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Citation

Burgers, A. M. G., Biermasz, N. R., Schoones, J. W., Pereira, A. M., Renehan, A. G., Zwahlen, M., ... Dekkers, O. M. (2011). Meta-Analysis and Dose-Response Metaregression: Circulating Insulin-Like Growth Factor I (IGF-I) and Mortality. *Journal Of Clinical Endocrinology And Metabolism*, 96(9), 2912-2920. doi:10.1210/jc.2011-1377

Version: Not Applicable (or Unknown)
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Downloaded from: <https://hdl.handle.net/1887/108912>

Note: To cite this publication please use the final published version (if applicable).

Meta-Analysis and Dose-Response Metaregression: Circulating Insulin-Like Growth Factor I (IGF-I) and Mortality

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Context: IGF-I plays a central role in metabolism and growth regulation. High IGF-I levels are associated with increased cancer risk and low IGF-I levels with increased risk for cardiovascular disease.

Objective: Our objective was to determine the relationship between circulating IGF-I levels and mortality in the general population using random-effects meta-analysis and dose-response metaregression.

Data Sources: We searched PubMed, EMBASE, Web of Science, and Cochrane Library from 1985 to September 2010 to identify relevant studies.

Study Selection: Population-based cohort studies and (nested) case-control studies reporting on the relation between circulating IGF-I and mortality were assessed for eligibility.

Data Extraction: Data extraction was performed by two investigators independently, using a standardized data extraction sheet.

Data Synthesis: Twelve studies, with 14,906 participants, were included. Overall, risk of bias was limited. Mortality in subjects with low or high IGF-I levels was compared with mid-centile reference categories. All-cause mortality was increased in subjects with low as well as high IGF-I, with a hazard ratio (HR) of 1.27 (95% CI = 1.08–1.49) and HR of 1.18 (95% CI = 1.04–1.34), respectively. Dose-response metaregression showed a U-shaped relation of IGF-I and all-cause mortality ($P = 0.003$). The predicted HR for the increase in mortality comparing the 10th IGF-I with the 50th percentile was 1.56 (95% CI = 1.31–1.86); the predicted HR comparing the 90th with the 50th percentile was 1.29 (95% CI = 1.06–1.58). A U-shaped relationship was present for both cancer mortality and cardiovascular mortality.

Conclusions: Both low and high IGF-I concentrations are associated with increased mortality in the general population. (*J Clin Endocrinol Metab* 96: 2912–2920, 2011)

Insulin-like growth factor I (IGF-I), a hormone mainly synthesized in the liver after stimulation of the GH receptor, plays a central role in cell metabolism and growth regulation. Risk of cancer as well as cardiovascular diseases (CVD) have been related to circulating total

IGF-I levels. In support of these epidemiological observations, IGF-I is pleiotropic in its cellular actions including mitogenesis, antiapoptosis, enhanced cell motility, and proangiogenesis (1). These mechanisms may contribute to the increased risk of incident cancer in persons with IGF-I

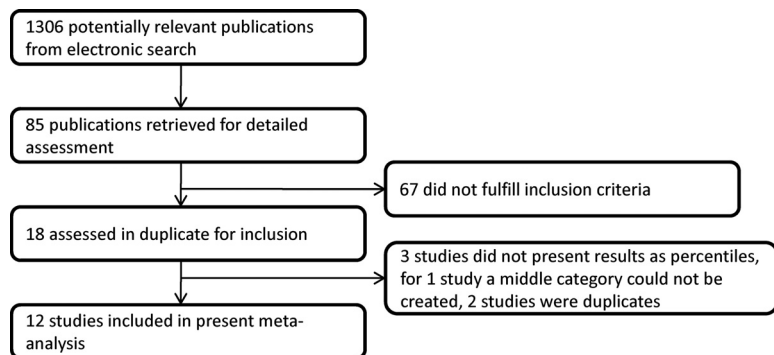


FIG. 1. Flowchart of study selection.

levels in the upper physiological ranges (2). Updated pooled analyses reveal that these associations exist for several common cancers including prostate, pre- and postmenopausal breast, and colorectal cancer (3). On the other hand, low levels of IGF-I are associated with increased risk of ischemic heart disease (IHD) (4), cardiovascular mortality (4, 5), and diabetes mellitus (6, 7). In several organisms such as fruit flies, worms, and rats, IGF-I is involved in the control of lifespan (8, 9). In most studies in mice, disruption of the GH/IGF-I axis results in an increase in lifespan (up to 55%) (10). However, in humans, the association between IGF-I levels and life expectancy is less obvious. Several population-based studies describing a relationship of IGF-I with mortality were published with conflicting results. Two studies showed higher mortality with higher IGF-I levels (11, 12), three showed higher mortality with lower IGF-I levels (13–15), whereas in six studies, no clear association between IGF-I and mortality was found (5, 16–20).

