0 (3.7) | 0.69 |
- **Physical activity, min/day (median, range)**: 137.3 (0 - 624) | 129.3 (0 - 625) | 128.9 (0 - 600) | 0.12 |
- **Albumin, g/l (mean, SD)**: 44.1 (2.8) | 44.5 (2.8) | 44.8 (2.5) | <0.001 |
- **No. of chronic diseases (median, range)**: 1 (0 - 5) | 1 (0 - 5) | 1 (0 - 5) | 0.23 |
- **MMSE score (median, range)**: 28 (12 - 30) | 28 (12 - 30) | 28 (10 - 30) | 0.01 |
- **Education (n, %)**: 0.54 |
  - Low: 248 (63.1) | 230 (58.7) | 239 (59.5) |  |
  - Middle: 99 (25.2) | 110 (28.1) | 119 (29.6) |  |
  - High: 46 (11.7) | 52 (13.3) | 44 (10.9) |  |
- **Systemic corticosteroids use (n, %)**: 7 (1.8) | 8 (2.0) | 7 (1.7) | 0.95 |
- **Antidepressant use (n, %)**: 12 (3.1) | 6 (1.5) | 9 (2.2) | 0.36 |
- **Benzodiazepine use (n, %)**: 37 (9.4) | 34 (8.7) | 26 (6.5) | 0.29 |

IGF-1, insulin-like growth factor 1; BMI, body mass index; MMSE, Mini-Mental State Examination

Normally distributed continuous variables are expressed as mean (SD), whereas skewed variables are expressed as median (range). Categorical variables are presented as number (percentage).

* Continuous variables were tested with either one-way analysis of variance (normally distributed variables) or the Kruskal-Wallis test (skewed variables). Categorical variables were examined with the Chi-square test.

*b-c Missing subjects: b n=3; c n=1
<table>
<thead>
<tr>
<th>IGF-1</th>
<th>Minor depression</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted model</td>
<td>Model 1</td>
<td>Model 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td></td>
<td>P-value</td>
<td>P-value</td>
<td>P-value</td>
<td>P-value</td>
</tr>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First tertile</td>
<td>0.85 (0.42 - 1.70)</td>
<td>0.60 (0.29 - 1.27)</td>
<td>0.55 (0.25 - 1.22)</td>
<td>0.64</td>
</tr>
<tr>
<td>Second tertile</td>
<td>0.41 (0.18 - 0.90)</td>
<td>0.34 (0.15 - 0.77)</td>
<td>0.35 (0.15 - 0.82)</td>
<td>0.03</td>
</tr>
<tr>
<td>Third tertile</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Continuous level</td>
<td>1.03 (0.83 - 1.28)</td>
<td>1.12 (0.89 - 1.40)</td>
<td>1.14 (0.91 - 1.45)</td>
<td>0.80</td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First tertile</td>
<td>1.33 (0.80 - 2.23)</td>
<td>1.27 (0.75 - 2.13)</td>
<td>1.38 (0.80 - 2.39)</td>
<td>0.27</td>
</tr>
<tr>
<td>Second tertile</td>
<td>1.35 (0.80 - 2.30)</td>
<td>1.31 (0.77 - 2.23)</td>
<td>1.13 (0.77 - 2.33)</td>
<td>0.27</td>
</tr>
<tr>
<td>Third tertile</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Continuous level</td>
<td>0.92 (0.79 - 1.06)</td>
<td>0.93 (0.80 - 1.08)</td>
<td>0.91 (0.78 - 1.06)</td>
<td>0.24</td>
</tr>
</tbody>
</table>
**Table 2** (continued)

