66° SIGG CONGRESSO NAZIONALE
ROMA, 1-4 DICEMBRE 2021
Geriatria e Rinascita
SOCIETÀ ITALIANA DI GERONTOLOGIA E GERIATRIA

RUOLO DEL SISTEMA IGF-1/INSULINA NELL'INVECCHIAMENTO IN BUONA SALUTE

Prof. Giovanni Vitale

Department of Medical Biotechnology and Translational Medicine, University of Milan

Laboratory of Geriatric and Oncologic Neuroendocrinology Research,
Istituto Auxologico Italiano IRCCS, Milan Italy

16:30–19:00 *Sessione 2*

Conduce: Maria Rosaria Rizzo (Napoli)

16:30–16:50 *Lettura*

RUOLO DEL SISTEMA IGF-1/INSULINA NELL'INVECCHIAMENTO IN BUONA SALUTE

Giovanni Vitale (Milano)

16:50–17:10 *Lettura*

BIOMARCATORI EPIGENETICI PREDITTIVI DI MORTALITÀ IN PAZIENTI CON MULTIMORBIDITÀ

Francesco Piacenza (Ancona)

17:10–17:30 *Lettura*

QUALI SONO LE PRIORITÀ PER I PAZIENTI A RISCHIO DI DECADIMENTO COGNITIVO E FUNZIONALE?

Luisa Sist (Bologna)

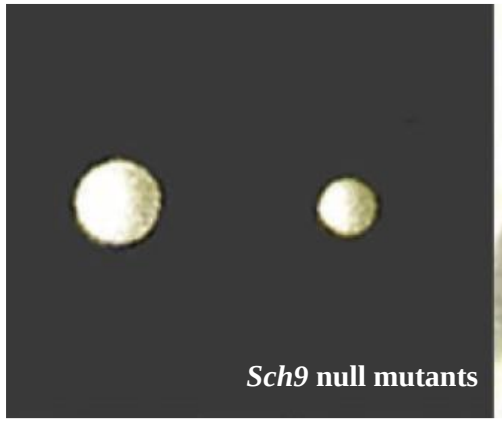
1958 2008 ISTITUTO AUXOLOGICO ITALIANO
istituto di ricovero e cura a carattere scientifico

Science
AAAS

Evolutionary Medicine: From Dwarf Model Systems to Healthy Centenarians?

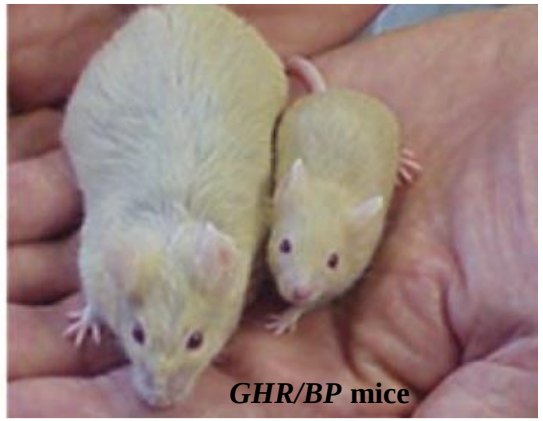
Valter D. Longo, *et al.*
Science **299**, 1342 (2003);
DOI: 10.1126/science.1077991

In several models mutations that affect the GH or insulin/IGF-I signaling generates mutants with smaller size but with a significant life-span extension.

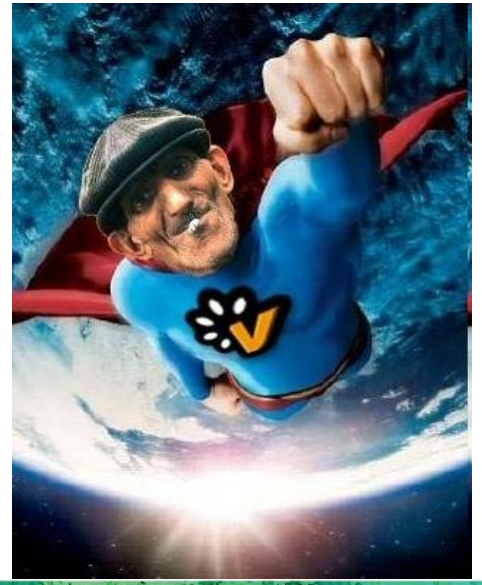


***Sch9* null mutants**

***Chico* homozygous mutant**

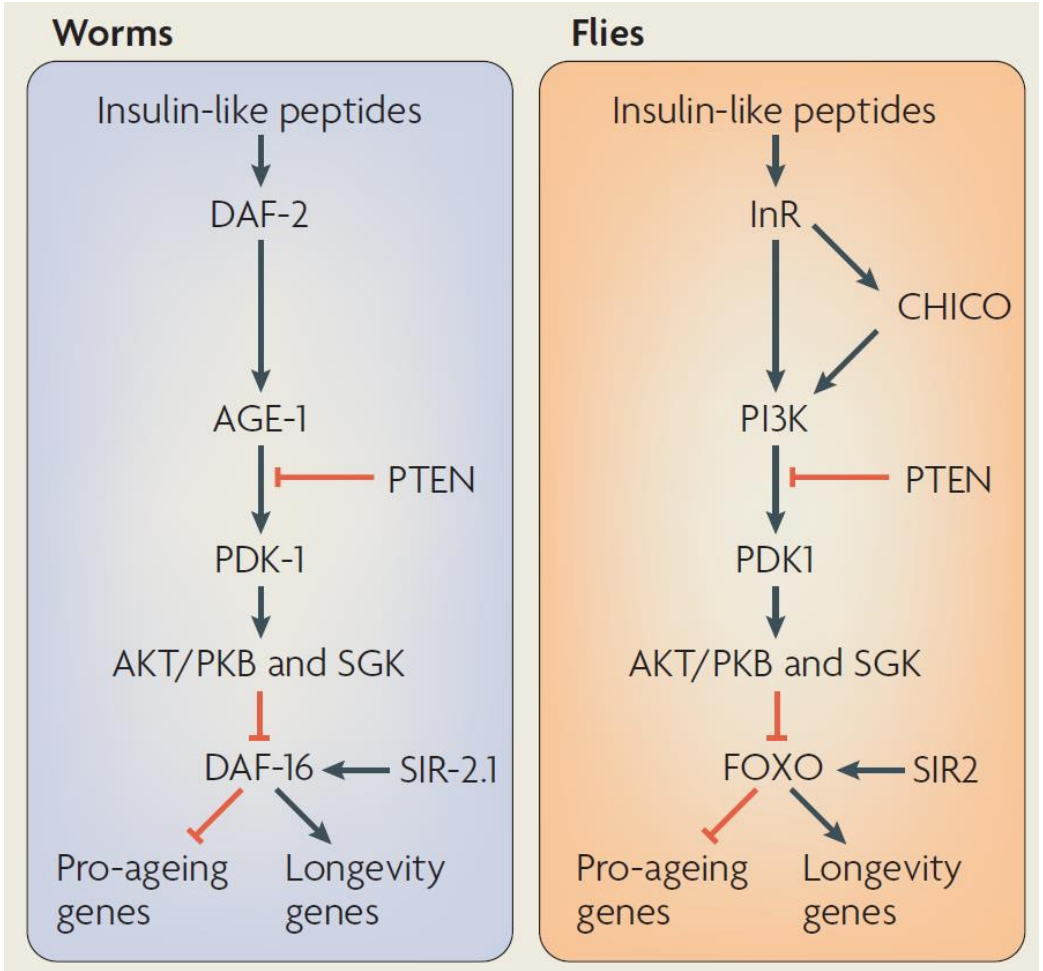


***GHR/BP* mice**



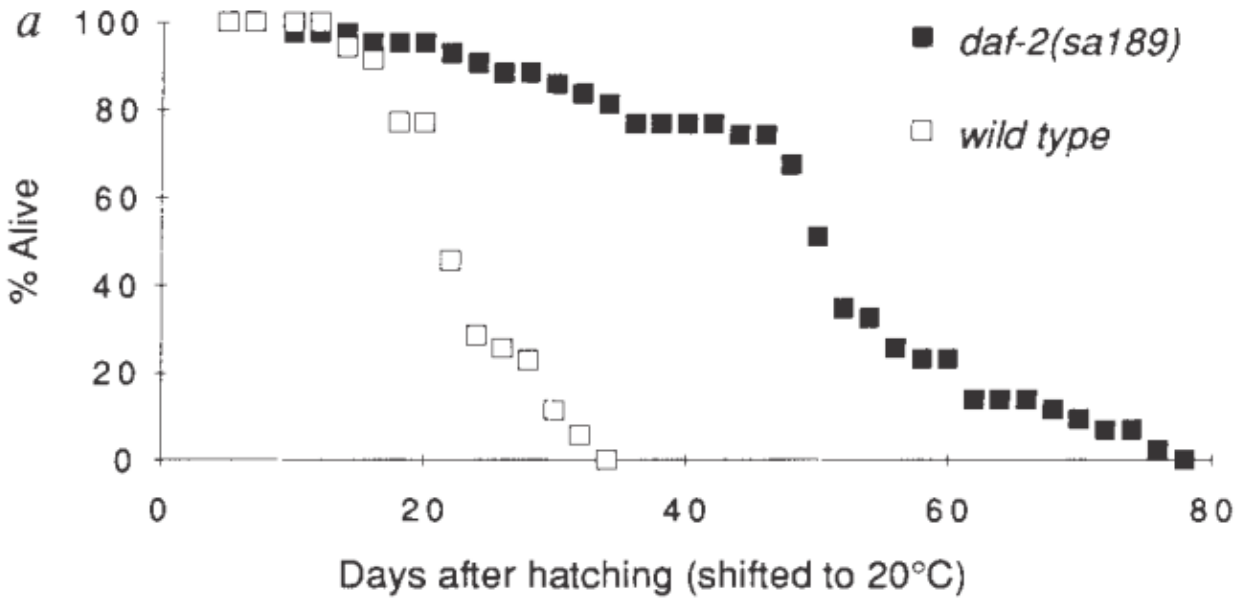
Nematode and Fly insulin-like signaling pathway

Caenorhabditis elegans

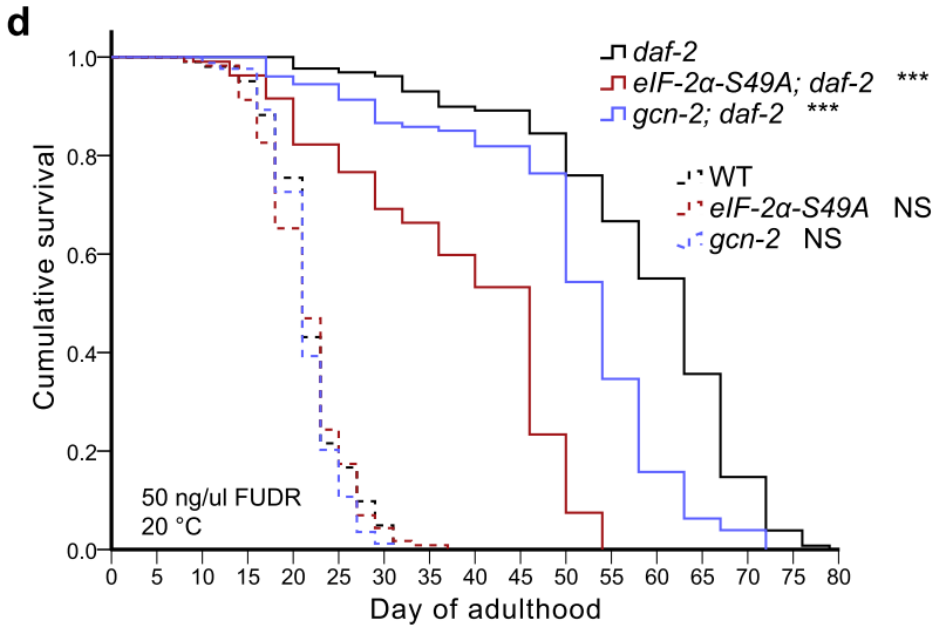


Drosophila melanogaster

NATURE · VOL 366 · 2 DECEMBER 1993



NATURE COMMUNICATIONS | (2021)12:4568



Caenorhabditis elegans Daf-2 mutants live more than twice as long as wild type.

Reducing the activity of IIS significantly extends lifespan primarily through phosphorylation

Table 1. Selective Mouse Models With GH/IGF Axis Mutations and Their Effect on Longevity

Mouse	Mutation	Mechanism	Maximum Life Span, % Increase	Reference
Ames dwarf	Prop1	Loss of Prop1 transcription factor leading to pituitary defect	68%	(52)
Snell dwarf	Pit1	Loss of Pit1 transcription factor leading to pituitary defect	42%	(53)
Little	(lit/lit), ghrhr$^{-/-}$	GHRH null mice leading to suppressed GH release	24%	(53, 54)
Laron	GHR/BP$^{-/-}$	GHR null mice: unresponsive to GH	55%	(55, 56)
IGF-1R KO	IGF-1R$^{+/-}$	Heterozygous for disrupted Igf1R allele	33% dependent on genetic background	(18, 57)
Midi	IGF-1 exon 3 $^{neo/neo}$	Hypomorphic for IGF-1 due to insertion in *Igf1* gene	10% in maximum life span	(58, 59)
p66^{sch} KO	p66^{sch} $^{-/-}$	Mice harboring null allele for p66, an intracellular signaling molecule responsive to IGF-1R	30% not reproduced in subsequent studies	(19, 60)
PAPPA KO	PAPPA$^{-/-}$	Mice null for PAPPA, a metalloproteinase, which cleave IGFBPs to increase bioavailability of IGF-1	41%	(61)
IRS-1 KO	IRS-1$^{-/-}$	Mice null for IRS-1a, a critical docking protein that binds the IGF-1R and serves to recruit multiple intracellular second-messenger proteins	32% females only	(21)
IRS-2 KO	IRS-2$^{+/-}$	IGF-1 intracellular signaling molecule highly homologous to IRS-1	17%, 18% in brain specific	(62)
LID	Liver-specific deletion of IGF-1	IGF-1 gene deletion mediated by Cre/lox system specifically in liver	No increase decrease in males	(25)
LiGHR	Liver-specific deletion of *GHR* gene	GHR gene deleted at 1 y through the use of inducible Cre/lox system	No increase	(25)

BP, binding protein; IRS, insulin receptor substrate; KO, knockout.

Extending Lifespan by Modulating the Growth Hormone/Insulin-like Growth Factor-1 Axis: Coming of Age

Pituitary. 2021 June ; 24(3): 438–456. doi:10.1007/s11102-020-01117-0.

Silvana Duran-Ortiz[1,2,3], Edward O. List[1], Reetobrata Basu[1], John J Kopchick[1,3,4]

Mouse Lines with Postnatal Reduction of GH/IGF-1 Signaling.