Because IGF-I is involved in many (patho)physiological processes, different IGF-I levels may translate in differences in associated mortality risks. The activity of IGF-I is influenced by at least six high-affinity binding proteins [IGF-binding protein (IGFBP)]; the most abundant is IGFBP-3, which binds more than 90% of IGF-I in the circulation. Although IGF-I and IGFBP-3 are typically well correlated, there is speculative evidence that it has an independent impact on disease risk, for example, incident cancer. Therefore, serum levels of IGFBP-3 might also be related to disease and longevity (16, 17).

We performed a meta-analysis and metaregression of population-based studies to assess the relationship between IGF-I and mortality in more detail. In a secondary analysis, we assessed the relationship between IGF-I and cancer and cardiovascular mortality. Moreover, a meta-analysis was performed on the association between IGFBP-3 and mortality.

Materials and Methods

Data sources and searches

We searched PubMed, EMBASE, Web of Science, and Cochrane Library from January 1985 (publications on IGF-I started 1985) to September 2010 to identify potentially relevant studies. The search strategy is shown in the *Appendix*. Potentially relevant articles were retrieved for detailed assessment. Cohort studies as well as (nested) case-control studies reporting data on the relation between circulating IGF-I and mortality were eligible for inclusion. The main aim was to assess the association between IGF-I, IGFBP-3, and mortality in the general

population; therefore, studies on selected cohorts with conditions like acromegaly, acute renal failure, or liver cirrhosis were not eligible. Furthermore, studies on intensive care and children were excluded. No language restriction was set in advance.

To be included, studies should have expressed the association between IGF-I and mortality as relative risks [odds ratios, rate ratios, or hazard ratios (HR)] and reported the association by comparing categories (for example tertiles, quartiles, or quintiles) of IGF-I or IGFBP-3 concentrations. Because IGF-I levels decline with age and are dependent on sex, data had to be adjusted for at least age and sex.

Study selection

Study selection was performed independently by two investigators, first by A.M.G.B. and second by either N.R.B. or O.M.D. In case of different opinions, the article was selected for more detailed assessment. The initial search included 1306 articles; 85 articles were selected for detailed assessment. Eighteen articles reported data of the relation between IGF-I and mortality. Three studies were excluded because we were unable to extract percentiles belonging to the HR presented (5, 15, 20). Another study was excluded because we were unable to create a middle category (12), as were two other studies reporting duplicate cases (21, 22). No attempt was made to get the original data from any of the assessed studies. Finally, 12 studies were included in the present meta-analysis (Fig. 1).

Data extraction and quality assessment

For all studies, maximally adjusted risk ratios (adjusted for at least age and sex) and their 95% confidence intervals (CI) were extracted. Data were extracted in duplicate using a standard spreadsheet (A.M.G.B. and either N.R.B. or O.M.D.). Differences were checked and corrected.

Assessment of study quality was based on study components that potentially bias an association between IGF-I and mortality: adequacy of exposure (IGF-I) measurement, adequacy of follow-up (loss to follow-up <5% was considered to represent a low risk of bias), and adequacy of the assessment of vital status at end of follow-up and the adjustment of potential confounding factors. This was assessed independently by two investigators (A.M.G.B. and O.M.D.) using a standard quality assessment form.

Data synthesis and analysis

Different immunoassays are used to measure IGF-I levels, each assay having specific reference ranges, which precludes a direct comparison of absolute IGF-I values (23). For this reason, the analyses were based on percentiles of IGF-I, assuming that different IGF-I assays reflect the same underlying distribution of IGF-I levels. Categorization of the IGF-I distribution was based on the data available in the articles. *A priori*, we hypothesized the relationship between IGF-I and mortality to be best described by a U-shaped curve. For this reason, we extracted both the relative risk for the lowest compared with the mid percentile and the relative risk for the highest compared with the mid percentile. If necessary, we recalculated HR in a way that the lowest and highest percentiles were compared with the mid-category. In case the mid-category comprised two categories (for example, in case of quartiles), we combined these with a fixed-effects meta-analysis to create a middle category.