<table>
<thead>
<tr>
<th>IGF-1</th>
<th>Unadjusted model</th>
<th></th>
<th>Model 1</th>
<th></th>
<th>Model 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P-value</td>
<td>OR (95% CI)</td>
<td>P-value</td>
<td>OR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First tertile</td>
<td>1.39 (0.19 - 9.98)</td>
<td>0.71</td>
<td>0.99 (0.13 - 7.41)</td>
<td>0.99</td>
<td>0.82 (0.10 - 6.62)</td>
<td>0.85</td>
</tr>
<tr>
<td>Second tertile</td>
<td>2.08 (0.38 - 11.51)</td>
<td>0.40</td>
<td>1.74 (0.31 - 9.80)</td>
<td>0.53</td>
<td>1.57 (0.27 - 9.31)</td>
<td>0.62</td>
</tr>
<tr>
<td>Third tertile</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Continuous level</td>
<td>0.86 (0.52 - 1.41)</td>
<td>0.54</td>
<td>0.94 (0.56 - 1.58)</td>
<td>0.82</td>
<td>1.01 (0.59 - 1.72)</td>
<td>0.98</td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First tertile</td>
<td>2.86 (1.03 - 7.94)</td>
<td>0.04</td>
<td>2.53 (0.90 - 7.12)</td>
<td>0.08</td>
<td>2.66 (0.89 - 7.89)</td>
<td>0.08</td>
</tr>
<tr>
<td>Second tertile</td>
<td>0.39 (0.075 - 2.05)</td>
<td>0.27</td>
<td>0.37 (0.07 - 1.97)</td>
<td>0.25</td>
<td>0.36 (0.07 - 1.95)</td>
<td>0.23</td>
</tr>
<tr>
<td>Third tertile</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Continuous level</td>
<td>0.70 (0.51 - 0.96)</td>
<td>0.03</td>
<td>0.73 (0.53 - 0.01)</td>
<td>0.05</td>
<td>0.72 (0.52 - 1.02)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

*IGF-1, insulin-like growth factor 1; OR, odds ratio; CI, confidence interval*  
*Distribution of IGF-1 concentration per tertile was as follows: first tertile ≤ 11.5 nmol/l, second tertile > 11.5 to ≤ 15.5 nmol/l, third tertile > 15.5 nmol/l.*  
*Referent depression outcome group was no depression. Analyses were stratified for gender (lowest p-value interaction terms for gender 0.02).*  
*Model 1 was adjusted for age.*  
*Model 2 was fully adjusted for age, alcohol consumption, albumin, smoking status, number of chronic diseases, BMI, and physical activity.*
Longitudinal associations

Of the 855 respondents without minor depression or MDD at baseline and who were included in the longitudinal analyses, 418 (48.9%) were female. The mean age was 74.6 (6.3) years. After a mean follow-up time of 3.0 (0.2) years, 100 (11.7%) participants had minor depression, while 15 (1.8%) had MDD.

Spearman correlation analysis demonstrated no significant correlation between baseline IGF-1 concentration and continuous CES-D score measured at follow-up ($r = -0.04, p = 0.22$).

Table 3 shows the results of the multinomial logistic regression analyses which were used to examine the longitudinal association between baseline IGF-1 concentration and incident minor depression and MDD during follow-up. The analyses were stratified for gender (p-value interaction term for gender 0.04).

In women, the odds for new minor depression after three years of follow-up were decreased in respondents with a baseline IGF-1 concentration in the middle tertile compared to those with an IGF-1 concentration in the highest tertile after adjustment for relevant confounders (age, albumin, alcohol consumption, BMI, physical activity, and number of chronic diseases).

No other significant associations between baseline IGF-1 concentration and incident minor depression or MDD were observed.

Exclusion of the aforementioned subgroups (users of antidepressants, systemic corticosteroids, benzodiazepines, and subjects with a decreased renal function) did not materially change the outcomes in the fully adjusted models. Similarly, sensitivity analysis using multiple imputation of missing CES-D data, which allowed inclusion of patients with incomplete depression data at three-year follow-up, did not alter the outcomes either.