Glucose metabolism and longevity of mice with postnatal disrupted GH and/or IGF-1 action. aGHRKO (adult onset growth hormone receptor knockout mice), AOiGHD (adult-inducible growth hormone deficient mice), UBIKOR (ubiquitous inducible insulin growth factor-1 receptor knockout mice), LI-IGF-$1^{-/-}$ (liver-specific IGF-1 inactivation mice), LID (liver-specific IGF-1 deficient mice), fPAPP-A/pos (floxed pregnancy-associated plasma protein-A positive).

	aGHRKO	AOiGHD	UBIKOR	LI-IGF-$1^{-/-}$	LID	L2-Cmu treated mice	fPAPP-A/pos
Strategy to reduce GH and/or IGF-1 action	Cre-lox system driven by the Rosa26 locus to ablate the Ghr gene	Somatotroph cell ablation by diphtheria toxin	Cre-lox system driven by the Ubiquitin promoter to ablate the Igf-1r gene	Cre-lox system driven by the Mx-Cre promoter to ablate the Igf-1 gene in the liver	Floxed Igf-1 gene. Cre (driven by either albumin or thyroxine binding globin promoter)	Use of an antibody (L2-Cmu) to target the IGF-1R	Cre-lox system driven by the chicken β-actin promoter to ablate the PAPP-A gene
Age of treatment	6 weeks	10–12 weeks	3 months	1 month	10 days, and 5 and 15 months	18 months and onwards	5 months
Body size	↓	↓	↓	↔	↓	↔	↔
Fat Mass	↑	**↔↑	↑	↓	*↔↓	↔	
Serum glucose	*↔↓	↓	↑	↔			
Serum insulin	↔↓	↓	↑	↑		↔	
Glucose tolerance	↑	**↔↓	↓	↔	↔*		
Insulin sensitivity	↑	↑	↓	↓	↓*	↔	
Longevity	↑*			↑*	↑*	↑*	↑*

Symbols indicate increases (↑), decreases (↓), no change (↔), changes in one sex (*), and diet dependent variations (**) relative to controls.

Reduction of the GH/IGF-1 axis at an adult age extends lifespan preferentially in females.

SOMATOTROPIC SIGNALING: TRADE-OFFS BETWEEN GROWTH, REPRODUCTIVE DEVELOPMENT, AND LONGEVITY

Andrzej Bartke, Liou Y. Sun, and Valter Longo

Physiol Rev 93: 571–598, 2013

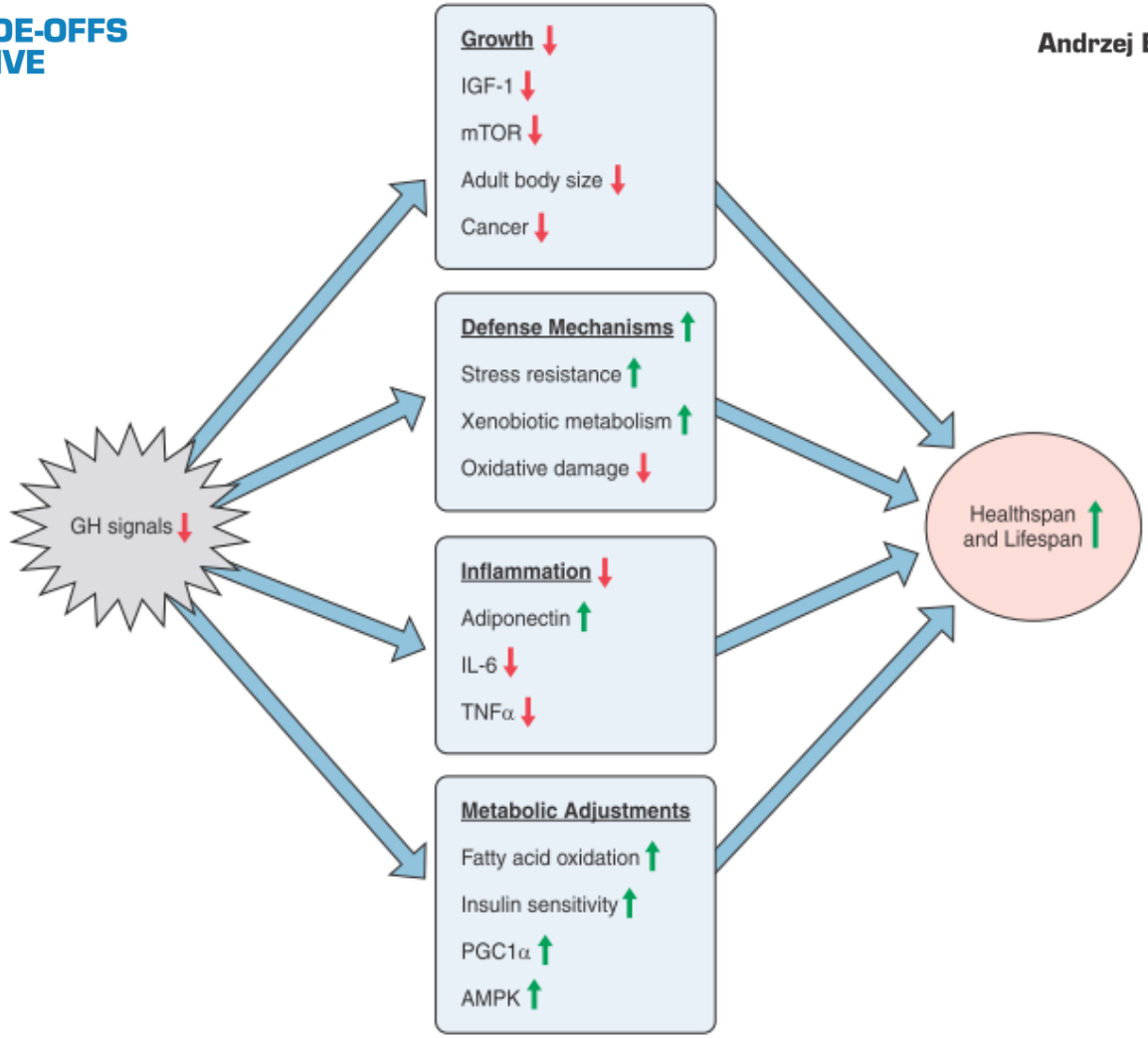


FIGURE 5. Mechanisms believed to be involved in linking GH signaling with healthspan and lifespan. Details and references are in the text and in **TABLE 2**.

Nat. Rev. Endocrinol. **9**, 366–376 (2013)

Table 1 | Mouse strains with altered GH/IGF-1 axis and effects on longevity

Mouse model	Size (% of control)	Lifespan (change in %)	Lifespan (days)		Background strain	Body fat	Insulin sensitivity	Tumour incidence	Stress resistance
			Mutant	Control					
Pit1 Snell[7,8,10–12,92]	25–33	F and M +42	F and M 1,178±235	F and M 832±158	C3H/HeJ x DW/J	↑	↑	↓	↑
Prop1 Ames[14,17,92,99,112]	33	F +68 M +49	F 1,206±32 M 1,076±56	F 718±45 M 723±54	ND	↑	↑	↓	↑
GHRHr *lit/lit*[10,24,97,100]	50–67	F +25 M +23	F 1,070±127 M 1,093±186	F 857±169 M 886±148	C57BL/6J	↑	ND	↓	↑
GHr *Ghr*$^{-/-}$[35-37,92,101]	<50	F +21 M +40	F 921±41 M 917±55	F 759±41 M 656±67	Ola-BALB/cJ	↑	↑	↓	↑
GH Bovine GH transgenic mouse[49,50]	200	M –45%	M 425±22	M 773	ND	↓	↓	↑	ND
GHr antagonism GHA transgenic mouse[35,36,46,47,102]	70	NS	F 839±25 M 790±41	F 771±26 M 758±40	C57BL/6	↑	↑	↓	ND
Inducible liver-specific IGF-1 null LI-*Igf1*$^{-/-}$[60,61]	75–100	F +16	F 812±33 (26.7±1.1 months)	F 700±21 (23.0±0.7 months)	C57BL/6	↓	↓	ND	ND
Liver-specific IGF-1 def LID[59,62,113]	100	M ↓	ND	ND	ND	↑	↓	↓	ND
Pappalysin-1 Pappa$^{-/-}$[64,65,67]	40	F and M +38	F and M 960±28	F and M 698±23	C57BL/6 x 129SV/E	ND	↔	↓	ND
IGF-1r *Igf1r*$^{+/-}$[68]	90	F +33 M NS	F 756±46 M 679±80	F 568±49 M 585±69	129/J	ND	↓	ND	↑
IGF-1r *Igf1r*$^{+/-}$[69]	90	NS	F 923±21 M 983±21	F 967±29 M 939±24	C57BL/6	ND	↓	↔	F ↑ M ↔
Klotho Klotho transgenic mouse[73]	100	F1 & F2 +19* M1 +20 M2 +31	F1 829±32 F2 830±29 M1 858±40 M2 936±47	F 697±45 M 715±44	C57BL/6 x C3H	ND	F ↔ M ↓	ND	↑
Irs1 *Irs1*$^{-/-}$[76–80]	70	F +17 M NS	F 891±39 M 897±41	F 763±21 M 786±21	C57BL/6	↓	↓	ND	ND
Irs2 *Irs2*$^{+/-}$[81,82]	100	F and M +17	F and M 905±22	F and M 775±10	C57BL/6	ND	↑	ND	ND
Irs2 *Irs2*$^{+/-}$[76,79]	100	F and N NS	F and M 788±17	F and M 755±22	C57BL/6	ND	↔	ND	ND
Irs2 *Irs2*$^{-/-}$[79]	90	F –26 M –84	F 560±63 M 123±20	F 755±23 M 767±40	C57BL/6	ND	↓	ND	ND
Brain specific Irs2 Brain-specific *Irs2*$^{+/-}$ and *Irs2*$^{-/-}$[81]	100	F and M (+/–) +18 F and M (–/–) +14	ND	ND	C57BL/6	↑	↓	ND	ND
P66^{shc} isoform of SHC-transforming protein1 *p66*$^{shc+/-}$ and *p66*$^{shc-/-}$[84,85]	100	F and M (+/–) +7 F and M (–/–) +28	F and M (+/–) 815±37 F and M (–/–) 973±37	F and M 761±19	129/SvEv	↓	↔	ND	↑

Oxidative stress and the ageing endocrine system

Nat. Rev. Endocrinol. **9**, 228–240 (2013);

Giovanni Vitale, Stefano Salvioli and Claudio Franceschi

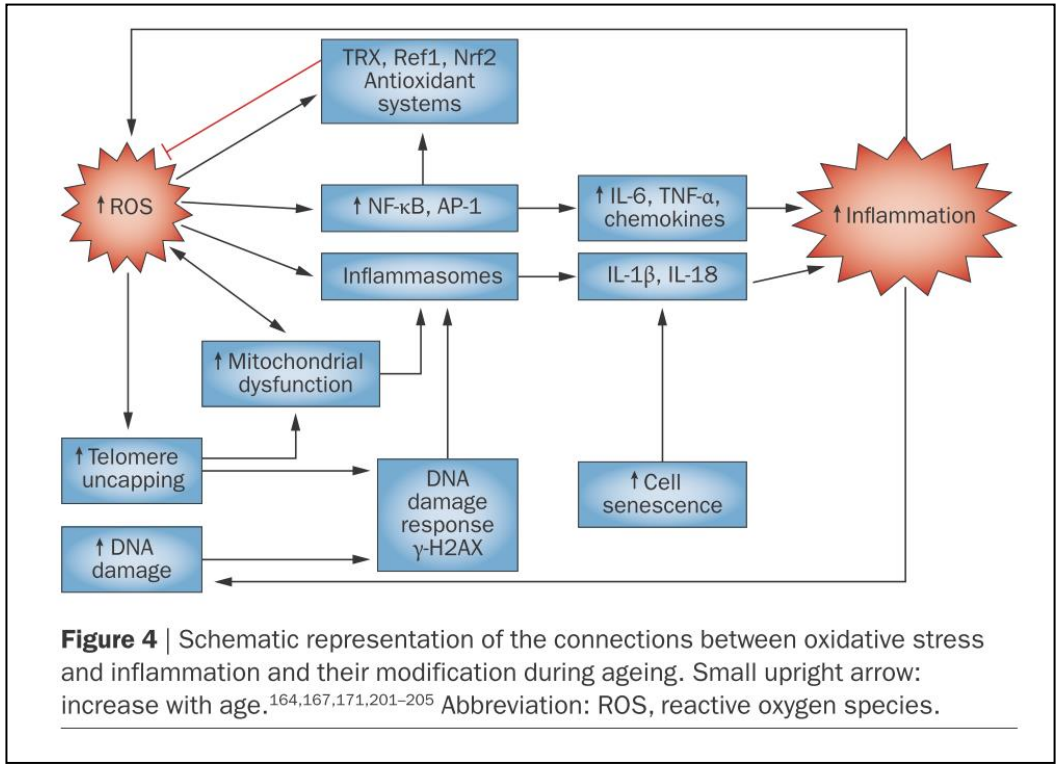
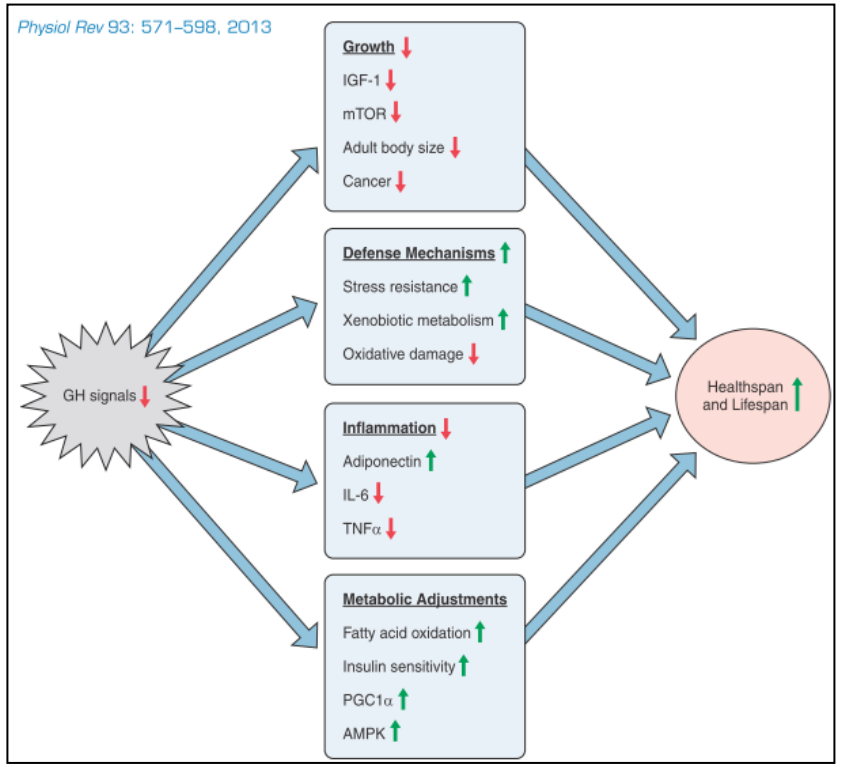