We performed random-effects meta-analysis using maximally adjusted HR and 95% CI. The HR were adjusted for at least age and sex. Results are expressed as HR and 95% CI. Heterogeneity was assessed with the I^2 statistic. This describes

the percentage of variation across studies that is due to heterogeneity rather than chance. We performed a metaregression to assess dose-response slopes for the association between IGF-I and mortality. In the metaregression, the addition of a quadratic term to the model was tested statistically to confirm or refute the assumption of a U-shaped relationship between IGF-I and mortality. The same statistical methods were used for the analyses of IGF-BP-3.

All analyses were performed separately for all-cause mortality, cancer mortality, and mortality due to cardiovascular causes. A subgroup analysis was performed for mean age under 60 *vs.* mean age over 60 yr. Statistical analyses were performed with Stata Statistical Software (Statacorp, College Station, TX), version 10.1.

Results

Study characteristics (Table 1)

Twelve studies were included in the present meta-analysis. Characteristics of the included studies, 10 cohort studies and two nested case-control studies, are presented

TABLE 1. Characteristics of included studies

Author, year (Ref.)	Study design	Endpoint	Included subjects (n)	Death (n)	Mean follow-up (yr)	Men (%)	Age range (yr)
Friedrich, 2009 (14)	Cohort	All-cause mortality (men)	1988	240	8.5	100	20–79
		All-cause mortality (women)	2069	240	8.5	0	
		Cancer mortality (men)	1988	79	8.5	100	
		CVD mortality (men)	1988	69	8.5	100	
		CVD mortality (women)	2069	31	8.5	0	
Arai, 2008 (24)	Cohort	All-cause mortality	252	208	6.2	22	100–108
Andreassen, 2009 (11)	Cohort	All-cause mortality	642	103	5	43	50–89
Brugts, 2008 (19)	Cohort	All-cause mortality	376	170	8.6	100	73–94
Kaplan, 2008 (16)	Cohort	All-cause mortality	1122	398	8	35	64–92
Maggio, 2007 (18)	Cohort	All-cause mortality	410	126	6	100	65–92
Cappola, 2003 (13)	Cohort	All-cause mortality	718	130	5	0	65+
Saydah, 2007 (17)	Cohort	All-cause mortality	6056	743	8.5	46	20+
		CVD mortality	6056	251	8.5		
		Cancer mortality	6056	181	8.5		
Kaplan, 2007 (28)	Nested case control	Mortality due to MI	1340	48	9.3	35 (controls) 48 (cases)	65–94
		Mortality due to CHD	1340	170	9.3		
Major, 2010 (26)	Cohort	Cancer mortality	633	74	18	100	51–98
Van Bunderen, 2010 (25)	Cohort	All-cause mortality	1273	633	11.6	50	64–88
		Cancer mortality	1119	88	11.6		
		CVD mortality	804	94	11.6		
Pham, 2010 (27)	Nested case control	Cancer mortality	3653	914	n.a.	57.8	40–79

TABLE 2. Exposure measurement, follow-up, and endpoint ascertainment

First author, year	IGF-I assay (company)	Follow up	Endpoint ascertainment	Adjustments in analyses
Friedrich, 2009	CIA (Nichols)	Complete	Local health authority	Waist circumference
Arai, 2008	RIA (SRL Ltd.)	2.3% missing	Telephone contact	BMI, smoking, comorbidities
Andreassen, 2009	ELISA (R&D Systems)	Complete	NDI	Smoking, diabetes, AF
Brugts, 2008	RIA (Mediagnost)	Complete	Contact GP	BMI, smoking, diabetes
Kaplan, 2008	ELISA (DSL)	Complete	NDI	BMI, smoking
Maggio, 2007	IRMA (DSL)	Complete	Mortality registry	BMI, smoking, comorbidities
Cappola, 2003	RIA (Nichols)	Complete	NDI	BMI, smoking, comorbidities
Saydah, 2007	ELISA (DSL)	5 persons missing	NDI	BMI, smoking
Kaplan, 2007	ELISA (DSL)	2% missing	NDI	Smoking
Major, 2010	RIA (Nichols)	Complete	Mailed questionnaires	Waist-hip ratio, smoking
Van Bunderen, 2010	IRMA (DSL)	Complete	NDI, death certificates	BMI, smoking, diabetes
Pham, 2010	IRMA (Daiichi)	Complete	Death certificates	BMI, smoking

