

Terapia del diabete mellito e protezione cerebrale

5° Congresso congiunto AMD-SID Sicilia 2020

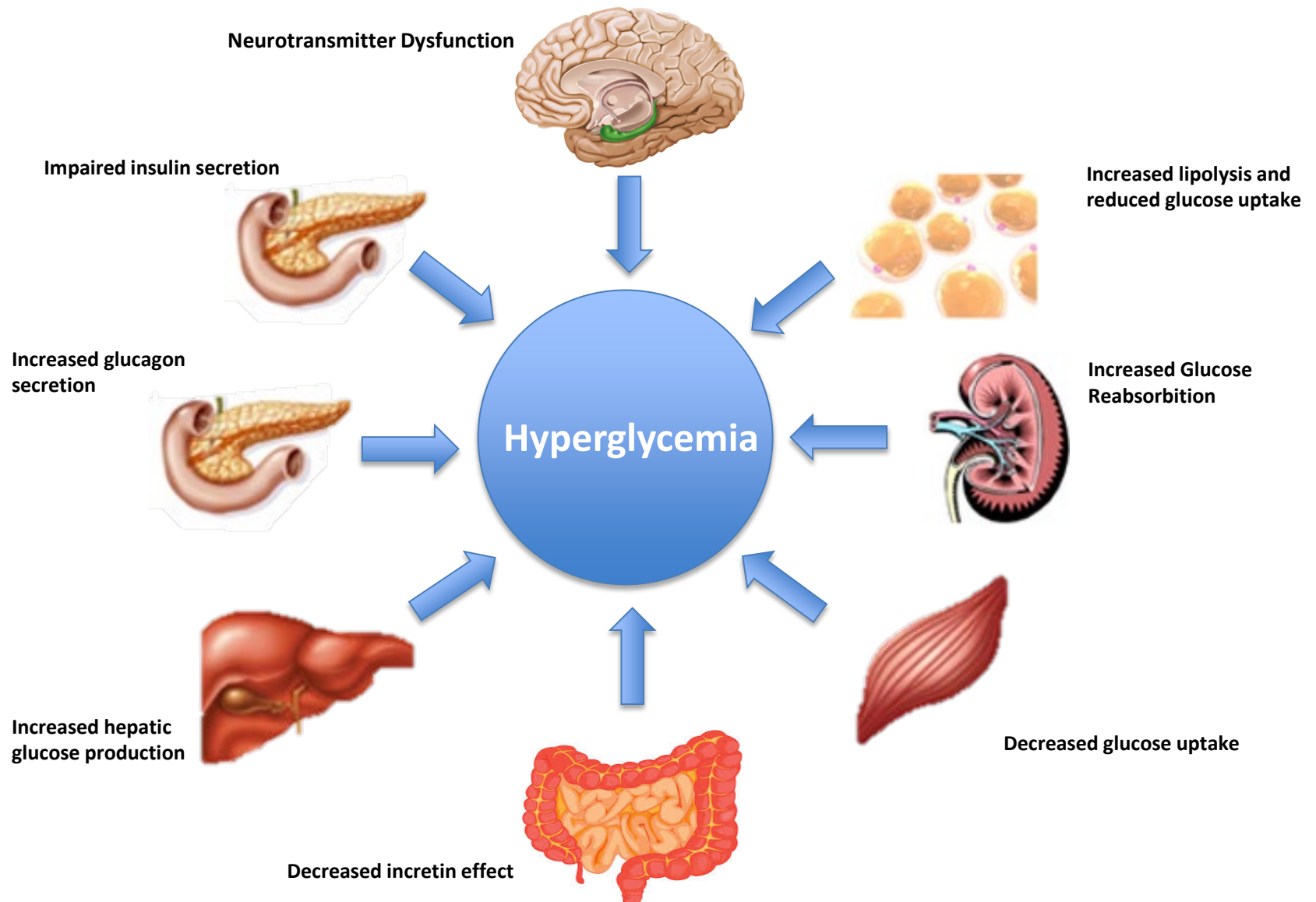
Il diabete in Sicilia: dalle problematiche territoriali alla terapia

19 - 20 novembre 2020

Aci Castello (CT) Grand Hotel Baia Verde

Il /la dr./sa Antonino Di Pino dichiara di **NON** aver ricevuto negli ultimi due anni compensi o finanziamenti da Aziende Farmaceutiche e/o Diagnostiche.