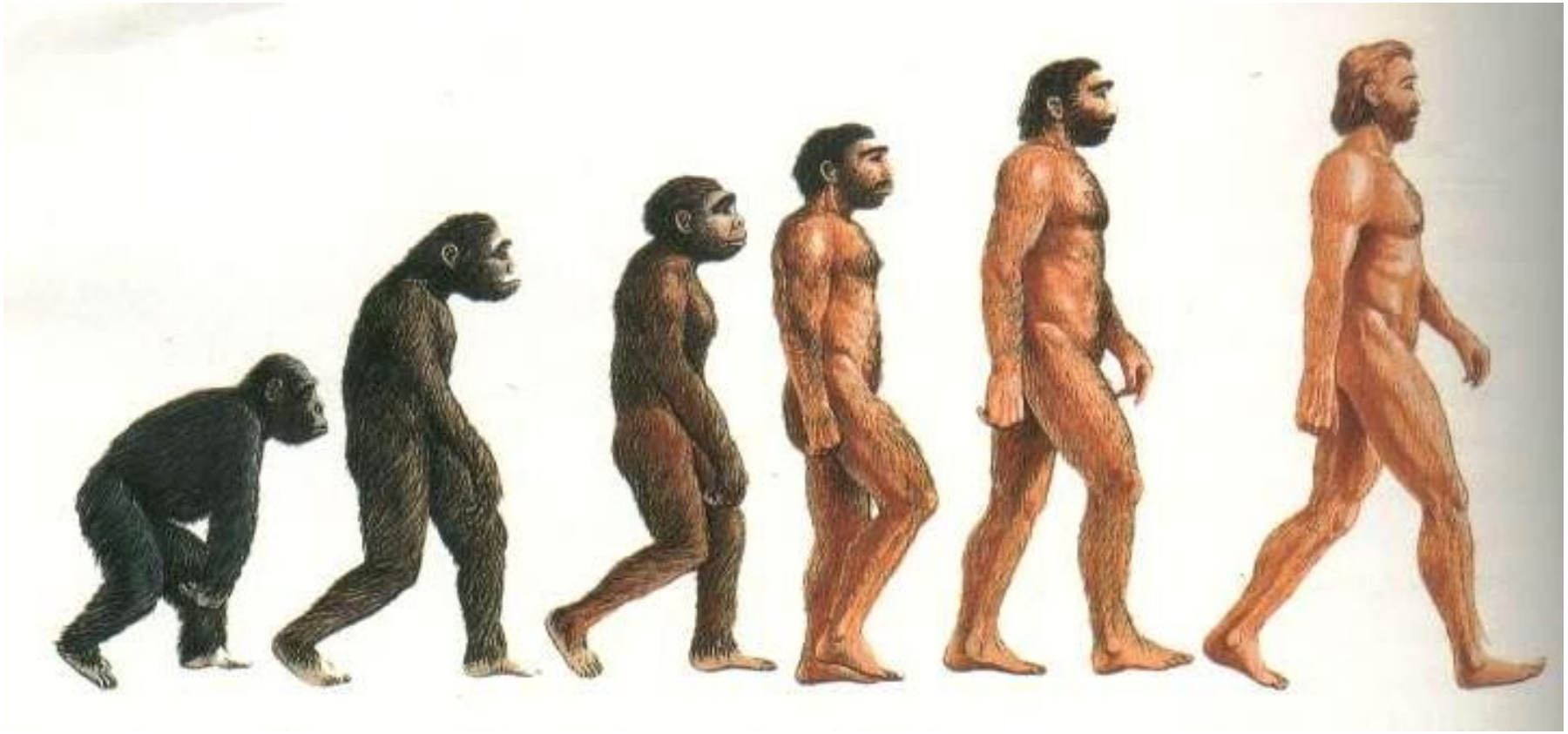
Figure 4 | Schematic representation of the connections between oxidative stress and inflammation and their modification during ageing. Small upright arrow: increase with age.[164,167,171,201–205] Abbreviation: ROS, reactive oxygen species.



'Inflamm-ageing': Human ageing is characterized by an increase in proinflammatory mediators. The majority of the age-associated diseases, such as type 2 diabetes mellitus, neurodegeneration, cancer, osteoarthritis, autoimmune and cardiovascular diseases, have an inflammatory background. Inflammation is intrinsically linked to oxidative stress. Thus, it can be surmised that unnecessary inflammatory responses characterize and probably cause the ageing phenotype.

A reduction in GH signaling may prolong lifespan through anti-inflammatory effects and an increase in stress resistance.

HUMANS



Contradictory results

ACROMEGALY/GIGANTISM

a. Andre Rousimoff 'Andre the Giant, le géant Férré', Francœ, 1946-1993, 2.18 m (7 ft. 2.in), wrestler, carrying four women.

The Hugo brothers, 'les Géants des Alpes' ('the Giants of the Alps'): Battista Ugo (Baptiste Hugo) 1876-1916, 2.30 m. (7 ft. 7 in.) and Paolo Antonio Ugo (Antoine Hugo) 1887-1914. 2.25 m. (7 ft. 5 in.) and their family.

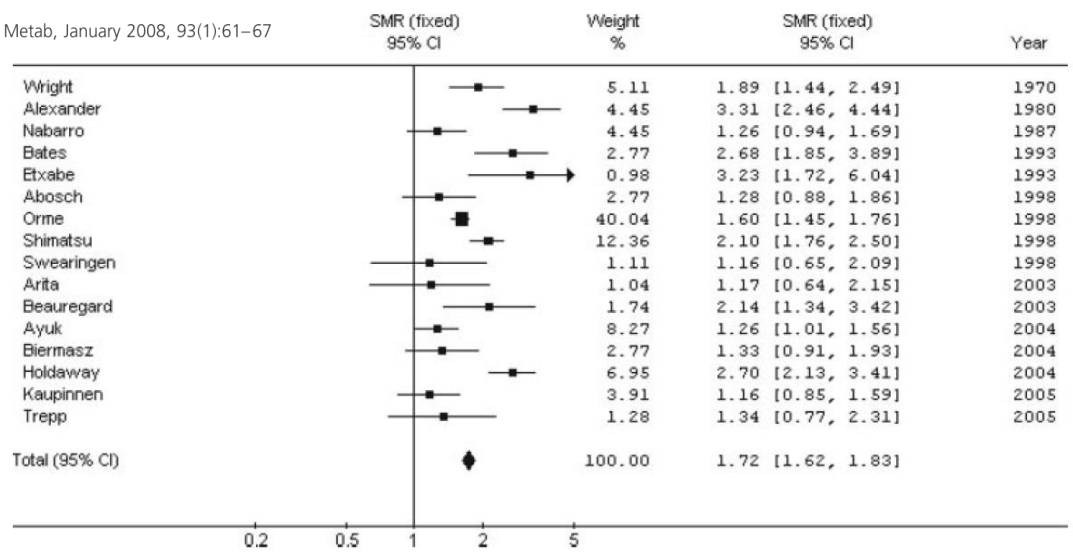
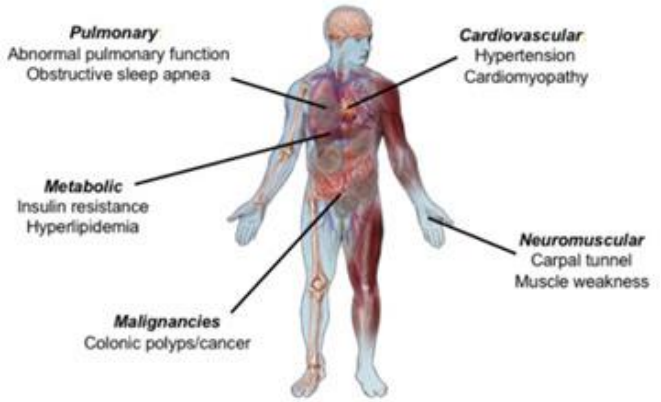


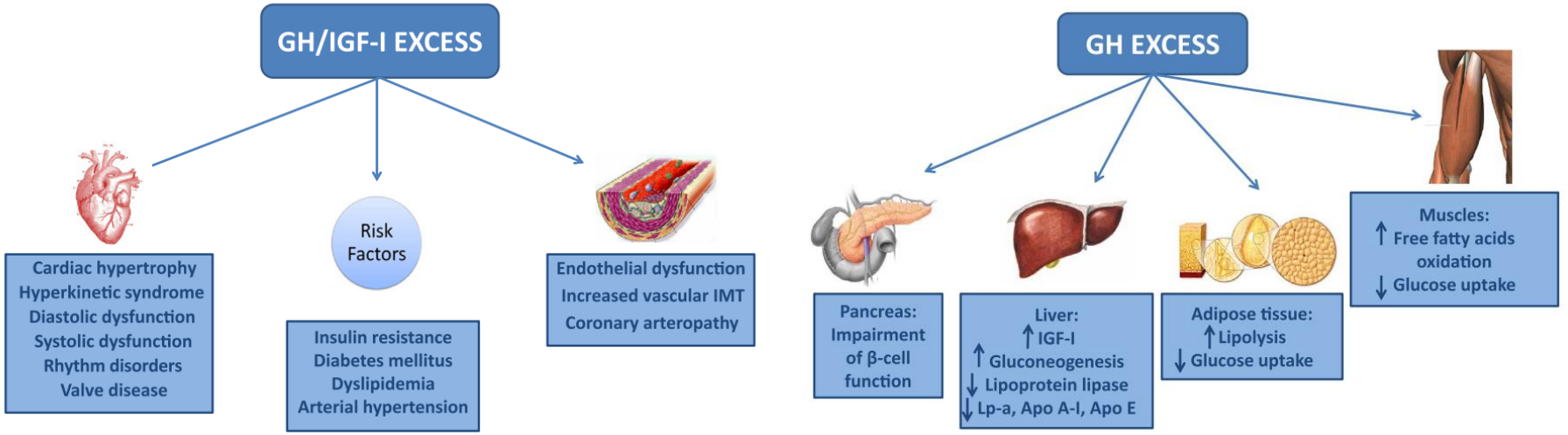
FIG 2. Metaanalysis of SMRs in acromegaly.



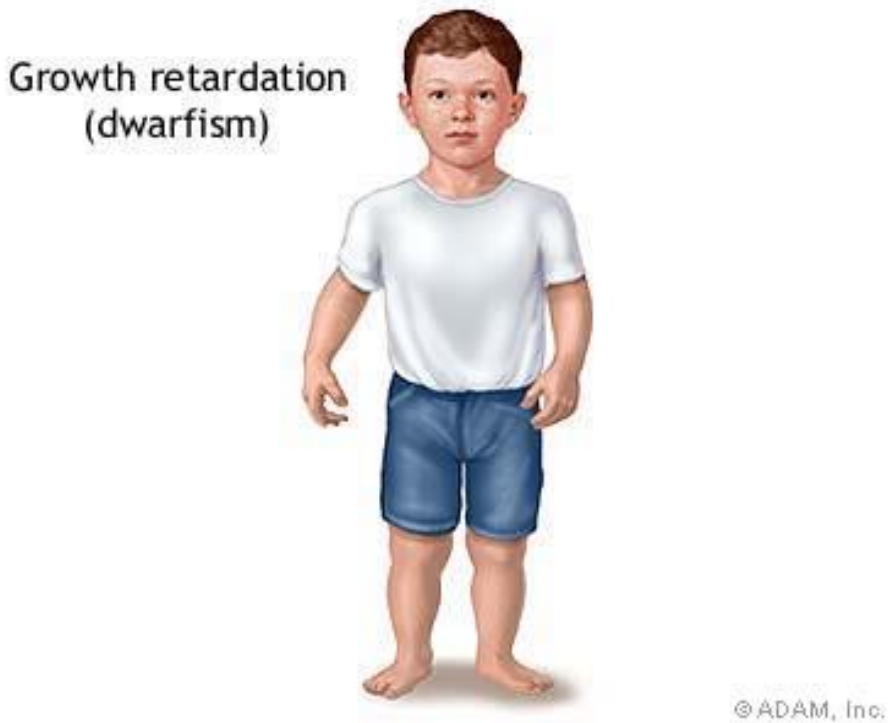
Complications of acromegaly: cardiovascular, respiratory and metabolic comorbidities

Rosario Pivonello[1] · Renata S. Auriemma[1] · Ludovica F. S. Grasso[1] · Claudia Pivonello[1] · Chiara Simeoli[1] · Roberta Patalano[1] · Mariano Galdiero[1] · Annamaria Colao[1]

Pituitary
Published online: 21 February 2017



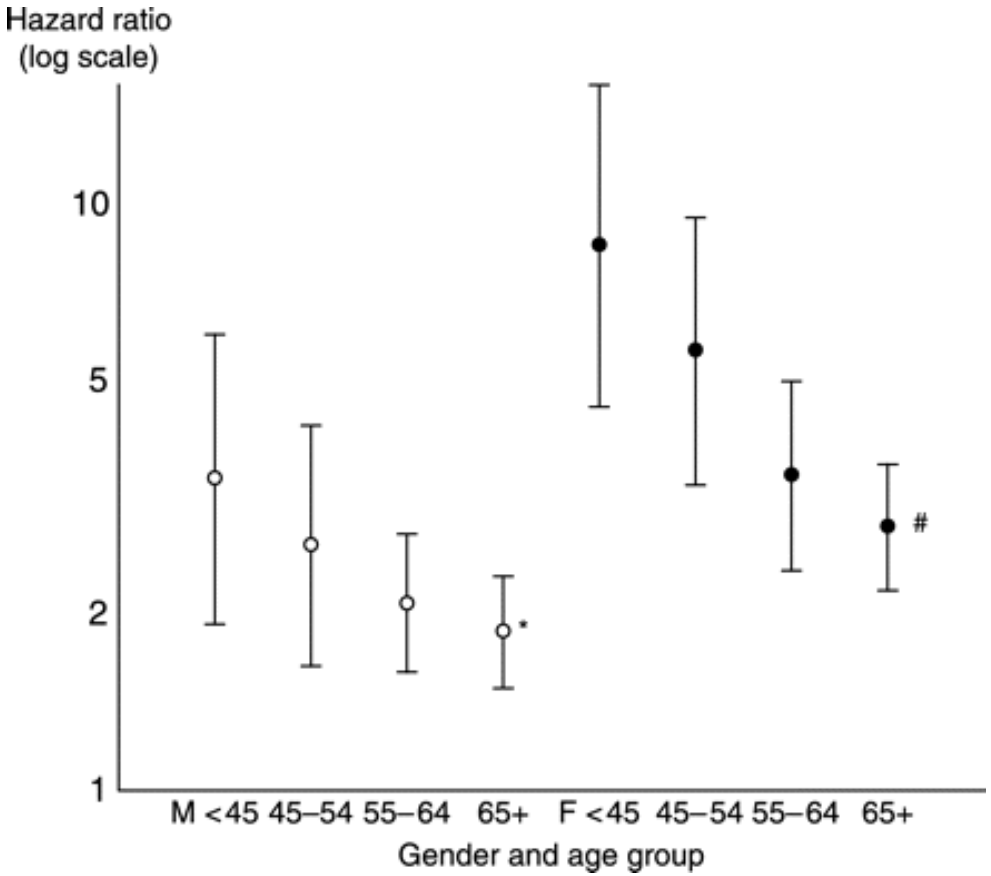
GH DEFICIENCY



Mortality and GH deficiency: a nationwide study

European Journal of Endocrinology (2007) 157 9–18

Kirstine Stochholm, Claus Højbjerg Gravholt, Torben Laursen[1], Peter Laurberg[2], Marianne Andersen[3], Lars Østergaard Kristensen[4], Ulla Feldt-Rasmussen[5], Jens Sandahl Christiansen, Morten Frydenberg[6] and Anders Green[7,8]



Hazard ratios of total mortality in adult-onset GHD, 1980–2004, subdivided into four age groups according to age at entry and gender. Open circles, males; black circles, females. Mortality is decreasing with increasing age at entry *$P < 0.05$ and $^{\#}P < 0.001$.