Discussion

To the best of our knowledge, this is the first large prospective study in community-dwelling older persons that examines the association between IGF-1 concentration and prevalent and incident minor depression and MDD, assessed with a diagnostic psychiatric evaluation, thereby taking into account potential confounding factors. The cross-sectional analyses showed that men, but not women, with an IGF-1 concentration in the mid-normal range were less likely to have minor depression than men with an IGF-1 concentration in the high-normal range. In women, a trend towards increased probability of prevalent MDD was observed in respondents with an IGF-1 concentration in the low-normal range.
<table>
<thead>
<tr>
<th>IGF-1</th>
<th>Minor depression</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Unadjusted model</td>
<td></td>
<td>Model 1</td>
<td>Model 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OR (95% CI)</td>
<td>P-value</td>
<td>OR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First tertile</td>
<td></td>
<td>1.66 (0.75 - 3.69)</td>
<td>0.21</td>
<td>1.29 (0.56 - 2.98)</td>
<td>0.56</td>
</tr>
<tr>
<td>Second tertile</td>
<td></td>
<td>1.67 (0.78 - 3.60)</td>
<td>0.19</td>
<td>1.48 (0.68 - 3.24)</td>
<td>0.32</td>
</tr>
<tr>
<td>Third tertile</td>
<td></td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Continuous level</td>
<td></td>
<td>0.97 (0.91 - 1.04)</td>
<td>0.40</td>
<td>0.99 (0.93 - 1.07)</td>
<td>0.87</td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First tertile</td>
<td></td>
<td>0.84 (0.44 - 1.61)</td>
<td>0.59</td>
<td>0.72 (0.37 - 1.40)</td>
<td>0.33</td>
</tr>
<tr>
<td>Second tertile</td>
<td></td>
<td>0.50 (0.24 - 1.08)</td>
<td>0.08</td>
<td>0.48 (0.22 - 1.03)</td>
<td>0.06</td>
</tr>
<tr>
<td>Third tertile</td>
<td></td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Continuous level</td>
<td></td>
<td>1.02 (0.97 - 1.07)</td>
<td>0.46</td>
<td>1.03 (0.98 - 1.09)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Table 3 | Results of multinomial logistic regression analyses for the association of IGF-1 concentration with incident minor and major depression during three years of follow-up
<table>
<thead>
<tr>
<th>IGF-1</th>
<th>Unadjusted model</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P-value</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First tertile</td>
<td>1.33 (0.18 - 9.57)</td>
<td>0.78</td>
<td>1.33 (0.16 - 11.18)</td>
</tr>
<tr>
<td>Second tertile</td>
<td>0.56 (0.05 - 6.22)</td>
<td>0.64</td>
<td>0.57 (0.05 - 6.54)</td>
</tr>
<tr>
<td>Third tertile</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
</tr>
<tr>
<td>Continuous level</td>
<td>1.09 (0.93 - 1.28)</td>
<td>0.54</td>
<td>1.10 (0.93 - 1.30)</td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First tertile</td>
<td>0.36 (0.07 - 2.03)</td>
<td>0.25</td>
<td>0.35 (0.06 - 2.01)</td>
</tr>
<tr>
<td>Second tertile</td>
<td>0.84 (0.21 - 3.44)</td>
<td>0.81</td>
<td>0.84 (0.20 - 3.49)</td>
</tr>
<tr>
<td>Third tertile</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
</tr>
<tr>
<td>Continuous level</td>
<td>1.05 (0.96 - 1.16)</td>
<td>0.28</td>
<td>1.06 (0.96 - 1.18)</td>
</tr>
</tbody>
</table>

IGF-1, insulin-like growth factor 1; OR, odds ratio; CI, confidence interval
Distribution of IGF-1 concentration per tertile was as follows: first tertile ≤ 12.0 nmol/l, second tertile > 12.0 to ≤ 15.9 nmol/l, third tertile > 15.9 nmol/l.
Referent depression outcome group was no depression. Analyses were stratified for gender (lowest p-value interaction terms for gender 0.04).
Model 1 was adjusted for age.
Model 2 was fully adjusted for age, albumin, alcohol consumption, BMI, physical activity, and number of chronic diseases.
Prospectively, besides a decreased likelihood of minor depression in women with a mid-normal IGF-1 concentration, no significant associations between baseline IGF-1 concentration and incident minor depression or MDD over time were demonstrated.