Terapia del diabete mellito e protezione cerebrale



Diabete e demenza

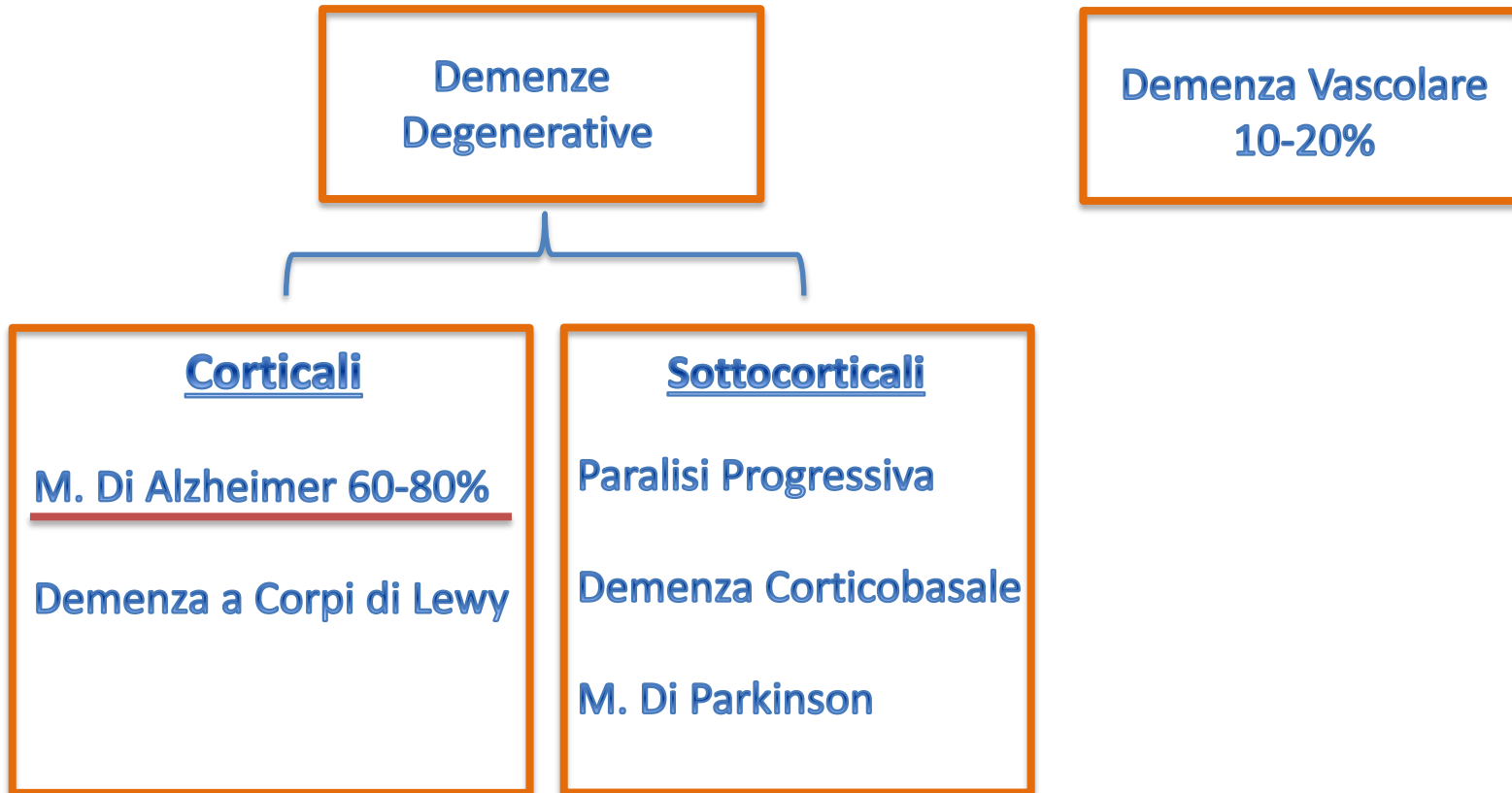


Verbale
Cognitivo
Motorio

Perdita dell'autosufficienza



Diabete e demenza