Deaths Among Adult Patients With Hypopituitarism: Hypocortisolism During Acute Stress, and De Novo Malignant Brain Tumors Contribute to an Increased Mortality

J Clin Endocrinol Metab, April 2013, 98(4):1466–1475

P. Burman, A. F. Mattsson, G. Johannsson, C. Höybye, H. Holmer, P. Dahlqvist, K. Berinder, B. E. Engström, B. Ekman, E. M. Erfurth, J. Svensson, J. Wahlberg, and F. A. Karlsson

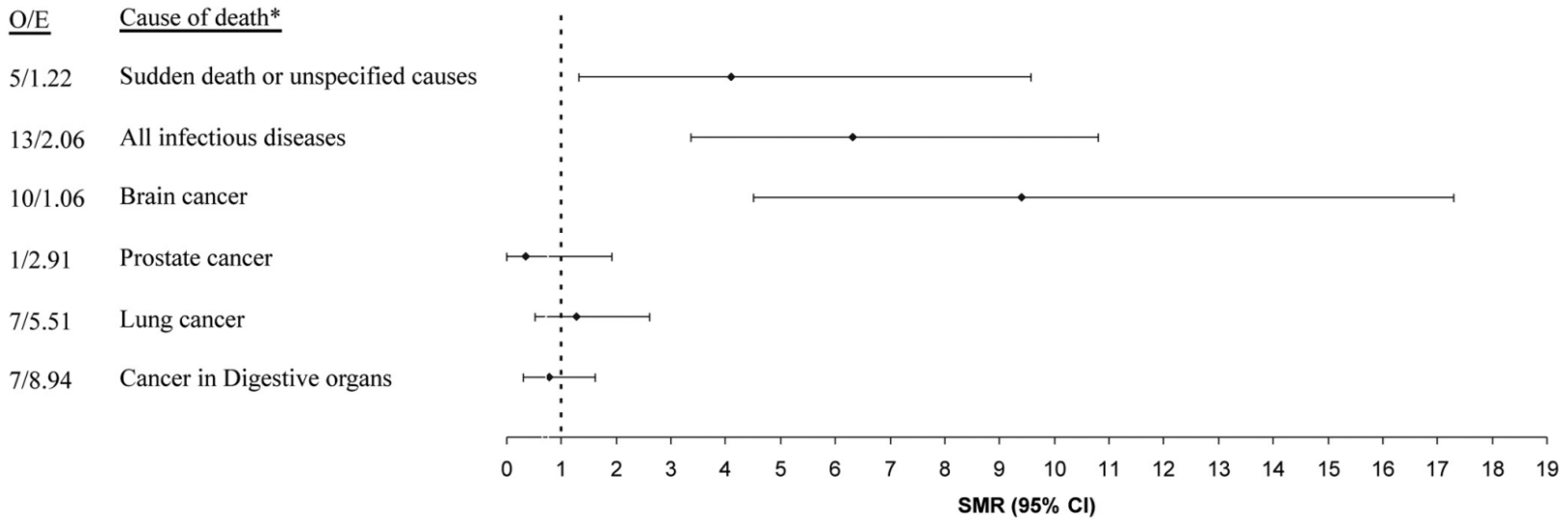


Figure 2. Cause-specific mortality for 1286 hypopituitary Swedish patients compared with the Swedish general population. The SMR (closed circles) and associated 95% CI were plotted for each cause of death. The observed (O) and expected (E) numbers of deaths for each cause of death are also shown. *Sudden death or unspecified causes: ICD-10: R96, R99. All infectious diseases ICD-10 codes: A08–09, A40–41, A46, A 48–49, B 99, J00–J22, G00–G09, K52. Brain cancer ICD-10: C70–C72. Prostate cancer ICD-10: C61. Lung cancer ICD-10: C34. Cancer in digestive organs: C15–C26. Breast cancer: C50. Note: There were no deaths from breast cancer vs an expected 1.84 deaths.

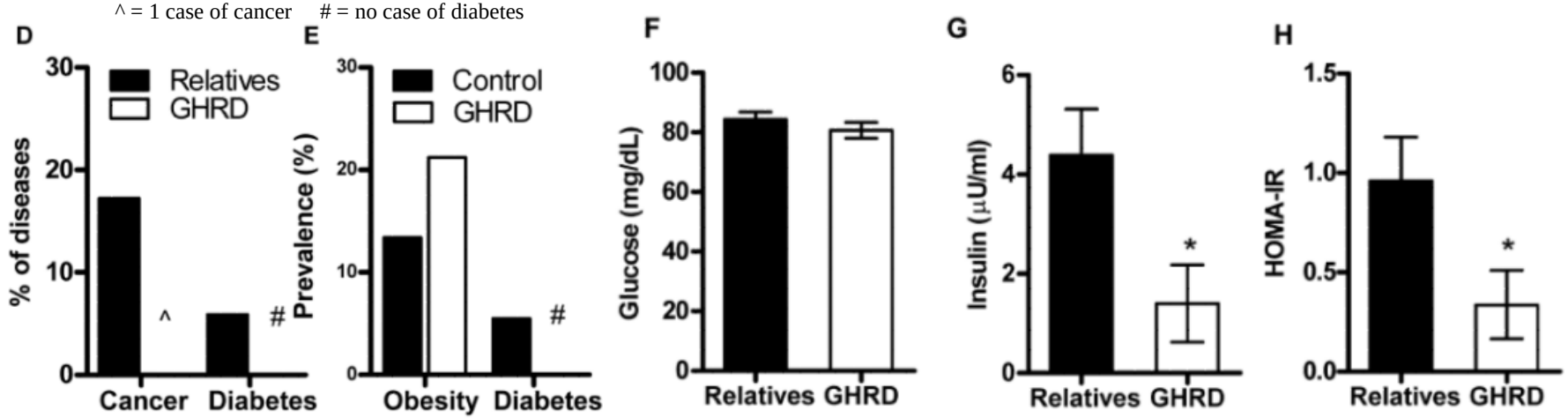
Two important causes of excess mortality were identified: first, *adrenal crisis* in response to acute stress and intercurrent illness; second, increased risk of a late appearance of de novo *malignant brain tumors* in patients who previously received *radiotherapy*.

Growth Hormone Receptor Deficiency is Associated With a Major Reduction in Pro-aging Signaling, Cancer and Diabetes in Humans

Jaime Guevara-Aguirre[1,*], Priya Balasubramanian[2,4,*], Marco Guevara-Aguirre[1], Min Wei[4], Federica Madia[4], Chia-Wei Cheng[4], David Hwang[5], Alejandro Martin-Montalvo[6,7], Jannette Saavedra[1], Sue Ingles[8], Rafael de Cabo[6], Pinchas Cohen[5], and Valter D. Longo[2,3,4]

Sci Transl Med. 2011 February 16; 3(70): 70ra13.

^ = 1 case of cancer # = no case of diabetes



Growth Defect Blocks Cancer and Diabetes

SCIENCE VOL 331 18 FEBRUARY 2011

Ecuadorian subjects with Laron syndrome mutations in the GH receptor (GHR) gene leading to severe IGF-I deficiency.

No change in life-span was observed in this population relative to control individuals. However, they showed an impressive protection from cancer and diabetes, despite the high prevalence of obesity.

J Clin Endocrinol Metab, July 2015, 100(7):2589–2596

GH Receptor Deficiency in Ecuadorian Adults Is Associated With Obesity and Enhanced Insulin Sensitivity

Jaime Guevara-Aguirre, Arlan L. Rosenbloom, Priya Balasubramanian, Enrique Teran, Marco Guevara-Aguirre, Carolina Guevara, Patricio Procel, Irene Alfaras, Rafael De Cabo, Stefano Di Biase, Luis Narvaez, Jannette Saavedra, and Valter D. Longo*

Table 1. Anthropometric Data, Lipid Metabolism, Carbohydrate Metabolism, and Insulin Sensitivity Measures for 35 Controls and 27 GHRD Subjects

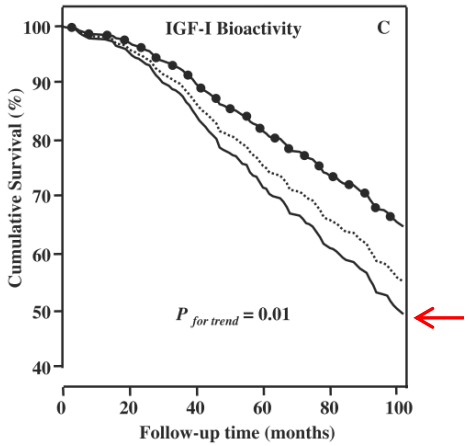
	Controls	GHRD	*P*
Anthropometrics			
Age, y	39.8 (13)	34.5 (11)	.09
SDS ht	−1.7 (1.2)	−7.4 (1.2)	<.0001
BMI, kg/m^2	29.4 (4.4)	27.6 (5.6)	.16
A/G fat	1.08 (0.18)	1.07 (0.09)	.79
% Fat	41.1 (6.6)	47.7 (8.9)	.0014
L/F	1.48 (0.47)	1.18 (0.48)	.016
Lipids			
Total C, mg/dL	199 (43.9)	229 (47.3)	.0124
HDL, mg/dL	43.5 (13.7)	50.9 (12.8)	.034
HDL-C, mg/dL	4.87 (1.33	4.65 (1.10)	.49
LDL, mg/dL	123.1 (37.5)	157.6 (37.4)	<.0001
Apo A, g/L	1.24 (0.23)	1.34 (0.23)	.0007
Apo B, g/L	0.95 (0.24)	1.085 (0.23)	.029
VLDL, mg/dL	31.5 (18.7)	20.2 (7.6)	.0044
TG, mg/dL	158.3 (95.3)	100.7 (37.8)	.0001
Carbohydrate metabolism, adipocytokines			
Fasting glucose, mg/dL	93.2 (22.4)	88.6 (10.6)	.34
Postprandial glucose, mg/dL	94.1 (35.4)	77.1 (13.4)	.027
Fasting insulin, μU/mL	13.8 (15.5)	4.29 (0.74)	.0034
HOMA2%B	141 (103)	90 (48)	.0206
HOMA2%S	108 (87)	261 (133)	<.0001
HOMA2-IR	1.74 (1.84)	0.59 (0.51)	.0025
Leptin, ng/mL	10.36 (5.24)	7.32 (4.7)	.0212
Adiponectin, mg/L	6.92 (4.41)	9.94 (4.84)	.0128
HMW adiponectin, mg/L	4.29 (2.89)	7.59 (4.07)	.0004

Abbreviations: SDS ht, SD score for height; C, cholesterol. Data are shown as mean (SD). Conversion factors: glucose to mmol/L, multiply by 0.0555; insulin to pmol/L, multiply by 6.945; LDL and VLDL to mmol/L, multiply by 0.0259; TGs to mmol/ L, multiply by 0.0113.

Low Circulating Insulin-Like Growth Factor I Bioactivity in Elderly Men Is Associated with Increased Mortality

J Clin Endocrinol Metab, July 2008, 93(7):2515–2522

M. P. Brugts, A. W. van den Beld, L. J. Hofland, K. van der Wansem, P. M. van Koetsveld, J. Frystyk, S. W. J. Lamberts, and J. A. M. J. L. Janssen



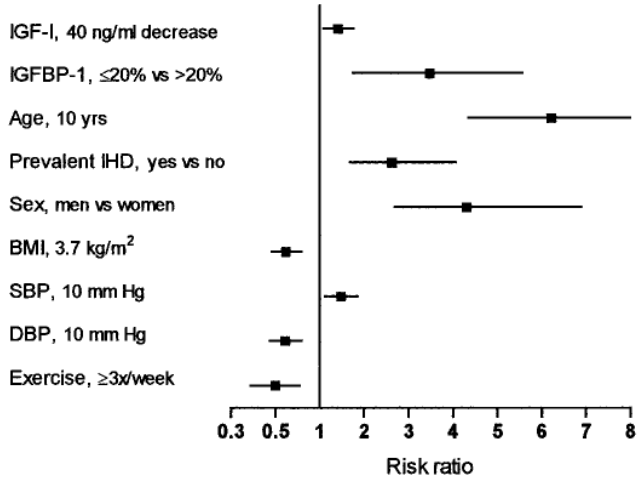
Group 1 (—): <25th percentile
Group 2–3 (– – –): between 25th and 75th percentile
Group 4 (-●-): >75th percentile.

Relatively *low circulating IGF-I bioactivity* in elderly men is associated with *reduced survival* and with increased cardiovascular risk.

The Prospective Association of Serum Insulin-Like Growth Factor I (IGF-I) and IGF-Binding Protein-1 Levels with All Cause and Cardiovascular Disease Mortality in Older Adults: The Rancho Bernardo Study

J Clin Endocrinol Metab, January 2004, 89(1):114–120

GAIL A. LAUGHLIN, ELIZABETH BARRETT-CONNOR, MICHAEL H. CRIQUI, AND DONNA KRITZ-SILVERSTEIN



Low baseline levels of IGF-I and IGFBP-1 **increase the risk of *fatal ischemic heart* disease among elderly men and women.**

GH as an antiaging therapy in elderly

IGF1 as predictor of all cause mortality and cardiovascular disease in an elderly population

Mikkel Andreassen[1], Ilan Raymond[2], Caroline Kistorp[1], Per Hildebrandt[3], Jens Faber[1] and Lars Østergaard Kristensen[1]

European Journal of Endocrinology (2009) **160** 25–31

High IGF-I **levels were independently associated with** ***increased*** **all cause** ***mortality***

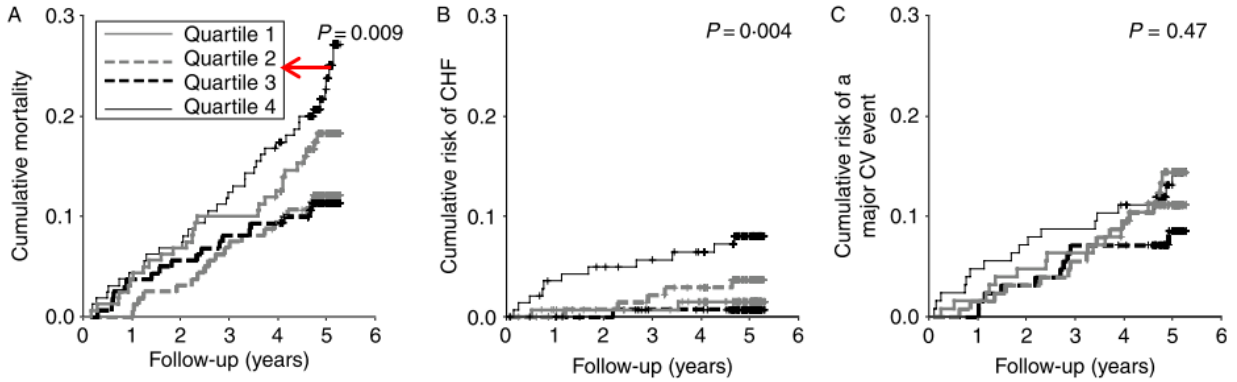
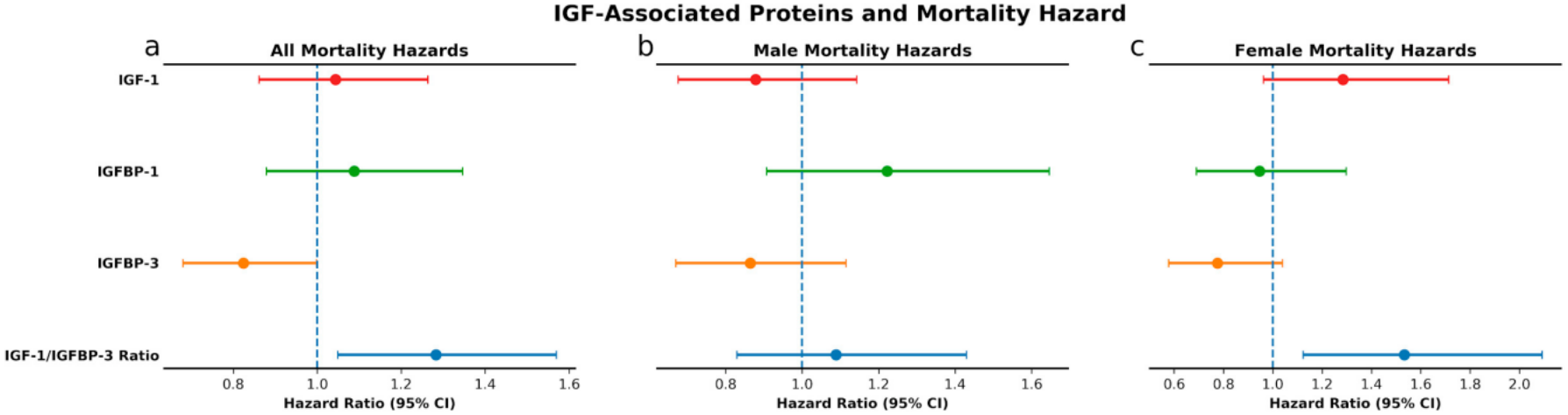


Figure 2 Kaplan–Meier curves of cumulative mortality (A), cumulative risk of CHF (B) and cumulative risk of a major CV event (C) according to quartiles of age-adjusted IGF1. *P* for differences across the quartiles was assessed by the log-rank test.