The cross-sectional finding of decreased prevalent minor depression in men with a mid-normal IGF-1 concentration, compared to men with a high-normal IGF-1 concentration, is partly in accordance with findings in other smaller studies that reported increased IGF-1 concentrations in depressed patients and a decline in IGF-1 concentration in patients responding to antidepressant treatment. In contrast, in a recent epidemiological study investigating the association between IGF-1 and any depressive disorder, the Study of Health in Pomerania (SHIP), no cross-sectional associations were observed between IGF-1 and any depressive disorder. Although possible explanations remain elusive, altered functioning of the GH-IGF-1 axis, with hypo- as well as hypersecretion being reported, has been suggested during depression. The trend of increased probability of prevalent MDD in women with low-normal IGF-1 concentrations, compared to women with high-normal IGF-1 concentrations, was not observed in men. Differences between the two genders have also been observed in studies exploring depression, the GH-IGF-1 axis in elderly, or the effects of GH replacement therapy in GHD or healthy adults. In the previously mentioned SHIP-study, sex differences were also evident. Whether these differences may be caused by variations across gender in sex hormones or GH- and IGF-1-binding protein levels, as has been hypothesized, still remains uncertain.

The cross-sectional findings in the present study were not supported by the longitudinal findings. This suggests that IGF-1 may not be of predictive value with regard to the development of depression over time in older individuals. This is in contrast with studies using animal models or adult patients with GHD (i.e. pathological GHD due to hypothalamic or pituitary defects) that did find supportive evidence for an association between the GH-IGF-1 axis and depression. Possibly, a longitudinal effect of IGF-1 on mood may only be present in a severe IGF-1 deficient state, during which other mechanisms may be involved than during the ‘somatopause’. Additionally, in GHD patients the imbalances of other pituitary hormones may also contribute to the development of depressive symptoms. Discrepancies in findings from preclinical studies and clinical studies exploring the GH-IGF-1 axis have been observed before. Possibly the functioning of the GH-IGF-1 axis differs between species. Although the results of the present study do not suggest that IGF-1 plays a predictive role in the development of future depression, this does not exclude the possibility of a more acute role of IGF-1 in current depression. Unfortunately, the IGF-1 concentration after
three years of follow-up, which would allow further evaluation of this possible role, was not measured in the present study.

The observed associations between IGF-1 and minor depression and MDD in our study did not show a straightforward linear trend. Other studies investigating the relation between hormonal secretion, e.g. cortisol, and depression, have also reported nonlinear associations, in particular U-shaped relationships. U-shaped relationships have also been reported in studies investigating the GH-IGF-1 axis. This is also reflected by reports of more mood disorders in adult patients with GHD (i.e. pathological GHD due to hypothalamic or pituitary defects) as well as in acromegalic patients with excess GH secretion. Therefore, a U-shaped association between depression and serum IGF-1 concentration, with more depression for both high and low concentrations, cannot be excluded. Since some observed associations in our study were still present after adjustment for relevant confounders, especially the cross-sectional association in men, it is possible that IGF-1 is associated with current depression. However, in light of the above, these associations appear to be highly complex and require further evaluation.

Depression is a heterogeneous disease with various etiological pathways. While some subtypes of depression may not be associated with IGF-1 concentration, others may be associated. In accordance with other studies, MDD was rare in the present study. Therefore, different subtypes of depression could not be studied and the power to detect difference between groups might have been influenced.