AF, Atrial fibrillation; BMI, body mass index; CIA, chemiluminescence immunoassay; GP, general practitioner; IRMA, immunoradiometric assay; NDI, national death index. Manufacturers are as follows: Diagnostic Systems Laboratories (DSL), Webster, TX; Nichols Advantage (Nichols), Bad Vibel, Germany; SRL Ltd., Tokyo, Japan; Mediagnost, Tübingen, Germany; R&D Systems, Minneapolis, MN; Daiichi Radioisotope Laboratories (Daiichi), Tokyo, Japan.

in Table 1. Nine studies reported on the association between IGF-I and all-cause mortality (11, 13, 14, 16–19, 24, 25), five on IGF-I and cancer mortality (14, 17, 25–27), and four on IGF-I and CVD mortality (14, 17, 25, 28). Respectively, a total of 14,906 (all-cause mortality), 13,449 (cancer mortality), and 12,257 (CVD mortality) subjects were included in the analyses. The association of IGF-I and all-cause mortality was reported in four studies ($n = 11,487$) (14, 16, 17, 24). In one study, all results were presented separately for men and women (14). The total number of participants per study ranged from 252 to 6056. Mean follow-up durations ranged from 5–18 yr.

Overall, the risk of bias in the included studies was limited. Measurement of IGF-I was performed with different assays with accompanying different referent ranges. Intra- and interassay coefficients of variation were reported in all but four studies. Both coefficients were missing in one study (24), two other studies reported only the interassay coefficient of variation (13, 25). In all studies, subjects had a single IGF-I measurement. Follow-up was complete for all but three studies, in which reported loss to follow-up was maximally 3% (17, 24, 28). In 11 studies endpoint was ascertained by linkage to death registries; three studies contacted only the general practitioner or patient (19, 24, 26). All studies adjusted the HR for at least age and sex (Table 2).

IGF-I and all-cause mortality (Table 3)

In a random-effect meta-analysis, a higher mortality risk for subjects in the lowest IGF-I category compared with the middle category was shown with a HR of 1.27 (95% CI = 1.10–1.46). Also, a higher mortality risk was shown for subjects in the highest IGF-I category compared with the middle category with a HR of 1.18 (95% CI = 1.04–1.34). I^2 of these two analyses were 32 and 0%,

respectively. Repeated analysis with minimally adjusted HR did not materially influence the study results. Stratified analysis according to age (mean age <60 *vs.* >60 yr) resulted in comparable effect estimates. Studies with mean age under 60 yr (14, 17) had high *vs.* middle HR of 1.09 (95% CI = 0.81–1.46) and low *vs.* middle HR of 1.10 (95% CI = 0.58–2.09). Studies with mean age over 60 yr (11, 13, 16, 18, 19, 24, 25) had high *vs.* middle HR of 1.21 (95% CI = 1.03–1.41) and low *vs.* middle HR of 1.28 (95% CI = 1.13–1.46).

IGF-I and cancer mortality (Table 3)

Five population-based studies reported data on cancer mortality: four cohort and one nested case-control study. Because the nested case-control study reported odds ratios with controls being selected from noncases at the end of follow-up (noninclusive sampling), this exposure odds ratio might slightly overestimate the HR (27). A random-effects meta-analysis for cancer mortality comparing subjects in the highest IGF-I category *vs.* the middle category showed a HR of 1.11 (95% CI = 0.79–1.55). Cancer mortality in subjects in the lowest category *vs.* the middle category showed a HR of 1.14 (95% CI = 0.98–1.33).

IGF-I and CVD mortality (Table 3)

From three cohort studies and one nested case-control study, data on the relation of IGF-I with mortality of a cardiovascular cause could be extracted. In the case-control study, controls were a random sample of the cohort at baseline (inclusive sampling), in which case the odds ratio is a direct estimate of the relative risk (28).