Insulin-like Growth Factor-1 and IGF Binding Proteins Predict All-Cause Mortality and Morbidity in Older Adults

William B. Zhang [1,†], Sandra Aleksic [1,†], Tina Gao [1], Erica F. Weiss [2], Eleni Demetriou [3], Joe Verghese [2,4], Roee Holtzer [2,3], Nir Barzilai [1,5] and Sofiya Milman [1,5,*]

Cells **2020**, *9*, 1368



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

J Clin Endocrinol Metab 96: 2912–2920, 2011

Anne Marij G. Burgers, Nienke R. Biermasz, Jan W. Schoones, Alberto M. Pereira, Andrew G. Renehan, Marcel Zwahlen, Matthias Egger, and Olaf M. Dekkers

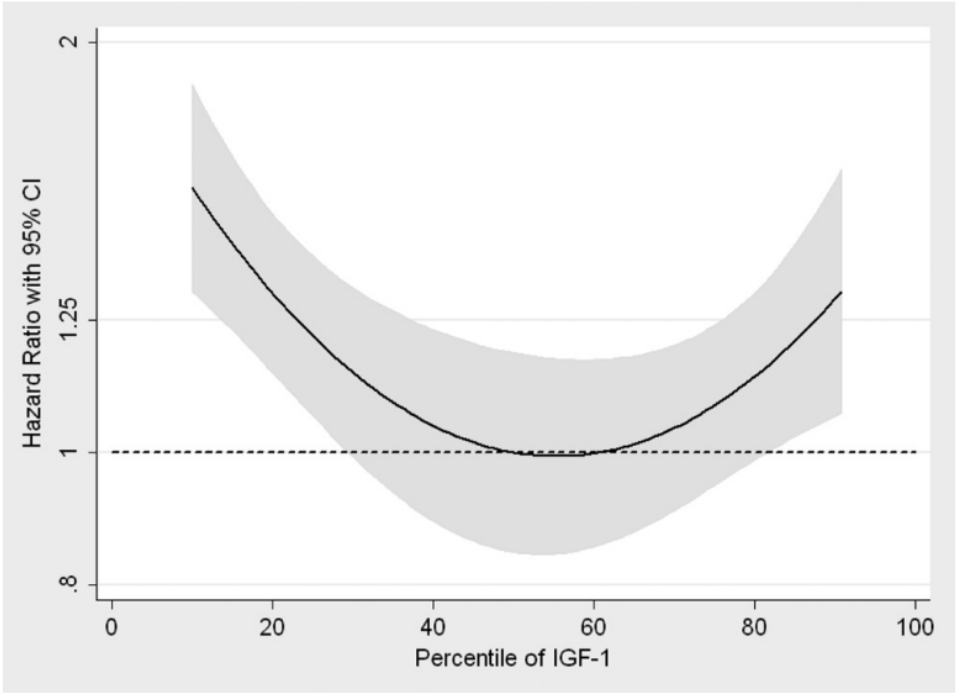


FIG. 2. Predicted HR for the association between IGF-I and all-cause mortality.

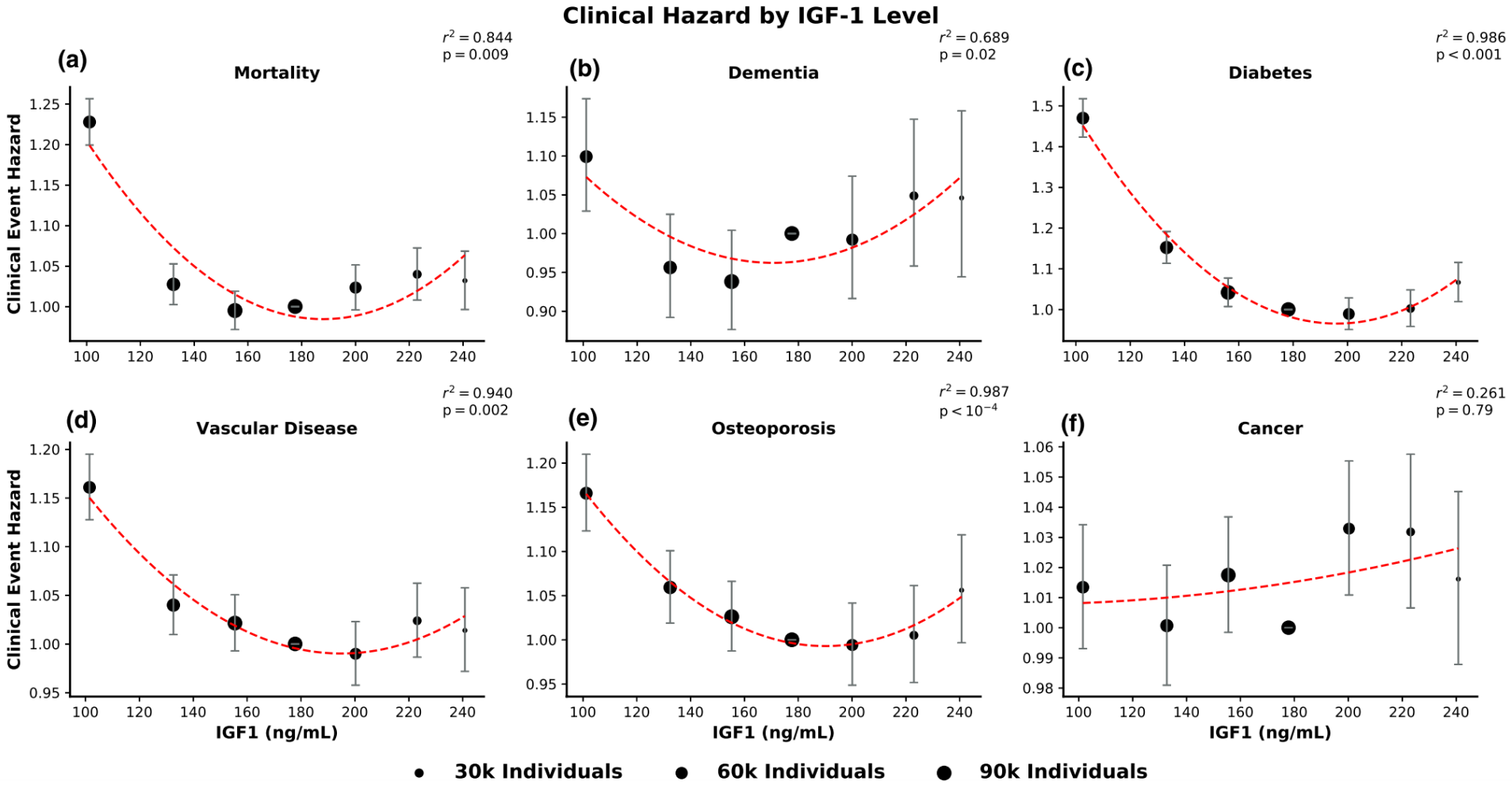
In medio stat virtus
(Virtue stands in the middle)

From this meta-analysis evaluating the relationship between circulating IGF-I levels and mortality, both low and high IGF-I concentrations were associated with increased mortality in the general population.
A U-shaped relationship was present for both cancer and cardiovascular mortality.

Aging Cell. 2021;20:e13443.

The antagonistic pleiotropy of insulin-like growth factor 1

William B. Zhang[1,2,3] | Kenny Ye[4,5] | Nir Barzilai[1,2] | Sofiya Milman[1,2]



UK Biobank (n = 440,185): **the association between IGF-1 and risk is generally U-shaped, with the exception of a more uniformly positive relationship between IGF-1 and cancer**

ROLE of IGF-1 System in the Modulation of Longevity: Controversies and New Insights From a Centenarians' Perspective

frontiers in Endocrinology

February 2019 | Volume 10 | Article 27

Giovanni Vitale[1,2], Giuseppe Pellegrino[3], Maria Vollery[4] and Leo J. Hofland[5]*

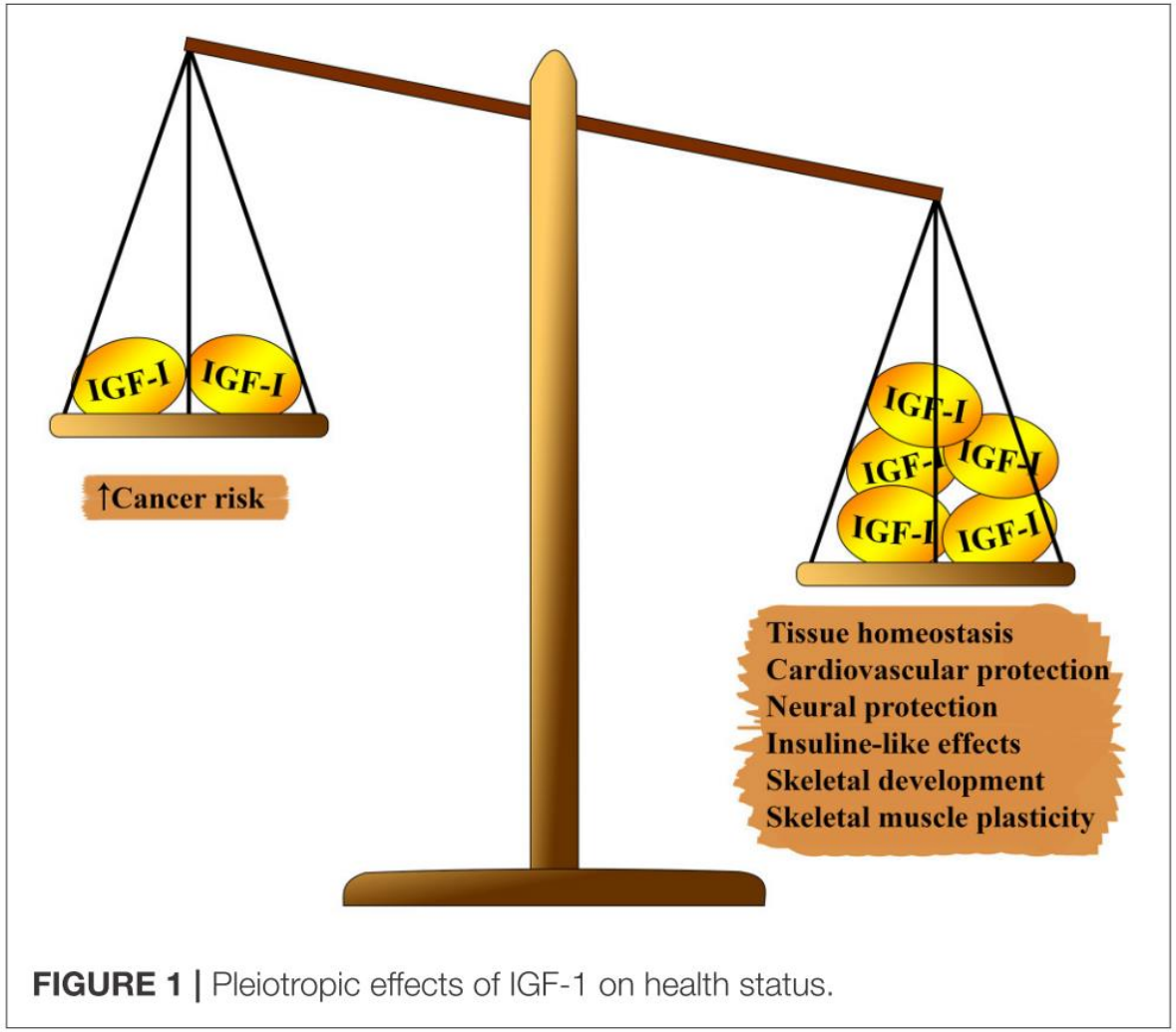
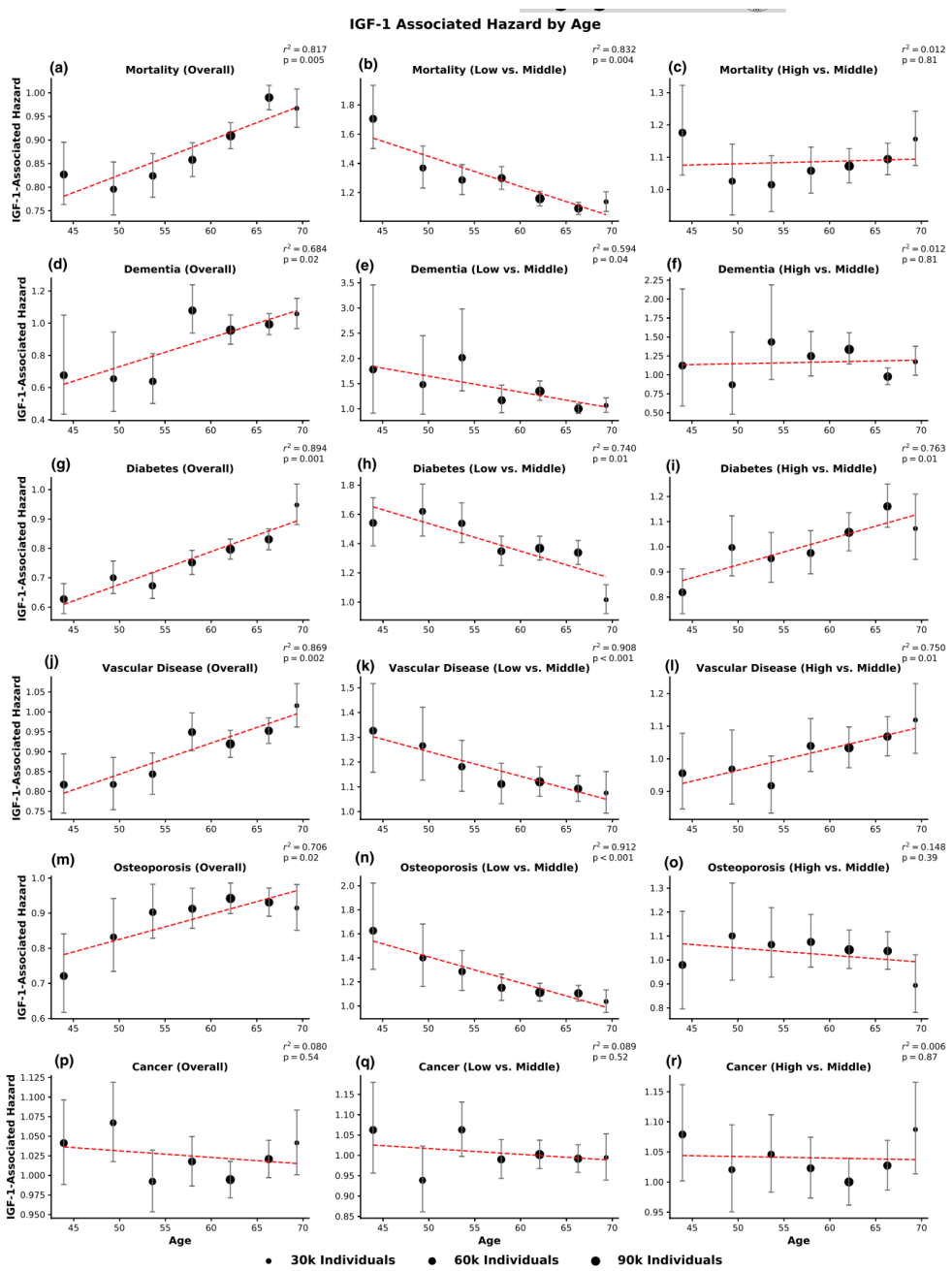


FIGURE 1 | Pleiotropic effects of IGF-1 on health status.