Diabete e demenza

- **Terapie ipoglicemizzanti e protezione cerebrale**
- **Ipoglicemia come fattore di rischio di demenza**

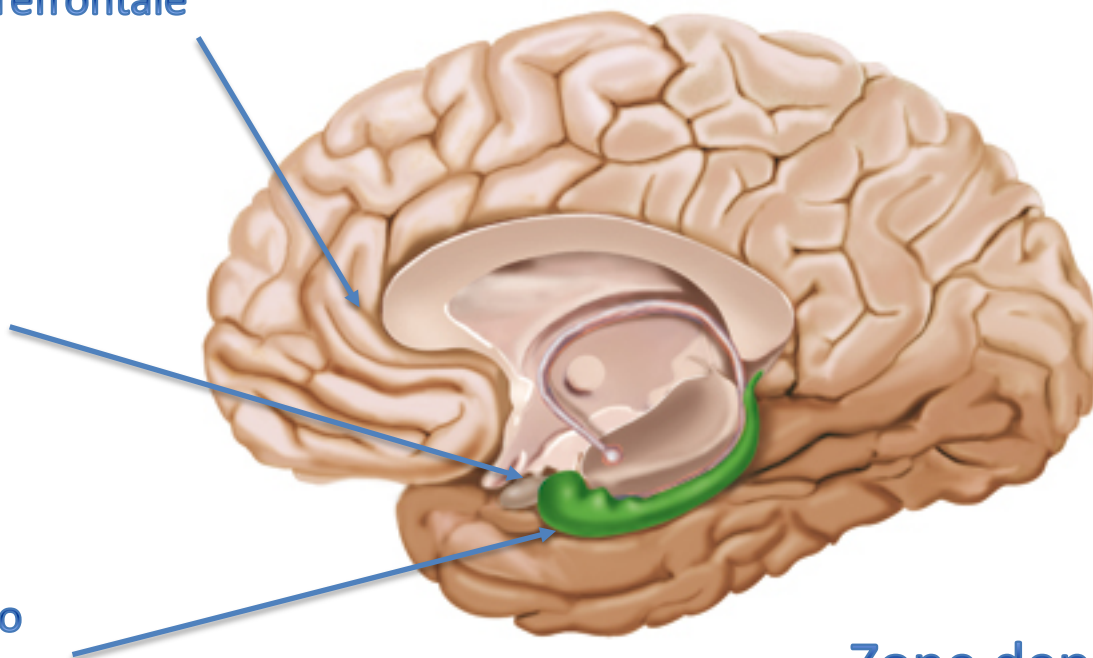
INSULINA, cervello e malattia di Alzheimer