All studies used different definitions of cardiovascular death. Friedrich *et al.* (14), van Bunderen *et al.* (25), and Saydah *et al.* (17) used ICD10 codes (I10–I79, I20–I79, and I00–I09, -11, -13, and -20–51). Kaplan *et al.* (28) defined

TABLE 3. Meta-analysis IGF-I and mortality

First author, year	Low IGF-I HR (95% CI)	Reference	High IGF-I HR (95% CI)	Categories
All-cause mortality				
Andreassen, 2009	— ^a	1.0	1.52 (1.01–2.28)	Quartiles ^b
Arai, 2008	1.35 (1.03–1.76)	1.0	1.05 (0.72–1.54)	Tertiles
Brugts, 2008	1.29 (0.76–2.18)	1.0	1.42 (1.00–2.00)	Quartiles
Van Bunderen, 2010	1.28 (1.01–1.63)	1.0	1.17 (0.90–1.53)	Quintiles
Cappola, 2003	1.29 (0.94–1.78)	1.0	— ^a	Quartiles ^c
Friedrich, 2009, men	1.92 (1.35–2.73)	1.0	1.24 (0.81–1.89)	Deciles
Friedrich, 2009, women	0.76 (0.40–1.47)	1.0	0.57 (0.25–1.31)	Deciles
Kaplan, 2008	1.18 (0.89–1.54)	1.0	0.99 (0.67–1.47)	Tertiles
Maggio, 2007	1.36 (0.78–2.38)	1.0	— ^a	Quartiles ^c
Saydah, 2007	0.83 (0.53–1.28)	1.0	1.15 (0.87–1.53)	Quartiles
Pooled estimate	1.27 (1.10–1.46)	1.0	1.18 (1.04–1.34)	
Cancer mortality				
Van Bunderen, 2010	1.09 (.54–2.22)	1.0	1.11 (0.41–3.00)	Quintiles
Friedrich, 2009	1.85 (1.00–3.45)	1.0	1.19 (0.57–2.48)	Deciles
Major, 2010	— ^a	1.0	1.82 (1.11–2.96)	46th percentile ^d
Pham, 2010	1.10 (0.93–1.28)	1.0	1.02 (0.74–1.41)	Quartiles
Saydah, 2007	1.07 (0.36–3.24)	1.0	0.67 (0.38–1.16)	Quartiles
Pooled estimate	1.14 (0.98–1.33)	1.0	1.11 (0.79–1.55)	
CVD mortality				
Van Bunderen, 2010	2.39 (1.22–4.66)	1.0	2.03 (1.02–4.06)	Quintiles
Friedrich, 2009 (men)	1.92 (1.00–3.71)	1.0	1.25 (0.57–2.75)	Deciles
Friedrich, 2009 (women)	0.83 (0.25–2.76)	1.0	0.67 (0.16–2.85)	Deciles
Kaplan, 2007 (MI)	1.25 (0.52–2.94)	1.0	1.38 (0.42–4.53)	Tertiles
Kaplan, 2007 (CHD)	0.98 (0.62–1.56)	1.0	0.98 (0.50–1.91)	Tertiles
Saydah, 2007	0.88 (0.37–2.06)	1.0	0.89 (0.54–1.47)	Quartiles
Pooled estimate	1.32 (0.93–1.89)	1.0	1.13 (0.84–1.53)	

^a No HR could be calculated.

^b Comparing highest quartile with lowest three quartiles.

^c Comparing lowest quartile with highest three quartiles.

^d Comparing people above with people below 46th percentile (author defined).

two groups: first, fatal myocardial infarction (MI) in patients who met all predefined criteria for MI, and second, deaths of coronary heart disease that did not meet the predefined criteria. Comparison of subjects in the lowest category *vs.* the middle category showed a HR of 1.32 (95% CI = 0.93–1.53). The HR for the comparison of the highest *vs.* the middle IGF-I category was 1.13 (95% CI = 0.84–1.53).