Aging Cell. 2021;20:e13443.

IGF-1 interacts with age to modify risk in a manner consistent with antagonistic pleiotropy:

- **younger individuals with high IGF-1 are protected from disease**
- **older individuals with high IGF-1 are at increased risk for incident disease or death**

European Journal of Epidemiology
https://doi.org/10.1007/s10654-020-00709-1

Pre-diagnostic circulating concentrations of insulin-like growth factor-1 and risk of COVID-19 mortality: results from UK Biobank

Xikang Fan[1] · Cheng Yin[2] · Jiayu Wang[1] · Mingjia Yang[1] · Hongxia Ma[1,3,4] · Guangfu Jin[1,3,4] · Mingyang Song[5,6,7] · Zhibin Hu[1,3,4] · Hongbing Shen[1,4] · Dong Hang[1,4]

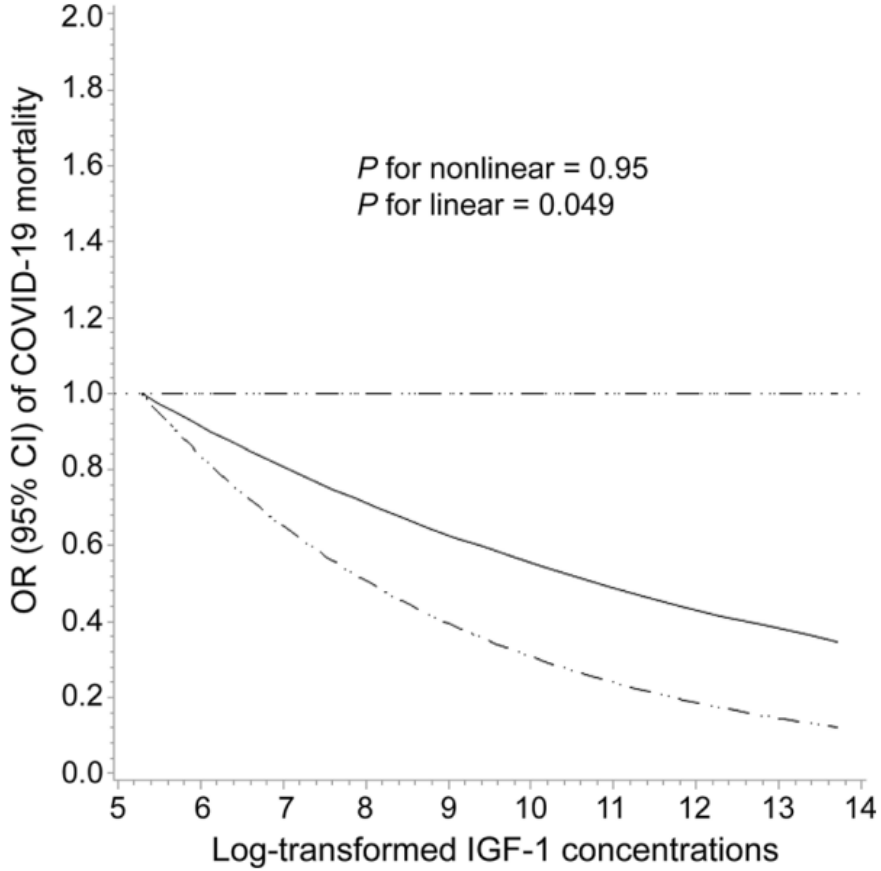
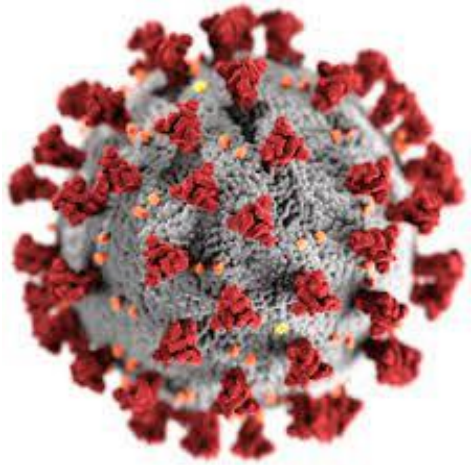


Fig. 2 The dose–response relationship between log-transformed IGF-1 concentrations and COVID-19 mortality according to restricted cubic spline regression analysis. The solid line represents estimates of odds ratios and the dashed lines represent 95% confidence intervals



UK BIOBANK: Higher serum IGF-1 concentrations are associated with a lower risk of COVID-19 mortality.

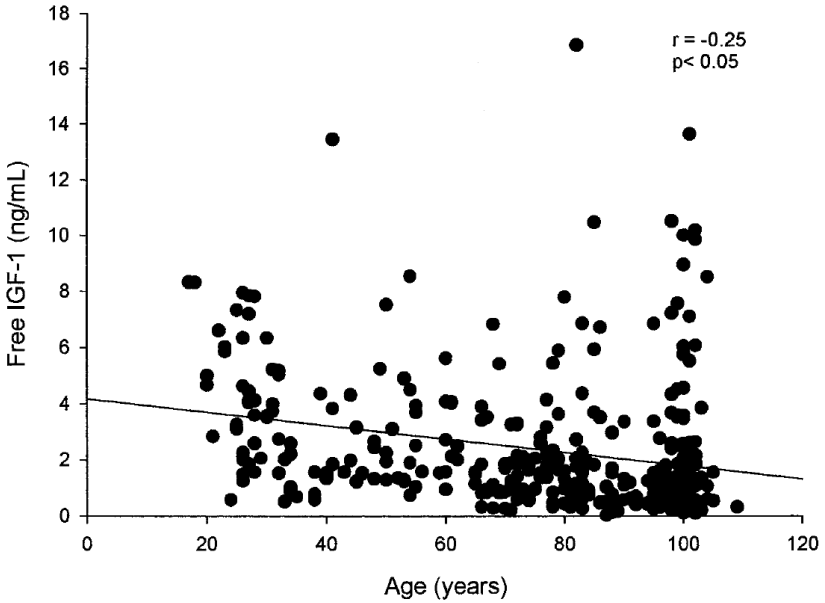
LONG-LIVED INDIVIDUALS
(Nonagenarians and centenarians)

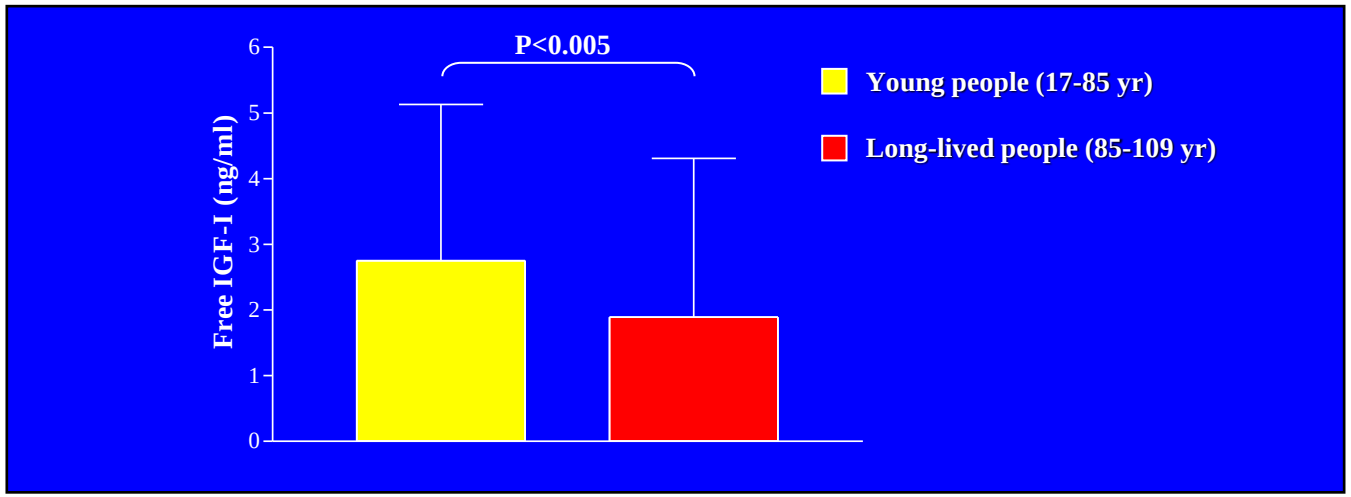
Centenarians represent an exceptional model to study *longevity* and *healthy aging* in humans. Many of these individuals are escaping from major common diseases such as cancer and diabetes.

Polymorphic Variants of Insulin-Like Growth Factor I (IGF-I) Receptor and Phosphoinositide 3-Kinase Genes Affect IGF-I Plasma Levels and Human Longevity: Cues for an Evolutionarily Conserved Mechanism of Life Span Control

J Clin Endocrinol Metab 2003;88:3299–3304

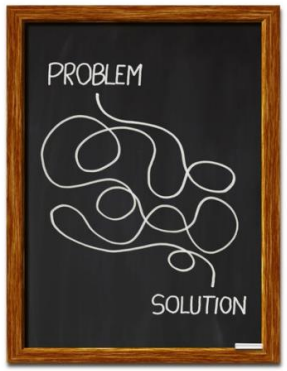
MASSIMILIANO BONAFÈ, MICHELANGELA BARBIERI, FRANCESCA MARCHEGIANI, FABIOLA OLIVIERI, EMILIA RAGNO, CLAUDIA GIAMPIERI, ELENA MUGIANESI, MATTEO CENTURELLI, CLAUDIO FRANCESCHI, AND GIUSEPPE PAOLISSO





Most of these studies have a cross-sectional design: centenarians have been often compared to a control group of younger subjects.
Therefore, it was not possible to conclude if IGF-I differences between both groups were expression of a different life span or of a physiological age-dependent IGF-I decline. Indeed, the absence of an appropriate control group, together with rarity and frailty related to extreme age, represent few limitations for the use of centenarians as a model to study longevity.

Some of these limitations have been overcome by studying centenarians' offspring.



Centenarians' offspring appear to be a new and promising approach to identify biological parameters which contribute to human aging and longevity, without the disadvantages observed in the studies of centenarians.

Centenarians' offspring have an average age of 70 years, appear to undergo an aging process "better" than that of subjects of the same age, are more numerous than centenarians and it is possible to compare them with a demographically-matched control group (subjects matched for age, sex, ethnicity, parent year of birth, but born from not long-lived parents) thus avoiding cohort effects.

Functionally significant insulin-like growth factor I receptor mutations in centenarians

Yousin Suh*, Gil Atzmon†, Mi-Ook Cho*, David Hwang‡, Bingrong Liu‡, Daniel J. Leahy§, Nir Barzilai†¶, and Pinchas Cohen‡

3438–3442 | PNAS | March 4, 2008 | vol. 105 | no. 9

Population: In a case control study, Ashkenazi Jews were recruited.

Three hundred and eighty four *probands* with exceptional longevity (286 females and 98 males, age range 95–108 years). The *offspring* group consisted of 114 females and 174 males (mean age 67.8). A unique cohort of Ashkenazi Jewish descent without a family history of unusual longevity served as *controls* (312, mean age 79.5).

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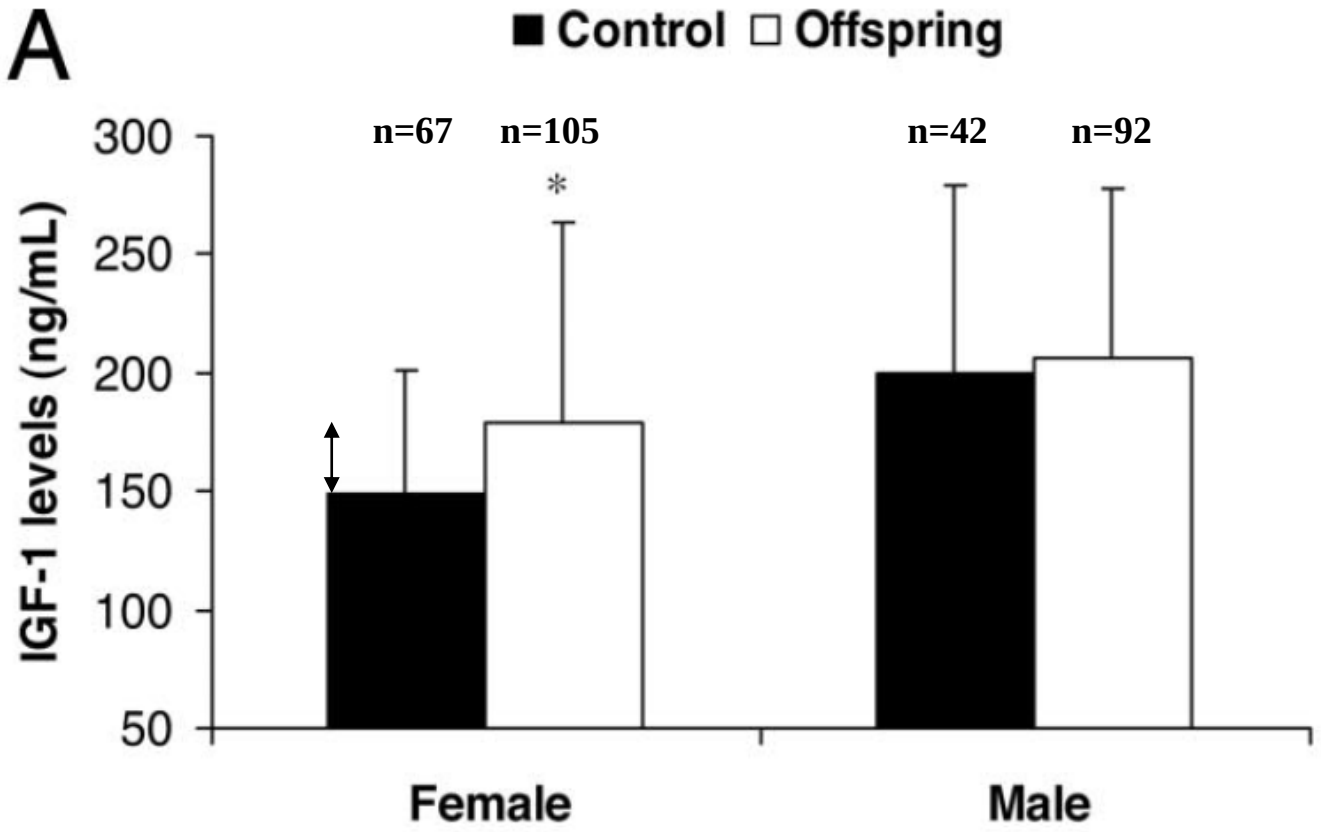