Corteccia prefrontale

Amigdala

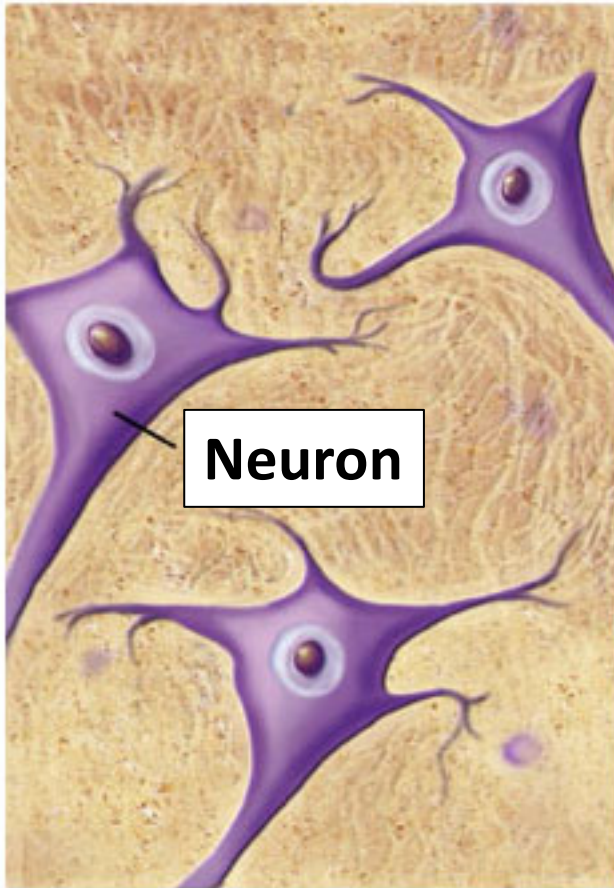
Ippocampo



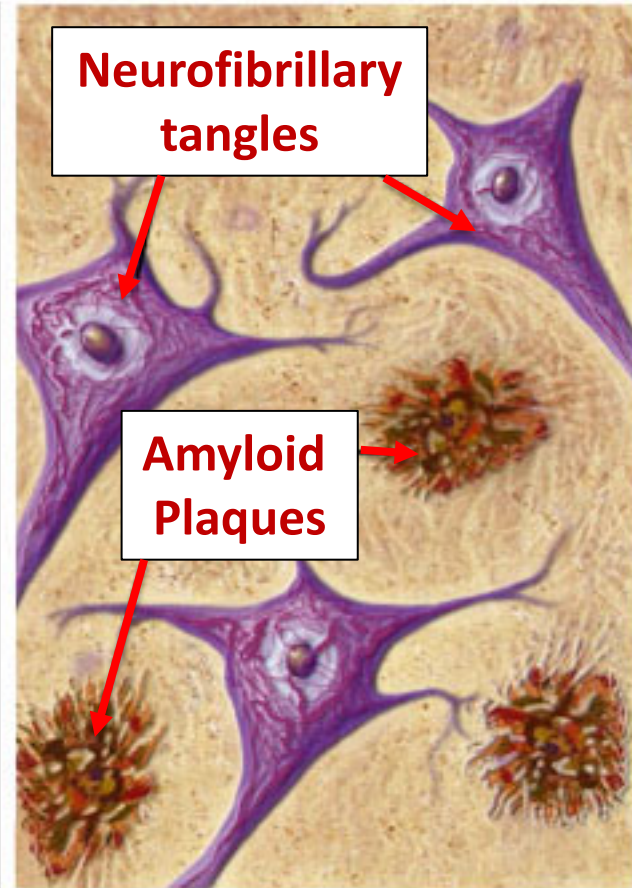
Zone deputate alla memoria

INSULINA, Cervello e Malattia di Alzheimer

Normal

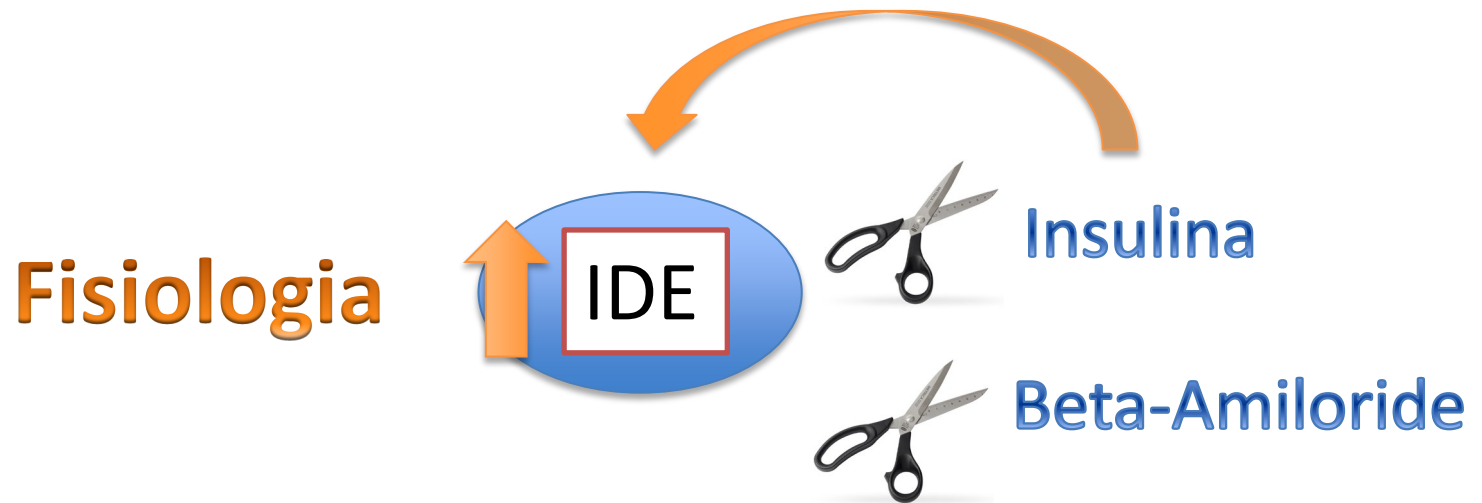


Alzheimer's disease