IGFBP-3 and all-cause mortality (Table 4)

Four studies reported on the relation of IGFBP-3 on all-cause mortality. Results were adjusted for IGF-I in one

study (17). Adjustment for IGF-I did not change the results in another study and was therefore not performed (14). The two remaining studies did not adjust their results for IGF-I. In our analyses, three of four studies reporting the relationship between IGFBP-3 and mortality adjusted results for smoking (16, 17, 24). A random-effects model showed a higher mortality for subjects in the lowest category of IGFBP-3 compared with the middle category with a HR of 1.40 (95% CI = 1.17–1.68). Subjects in the highest category of IGFBP-3 compared with the middle category showed a HR of 0.90 (95% CI = 0.75–1.08).

TABLE 4. Meta-analysis of IGFBP-3 and all-cause mortality

First author, year	Low IGFBP-3 HR (95% CI)	Reference	High IGFBP-3 HR (95% CI)	Categories
Arai, 2008	1.19 (0.71–1.99)	1.0	0.96 (0.67–1.38)	Tertiles
Friedrich, 2009 (men)	1.87 (1.31–2.67)	1.0	1.04 (0.66–1.64)	Deciles
Friedrich, 2009 (women)	1.63 (0.96–2.77)	1.0	0.63 (0.27–1.47)	Deciles
Kaplan, 2008	1.23 (0.94–1.61)	1.0	1.02 (0.69–1.51)	Tertiles
Saydah, 2007	1.26 (0.80–1.98)	1.0	0.78 (0.57–1.07)	Quartiles
Pooled estimate	1.40 (1.17–1.68)	1.0	0.90 (0.75–1.08)	

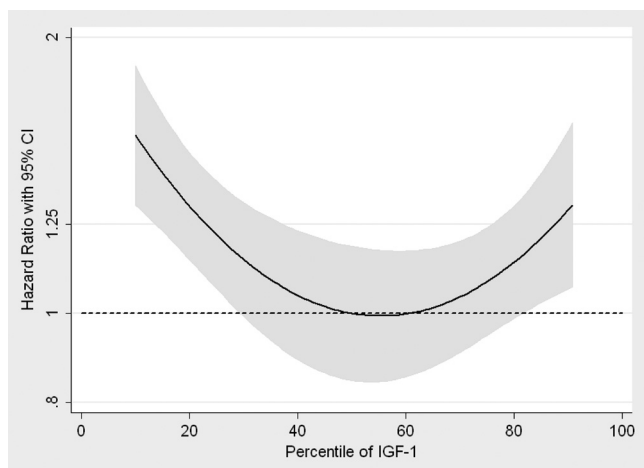


FIG. 2. Predicted HR for the association between IGF-I and all-cause mortality.

IGF-I and mortality: dose response meta-regression (Fig. 2)

We performed a meta-regression for a more detailed assessment of the effect of IGF-I on mortality. Because of the expected U-shaped association between IGF-I and mortality, IGF-I was also included as the quadratic term. This quadratic term was significantly associated with mortality ($P = 0.003$). The calculated IGF-I percentile associated with the lowest mortality was the 55th percentile. The predicted HR for the increase in mortality comparing the 10th IGF-I percentile with the 50th percentile was 1.56 (95% CI = 1.31–1.86); the predicted HR for the increase in mortality comparing the 90th with the 50th percentile was 1.29 (95% CI = 1.06–1.58).

For cancer mortality (HR = 1.91; 95% CI = 1.71–2.14) and CVD mortality (HR = 1.80; 95% CI = 1.61–2.00), mortality was increased in the 10th IGF-I percentile compared with the 50th percentile. Also for the 90th compared with the 50th percentile, cancer mortality (HR = 1.16; 95% CI = 1.07–1.27) and CVD mortality (HR = 1.17; 95% CI = 1.06–1.29) were increased.

Discussion

The present meta-analysis showed a significant but non-linear relationship between IGF-I and mortality, because both low and high IGF-I appear to be determinants for increased all-cause mortality. Surprisingly, cancer mortality as well as cardiovascular mortality was higher in both subjects with low and subjects with high IGF-I levels.

A major strength of the meta-analysis is the large number of included participants (14,906). Moreover, the adequacy of follow-up in all included studies as well as the study endpoint (mortality), which is relatively resistant to

misclassification, contribute to the robustness of the results. However, not all studies assessing the association between IGF-I and mortality were suitable for inclusion in the analysis. Two of these excluded studies showed a non-significant effect of IGF-I on all-cause mortality (5, 20), the others showed a protective effect of high IGF-I (15) and a protective effect of low IGF-I (12), respectively.