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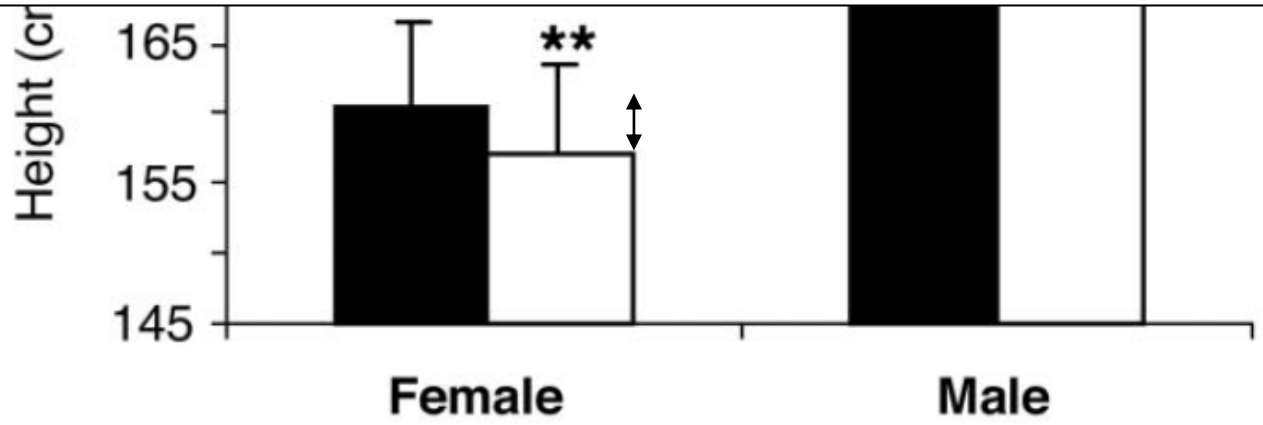
3438–3442 | PNAS | March 4, 2008 | vol. 105 | no. 9

Thus, a likely explanation for this finding is that the higher IGF-I levels represent a compensatory response to reduced IGF-IR signaling, which would also be associated with a small decrease in maximal height (although a less bioactive IGF-I molecule is also a possibility).



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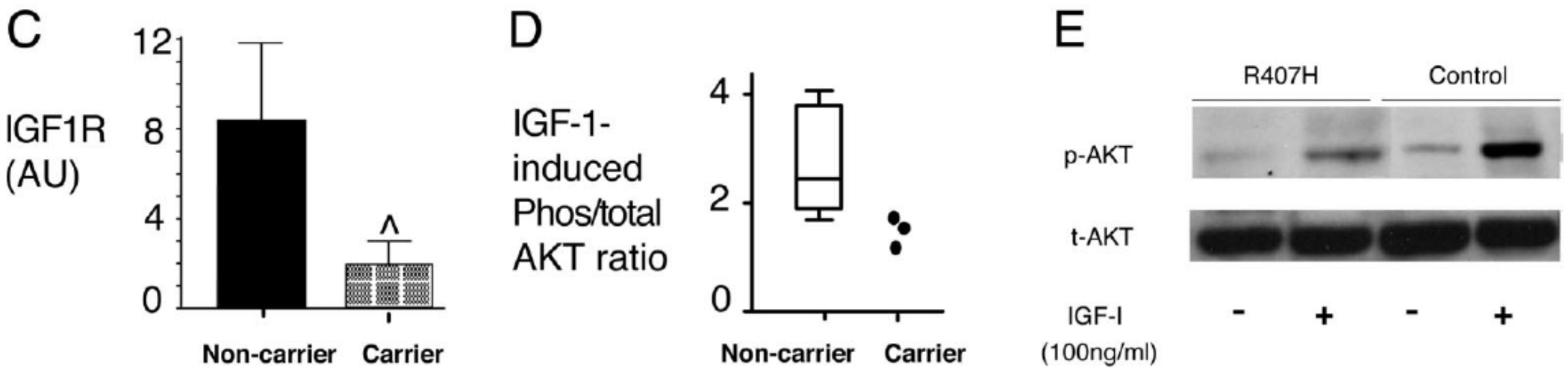
3438–3442 | PNAS | March 4, 2008 | vol. 105 | no. 9



(*C*) Immortalized lymphocytes from the female centenarians carrying mutations (Carrier) in *IGF1R* (Ala-37–Thr, Arg-407–His, and Thr-470–Thr) show significant reductions in IGFIR levels compared with immortalized lymphocytes from female centenarians with no mutations (Noncarrier, *n*10) as measured by ELISA (*P*=0.03). (*D*) IGF signaling is defective in the *IGF1R* mutation carriers (Carrier) of female centenarians as compared with female centenarians with no mutations (Noncarrier, *n*10) as measured by immunoblot analysis of the ratio of phosphorylated to total AKT in response to IGFI treatment in immortalized lymphocytes. (*E*) A representative immunoblot for total and phosphorylated AKT in immortalized lymphocytes from a centenarian carrying the Arg-407–His mutation and a control centenarian without the mutation.

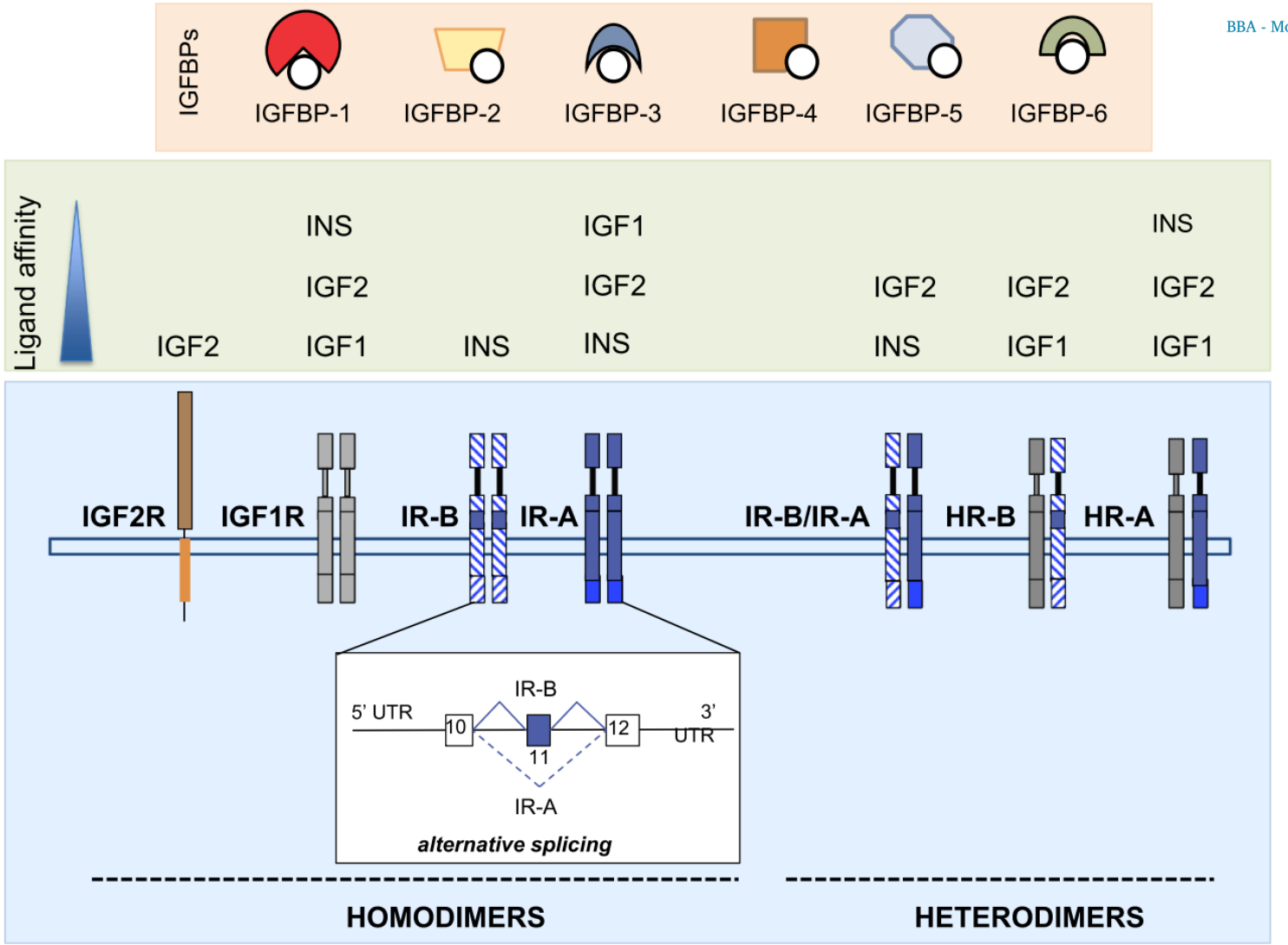
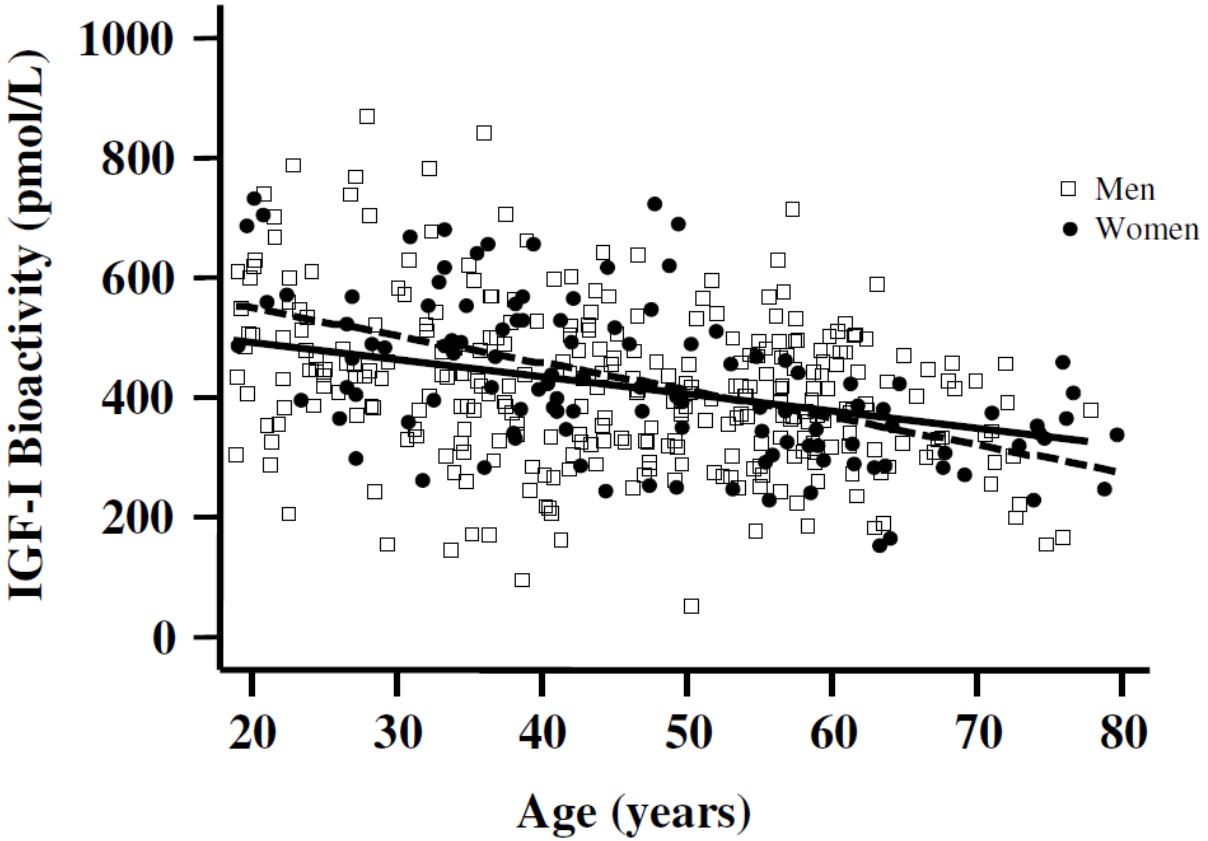


Fig. 1. Overview of the IIGF system. The IGF system includes three receptors: IGF2R, IGFR, IR. These receptors have been shown to interact with different binding affinities with at least three ligands: IGF1, IGF2, and insulin. In addition, this scenario is further complicated by the presence of hybrid receptors. Variable tetrameric assembly of IR isoforms and IGF1R moieties confers different ligand binding preferences and different signaling capabilities. IGFBPs, present in circulation and extravascular fluids, prolong the half-life of the IGFs modulating their bioavailability and activity.

(Brugts MP et al. J Clin Endocrinol Metab 2008)

IGF-I kinase receptor activation assay (KIRA): a highly sensitive and specific assay for determination of IGF-I bioactivity in human serum.



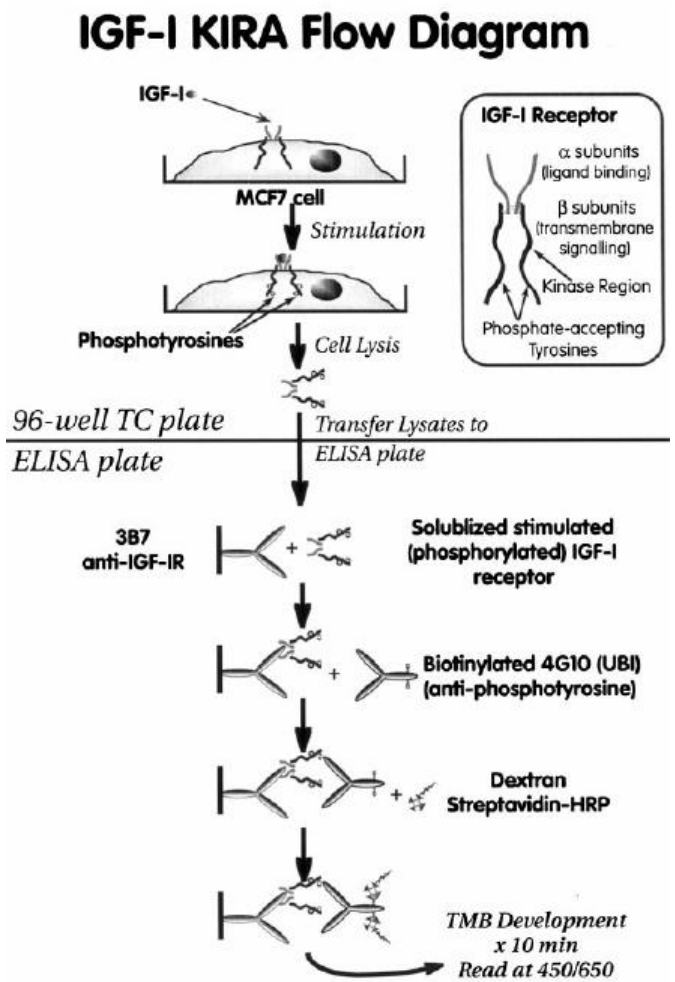


Fig. 2. Schematic diagram of the IGF-I KIRA.