INSULINA, Cervello e Malattia di Alzheimer

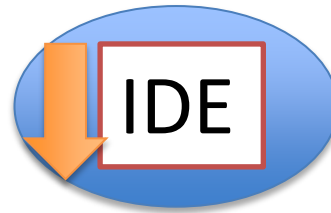
IDE (insulin-degrading enzyme)



INSULINA, Cervello e Malattia di Alzheimer

IDE (insulin-degrading enzyme)

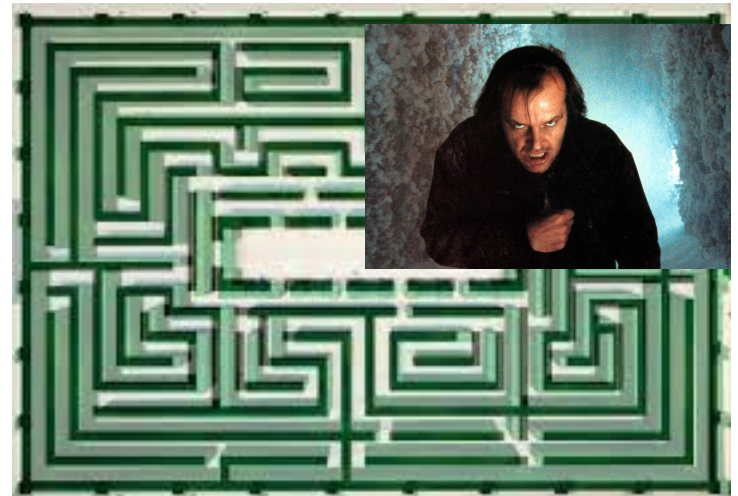
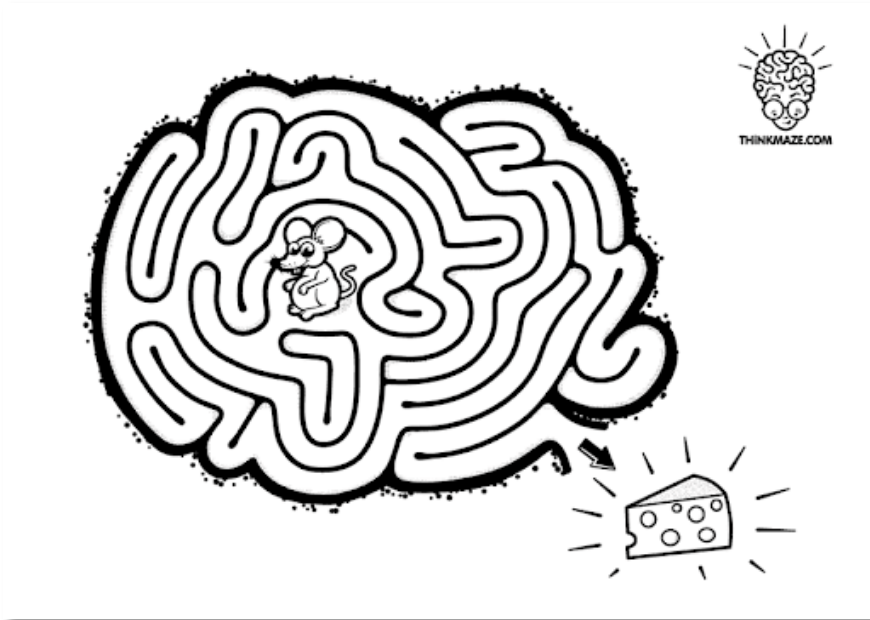
Ipoinsulinemia
Insulino/Resistenza