Statistical modeling of the data in a dose-response meta-regression confirmed a U-shaped association between IGF-I and mortality. This confirmed that low as well as high levels of IGF-I translate into an increased mortality risk. The U-shaped relationship between IGF-I and mortality was expected based on pathophysiological effects of IGF-I, thereby reflecting a causal relationship between IGF-I and mortality. First, in acromegaly, a high IGF-I state is associated with increased all-cause mortality (29). Conversely, GH deficiency, a state of IGF-I deficiency, is associated with increased mortality as well (30). It should, however, be kept in mind that the association between IGF-I and mortality might be due to confounding. For example, patients with a bad nutritional state, muscle weakness, and immobility generally have lower IGF-I levels (13, 31). Such conditions can clearly confound the association between IGF-I and mortality, and it is hardly possible to adjust adequately for such difficult-to-measure variables as nutritional state or immobility.

Also for cancer mortality and CVD mortality, the data were best described by a U-shaped curve. It has already been shown that the risk of common cancers is enhanced with higher IGF-I levels (2). This effect is probably caused by the tumor-promoting effects of IGF-I. The reason for the observed association between cancer mortality and low IGF-I levels is less easily explained. Probably confounding may play a role, with cancer inducing lower IGF-I levels. However, in cohort studies with reasonably long follow-up, confounding due to the presence of cancer is a less likely explanation for the association between low IGF-I and cancer risk. The shortest follow-up in our meta-analysis was 5 yr.

Low as well as high IGF-I levels were associated with increased cardiovascular mortality. GH deficiency, reflected by low IGF-I levels, is a syndrome characterized by increased central adiposity, dyslipidemia, and an increased intima media thickness (32–35). These risk factors for CVD may explain the higher mortality of IHD and stroke in GH-deficient patients but also in subjects with low IGF-I levels. We hypothesize that the excess CVD mortality in subjects with high IGF-I levels could be due to other CVD like cardiac hypertrophy and valve calcification. This is seen in patients with acromegaly, a condition defined by persistent high IGF-I levels, where cardiovascular mortality is increased. Laughlin *et al.* (5) examined the influence of IGF-I on cardiovascular mortality, but

because results were not presented according to percentiles, this study was unsuitable for inclusion. In that study, low IGF-I levels were associated with higher mortality from IHD with a risk ratio of 1.38 (1.09–1.76), but not with non-IHD CVD mortality with a risk ratio of 1.03 (0.83–1.28) (5). These data support the results from our meta-analysis that low IGF-I increases the risk of CVD mortality and strengthen the hypothesis that CVD mortality of non-IHD causes may be increased in subjects with high IGF-I levels.

The study by Friedrich *et al.* (14) showed clear gender differences. Women with either low or high IGF-I levels showed a decreased all-cause and cardiovascular mortality compared with the mid category, whereas men showed an increased mortality. Only one of the other studies analyzed women separately and found a nonsignificant increase in mortality with lower IGF-I levels (13). Because the majority of studies adjusted their results for sex but did not analyze their data by sex, we were not able to perform additional analyses stratified by gender.

There are clinical implications from these data, especially for adult patients treated for GH deficiency. First, low IGF-I levels especially increase mortality, suggesting that GH therapy may probably reduce mortality. However, it is important to notice that causal interpretation for the association found between IGF-I and mortality is not straightforward (36). Second, administration of GH is generally monitored by regular measurement of IGF-I levels. Our data are suggestive of optimal IGF-I levels between 0 and +1 SD. Titration to higher levels of IGF-I might even be associated with an increased mortality risk.

In contrast to associations with total IGF-I, our meta-analysis showed that low, but not high, IGFBP-3 levels were associated with increased mortality. A possible explanation might be found in the earlier epidemiology studies that observed that low circulating IGFBP-3 levels (or a high IGF-I to IGFBP-3 ratio) were associated with increased cancer risk and, by extrapolation, cancer mortality. However, a recent review summarizing updated pooled analyses of these associations shows that the previously noted inverse associations are now, in the main, positive (*e.g.* prostate, breast, and colorectal cancers) (3). A more likely explanation is found in the interrelationship between IGFBP-3 and smoking, the latter being a major risk factor for mortality. Thus, cigarette smoking consistently is associated with lower IGFBP-3 levels (approximately 20% reduction in mean levels) in a dose-dependent manner, particularly in men (37–39). However, this potential explanation is not directly supported by our analysis, because the majority of studies analyzing the association between IGFBP-3 and mortality, adjusted for smoking.