In the SHIP-study, low baseline IGF-1 concentrations in females and high baseline IGF-1 concentrations in males predicted the development of any depressive disorder over time. These longitudinal associations were not observed in the present study, which may be due to several differences. Mean age in the SHIP-study was 50 (16.4) years, while mean age in the present study was 75.4 (6.5) years. Possibly, the relation between IGF-1 and depression changes with age. In addition, the results of the SHIP-study have to be interpreted with caution as only a self-report questionnaire was used to screen for any depressive disorders, while in the present study both a symptom rating scale and a psychiatric diagnostic evaluation were used, providing more accurate diagnostic information. Besides the SHIP-study, only few other studies, some of which were reported in the 1980s, have explored the relation between IGF-1 and depression in humans, with various results. Deuschle et al. observed in 1997 that the mean plasma IGF-1 concentration was significantly higher in 24 patients with MDD, according to DSM-III criteria, than in 33 healthy controls, while the GH and GH- and IGF-binding protein levels were not increased. After treatment with antidepressants, a significant decrease in IGF-1 concentration was only detected in nine patients who
were defined as treatment responders. Similar results were reported by Weber-Hamann et al. In contrast, Schilling et al. recently demonstrated an increase in cerebrospinal fluid IGF-1 concentrations in 11 out of 12 depressed patients treated with various antidepressants for various durations. Another study, which compared 19 women with MDD with 16 healthy controls, suggested that other factors besides depression play an important role in the regulation of IGF-1.

Differences in results between these studies and our study may be due to differences in the study population. The aforementioned reports in the literature had smaller sample sizes and included (much) younger individuals. Furthermore, while in one study separate gender analyses could not be performed, the other study included only women. Also, all of these studies included patients with psychiatric diagnoses of depression, while in the present study community-dwelling elderly with MDD as well as minor depression were studied. Additionally, due to the cross-sectional design or short follow-up time of these studies, no firm conclusions about the direction of the association between IGF-1 and depression could be drawn.

Our study has both strengths and limitations. Major strengths of the present study include the large and nationally representative sample of older people and the longitudinal design. Additionally, the use of both psychiatric diagnoses of MDD and a depression symptom rating scale provided accurate information. A possible limitation is that only total serum IGF-1 concentration was measured, which may not directly reflect the level of bioactive IGF-1. Additionally, the levels of IGF-binding proteins (IGFBPs), which modulate the bioactivity and availability of IGF-1, were not measured. However, Deuschle et al. reported no difference in IGFBPs between depressed and nondepressed persons. Other limitations are nonresponse and loss to follow-up of some participants. Nonresponders were older and had more often depressive symptoms. Those lost to follow-up for the prospective analyses were also older and had lower baseline IGF-1 concentrations. This might have led to underestimation of the observed associations. However, sensitivity analysis using multiple imputation of missing values for respondents with missing CES-D data at three-year follow-up, did not change the outcomes.

Furthermore, even though our analyses were adjusted for a variety of confounders, we cannot exclude the possibility that the observed associations may partly be explained by other variables that were not measured. As our study population consisted primarily of relatively healthy, Caucasian, older individuals, it would be very interesting to investigate the associations in another population.

In conclusion, this is the first large population-based study in older persons to explore the cross-sectional and longitudinal association between IGF-1 concentration
and minor and major depression. Several associations were observed between IGF-1 and depression.

The observed cross-sectional associations suggest a possible acute role of IGF-1 in current depression, which differs between the two genders. The inconsistency between the cross-sectional and longitudinal findings, however, indicates that IGF-1 may not play an important predictive role in the development of depression over time. More investigations are required to elucidate the complex associations between IGF-1 and depression. Further studies are needed to advance our understanding of late-life depression in order to optimize treatment and prevention of this burdensome disease.

**Acknowledgements**

This study is based on data from The Longitudinal Aging Study Amsterdam, which is largely supported by a grant from the Netherlands Ministry of Health Welfare and Sports, Directorate of Nursing Care and Older persons. The funding source had no role in the study design, data collection, analyses, writing process or the decision to submit the paper for publication. The authors would like to thank Jan Poppelaars for his assistance in providing the data.
References