Low circulating IGF-I bioactivity is associated with human longevity: Findings in centenarians' offspring

Giovanni Vitale[1,2], Michael P Brugts[3], Giulia Ogliari[1,4], Davide Castaldi[2,5], Letizia M. Fatti[2], Aimee J. Varewijck[3], Steven W. Lamberts[3], Daniela Monti[6], Laura Bucci[7], Elisa Cevenini[7], Francesco Cavagnini[2], Claudio Franceschi[7,8], Leo J Hofland[3], Daniela Mari[1,4], and Joseph A.M.J.L. Janssen[3]

AGING, September 2012, Vol 4 N 9

Table 3. Parameters of the IGF-I/insulin system in the study population*

	Offspring matched-controls (n=80)	Centenarians' Offspring (n=192)	Centenarians (n=106)	P[1]	P[2]
IGF-I Bioactivity (pmol/L)	161 (134-187)	144 (119-170)	132 (107-157)	<0.01	0.09
Total IGF-I (nmol/L)	17 (13.6-20.8)	14.4 (11.9-18.2)	9.3 (7.1-12.9)	<0.01	<0.001
IGFBP-2 (μg/L)	546 (345-665)	566 (400-678)	728 (603-898)	0.50	<0.001
IGFBP-3 (nmol/L)	101.3 (82.7-128.5)	125.8 (107.1-154.5)	79.8 (67.9-92.2)	0.01	<0.001
Total IGF-I/IGFBP-3 (molar ratio)	0.15 (0.13-0.17)	0.12 (0.10-0.14)	0.13 (0.09-0.16)	<0.001	0.42
Total IGF-II (nmol/L)	114 (89-137)	134 (92-168)	72 (55-117)	0.15	<0.001
Glucose (mmol/L)	4.9 (4.5-5.4)	4.8 (4.3-5.4)	4.6 (4.2-5.1)	0.38	0.09
Insulin (pmol/L)	74 (51-105)	71 (44-103)	39 (27-70)	0.92	<0.001
HOMA2-B%	128 (98-166)	137 (100-174)	109 (81-152)	0.94	<0.01
HOMA2-S%	62 (44-93)	68 (45-110)	122 (68-174)	0.90	<0.001

* Results are reported as medians with interquartile ranges (25th-75th percentiles) for data not normally distributed.

[1]: Offspring matched-controls vs. Centenarians' Offspring

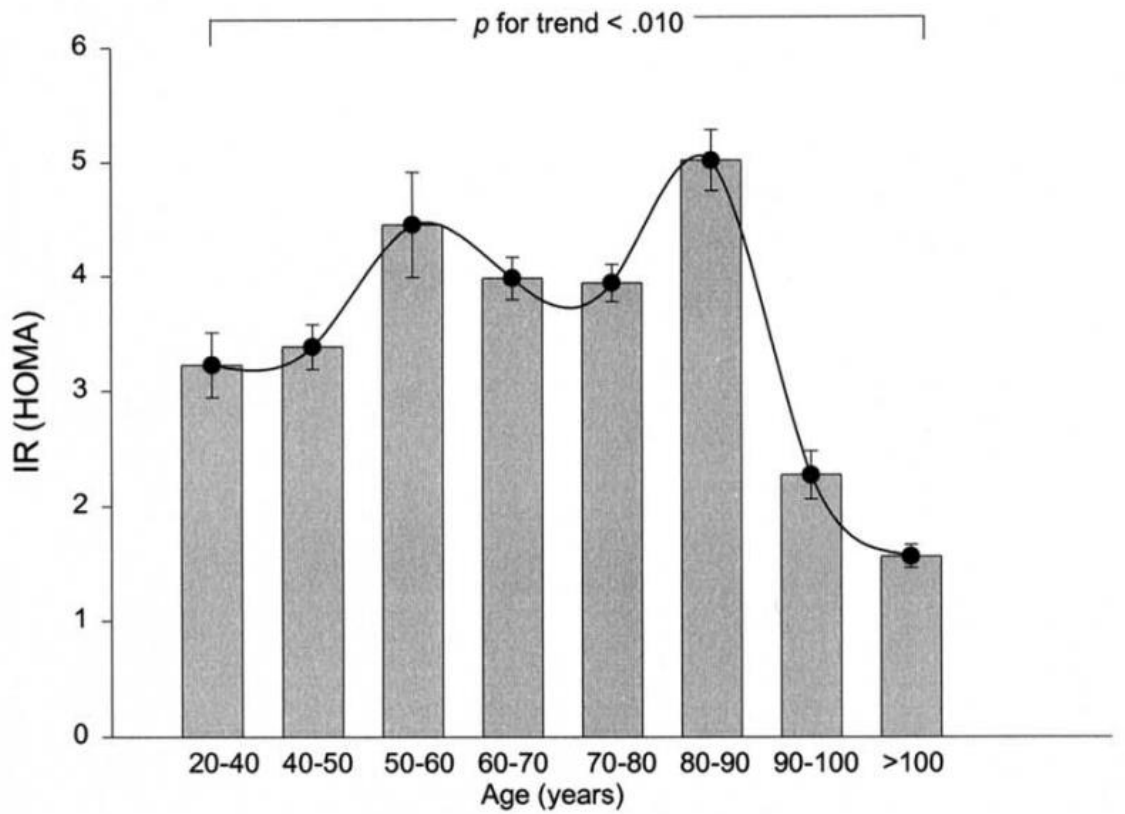
[2]: Centenarians' Offspring vs. Centenarians

Experimental Gerontology 37 (2001) 149–156

Low insulin resistance and preserved β-cell function contribute to human longevity but are not associated with TH–INS genes

Giuseppe Paolisso[a,*], Michelangela Barbieri[a], Maria Rosaria Rizzo[a], Carlo Carella[b], Mario Rotondi[b], Massimiliano Bonafè[c], Claudio Franceschi[c], Giuseppina Rose[d], Giovanna De Benedictis[d]

Experimental Gerontology



Beyond the ages of 85-90 years, insulin resistance declined again and a group of subjects with a lower degree of insulin resistance emerged.

GH/IGF-I/insulin system in centenarians

Giovanni Vitale [a,b,*], Michelangela Barbieri [c], Marina Kamenetskaya [a], Giuseppe Paolisso [c,**]

Mechanisms of Ageing and Development 165 (2017) 107–114

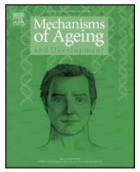


Table 1
Characterization of the GH/IGF-I/insulin system in centenarians and their offspring.

	IGF-I	IGFBP-3	IGF-I bioactivity	HOMA-IR	WBGD[d]	Insulin	Reference
Centenarians *vs* aged	=	↓	↑[a]		↑	↓	Paolisso et al. (1997a)
subjects (65–99yrs)	↓	↓	↓[b]	↓		↓	Vitale et al. (2012)
					↑	↓	Paolisso et al. (1996)
Centenarians *vs* adults	↓	↓	↓[a]		=	↓	Paolisso et al. (1997a)
(<50yrs)					=	=	Paolisso et al. (1996)
Centenarians *vs* non centenarians (<99yrs)				↓		↓	Paolisso et al. (2001)
Long-lived subjects (86–109 yrs) vs controls (<85 yrs)			↓[c]	↓		↓	Bonafe et al. (2003)
Centenarians'offspring	↑[e]						Suh et al. (2008)
vs matched controls	↓	↑	↓[b]	=		=	Vitale et al. (2012)

[a] Measured as IGF-I/IGFBP-3 ratio.
[b] Measured as KIRA.
[c] Measured as free IGF-I.
[d] WBGD = Whole body glucose disposal.
[e] In females; =: no significant difference between groups.

The metabolic syndrome, IGF-1, and insulin action

Molecular and Cellular Endocrinology 299 (2009) 124–128

Yasumichi Arai[a,*], Toshio Kojima[b], Michiyo Takayama[a], Nobuyoshi Hirose[a]

Table 1
Comparison of long-lived mouse models with centenarians

	CR[a]	Dwarf[b]	FIRKO[c]	ADPN Tg[d,e]	Centenarians[f]
Glucose metabolism					
Plasma insulin	↓	↓	↓	↓	↓
Plasma glucose	↓	↓	↓	↓	↓
Insulin sensitivity	↑	↑	↑	↑	↑
Somatotrophic axis					
Plasma IGF-1	↓	↓↓	↓	NA	↓ or →
Adipose tissue metabolism					
Body adiposity	↓	↑ (with aging) or ↓	↓	↓	↓
Plasma leptin	↓	↓	↑	↓	↓ or ↑
Plasma ADPN	↑	↑	↑	↑↑	↑

NA: no available data; CR: calorie restriction; FIRKO: fat-specific insulin receptor knockout; ADPN: adiponectin.

The biochemical profile observed in centenarians was comparable to that observed in several other models of exceptional longevity, suggesting a potential crosstalk between GH/IGF-1/insulin pathways and adipose tissue metabolism in regard to life extension.

Review

Intermittent and Periodic Fasting, Hormones, and Cancer Prevention

Cancers **2021**, *13*, 4587.

Giulia Salvadori [1,2], Mario Giuseppe Mirisola [3] and Valter D. Longo [2,4,*]

Table 1. Metabolic, molecular and cellular mechanisms induced by CR to prevent cancer.

	Metabolic Adaptations	Molecular Adaptations	Cellular Adaptations
Calorie Restriction (CR)	↓ IGF-1 ↓ Insulin ↓ Oxidative stress ↓ Inflammation ↑ Cortisol	↓ PI3K/Akt/S6K ↓ mTOR ↓ Ras/MAPK ↑ Nrf2 ↑ FOXO ↑ PTEN	↓ Cell proliferation ↓ Oxidative damage ↑ DNA repair ↑ Genome instability

Several studies showed that CR increases lifespan in multiple organisms including yeast, flies, worms, rodents and monkeys, protecting from disorders and decline in functions related to aging

In long-lived individuals:

GH, IGF-I, IGF-II, IGFBP…

	Offspring matched-controls (n=80)	Centenarians' Offspring (n=192)	Centenarians (n=106)	P[1]	P[2]
IGF-I Bioactivity (pmol/L)	161 (134-187)	144 (119-170)	132 (107-157)	<0.01	0.09
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Glucose (mmol/L)	4.9 (4.5-5.4)	4.8 (4.3-5.4)	4.6 (4.2-5.1)	0.38	0.09
Insulin (pmol/L)	74 (51-105)	71 (44-103)	39 (27-70)	0.92	<0.001
HOMA2-B%	128 (98-166)	137 (100-174)	109 (81-152)	0.94	<0.01
HOMA2-S%	62 (44-93)	68 (45-110)	122 (68-174)	0.90	<0.001

IGF-I Bioactivity

IGF-I Bioactivity

IGF-IR expression and IGF-IR sensitivity

IGF-IR expression
IGF-IR sensitivity

IGF-IR sensitivity → **Down-regulation of the IGF-I system**

IGF-IR sensitivity → **Well-preserved IGF-I system**

Role of epigenetics in human aging and longevity: genome-wide DNA methylation profile in centenarians and centenarians' offspring

Davide Gentilini · Daniela Mari · Davide Castaldi · Daniel Remondini · Giulia Ogliari · Rita Ostan · Laura Bucci · Silvia M. Sirchia · Silvia Tabano · Francesco Cavagnini · Daniela Monti · Claudio Franceschi · Anna Maria Di Blasio · Giovanni Vitale

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Table 3 Gene ontology analysis of CpG sites hypermethylated and hypomethylated between centenarians' offspring and old controls

GO term	Description	*p* value
Hypermethylated		
GO:0009112	Nucleobase metabolic process	(9.35×10^{-4})
GO:0034404	Nucleobase, nucleoside, and nucleotide biosynthetic process	(9.37×10^{-4})
GO:0034654	Nucleobase, nucleoside, nucleotide, and nucleic acid biosynthetic process	(9.80×10^{-4})
Hypomethylated		
GO:0023050	Consequence of signal transmission	(9.40×10^{-4})

p values were derived using hypergeometric tests

This category includes steps whereby the downstream processes started by a signal are brought to a conclusion.

We cannot exclude that a slower cell growing/metabolism and a better control in signal transmission through epigenetic mechanisms may be involved in the process of longevity

Conclusions

- **Several mutations that decrease the activity of the GH/IGF-I/insulin system are associated with extended longevity in organisms ranging from yeast, nematodes, and fruit flies to mice.**
- **The relationship of the GH/IGF-I/insulin signaling to human aging is less striking, and more complex and controversial.**

- **Indeed, the increased complexity of this network in humans has made it difficult to disentangle the role of each factor in the modulation of the life-span and healthy aging.**
- **Longitudinal studies with a better and repeated characterization of this system are needed.**

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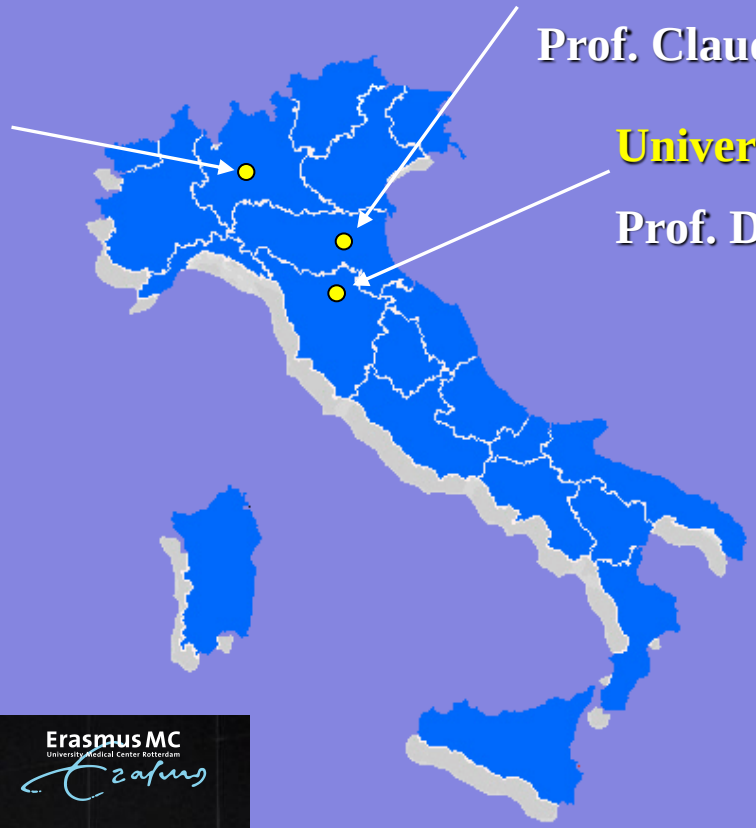

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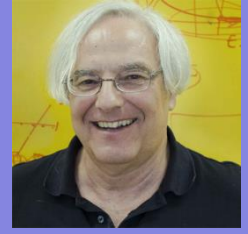

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