In conclusion, our findings suggest that IGF-I and IGFBP-3 are associated with mortality. Both low and high IGF-I increased all-cause, CVD, and cancer mortality, whereas only low IGFBP-3 is associated with mortality. Our data are suggestive of optimal IGF-I levels between 0 and +1 SD in adult patients. Whether this can be generalized to patients with GH deficiency needs to be investigated.

Appendix: Search Strategy

PubMed

(Insulin-like Growth Factor 1 OR Insulin-like Growth Factor I OR IGFBp-3 OR IGFBp3 OR IGFBP* OR Insulin-Like Somatomedin Peptide I OR Insulin Like Somatomedin Peptide I OR Somatomedin C OR IGF-I-SmC OR IGF-I OR IGF-I OR IGF1 OR IGFI OR Insulin Like Growth Factor I OR Insulin-Like Growth Factor Binding Proteins OR Insulin-Like Growth Factor Binding Protein OR Insulin Like Growth Factor Binding Proteins OR Insulin Like Growth Factor Binding Protein) AND (mortality OR ((death OR deaths) NOT (“cell death” OR “apoptotic death”))) NOT (“animals”[MeSH Terms:noexp] NOT “humans”[MeSH Terms]).

EMBASE (OVID version)

(*somatomedin binding protein/ OR *somatomedin binding protein 1/ OR *somatomedin binding protein 2/ OR *somatomedin binding protein 3/ OR *somatomedin binding protein 4/ OR *somatomedin binding protein 5/ OR *somatomedin binding protein 6/ OR *somatomedin/ OR *somatomedin A/ OR *somatomedin B/ OR *somatomedin C/ OR *somatomedin C derivative/ OR (Insulin-like Growth Factor 1 OR Insulin-like Growth Factor I OR IGFBp-3 OR IGFBp3 OR IGFBP* OR Insulin-Like Somatomedin Peptide I OR Insulin Like Somatomedin Peptide I OR Somatomedin C OR IGF-I-SmC OR IGF-I OR IGF-I OR IGF1 OR IGFI OR Insulin Like Growth Factor I OR Insulin-Like Growth Factor Binding Proteins OR Insulin-Like Growth Factor Binding Protein OR Insulin Like Growth Factor Binding Proteins OR Insulin Like Growth Factor Binding Protein).ti) AND (exp mortality/ OR mortality.mp).

Web of Science

TI = (somatomedin* OR Insulin-like Growth Factor* OR Insulin-like Growth Factor* OR IGFBp-3 OR IGFBp3 OR IGFBP* OR IGF-I-SmC OR IGF-I OR IGF-I OR IGF1 OR IGFI OR Insulin Like Growth Factor*) AND TS = mortalit* NOT TI = (mice OR mouse OR rat OR rats OR animal).

Cochrane Library

- #1 MeSH descriptor Somatomedins explode all trees.
- #2 MeSH descriptor Insulin-Like Growth Factor Binding Proteins explode all trees.
- #3 (Insulin-like Growth Factor 1 OR Insulin-like Growth Factor I OR IGFBp-3 OR IGFBp3 OR IGFBP* OR Insulin-Like Somatomedin Peptide I OR Insulin Like Somatomedin Peptide I OR Somatomedin C OR IGF-I-SmC OR IGF-I OR IGF-I OR IGF1 OR IGFI OR Insulin Like Growth Factor I OR Insulin-Like Growth Factor Binding Proteins OR Insulin-Like Growth Factor

Binding Protein OR Insulin Like Growth Factor Binding Proteins OR Insulin Like Growth Factor Binding Protein):ti,ab,kw.

#4 (#1 OR #2 OR #3).

#5 MeSH descriptor Mortality explode all trees.

#6 (mortality):ti,ab,kw.

#7 (#5 OR #6).

#8 (#7 AND #4).

Acknowledgments

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Disclosure Summary: A.G.R. received research grants from Novo Nordisk. The other authors have nothing to disclose.

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