Beta-Amilorida



INSULINA, Cervello e Malattia di Alzheimer



INSULINA, Cervello e Malattia di Alzheimer

ORIGINAL ARTICLE

Enhancement of Memory in Alzheimer Disease With Insulin and Somatostatin, but Not Glucose

Suzanne Craft, PhD; Sanjay Asthana, MD; John W. Newcomer, MD; Charles W. Wilkinson, PhD; Iris Tio Matos, MD; Laura D. Baker, PhD; Monique Cherrier, PhD; Cassin Lofgreen, RN; Shawn Latendresse; Andreana Petrova; Stephen Plymate, MD; Murray Raskind, MD; Karla Grimwood, MS; Richard C. Veith, MD

23 Pazienti con Malattia di Alzheimer

- ➡ Iperinsulinemia + Normoglicemia (100 mg/dL)
- ➡ Iperglicemia + Normoinsulinemia (Somatostatin infusion)
- ➡ Placebo

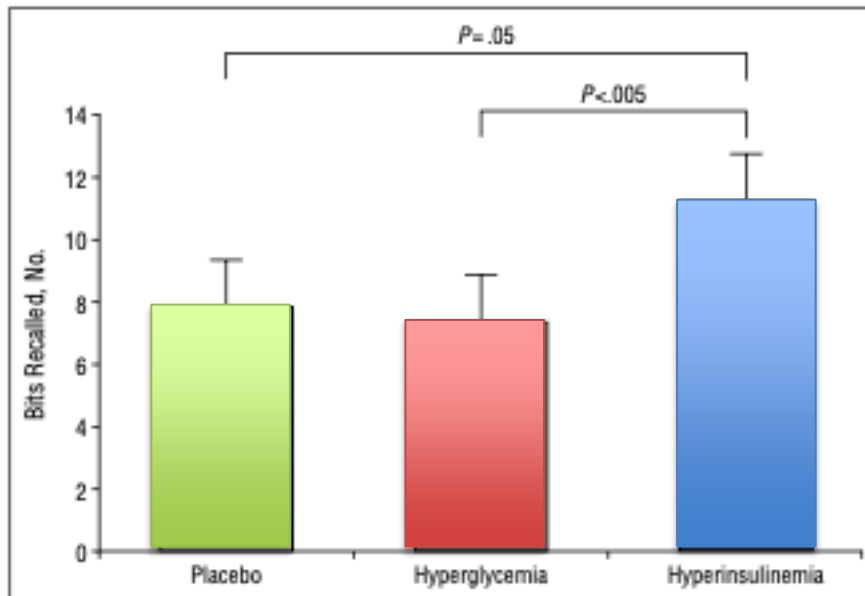
➡ Story Recall test

INSULINA, Cervello e Malattia di Alzheimer

ORIGINAL ARTICLE

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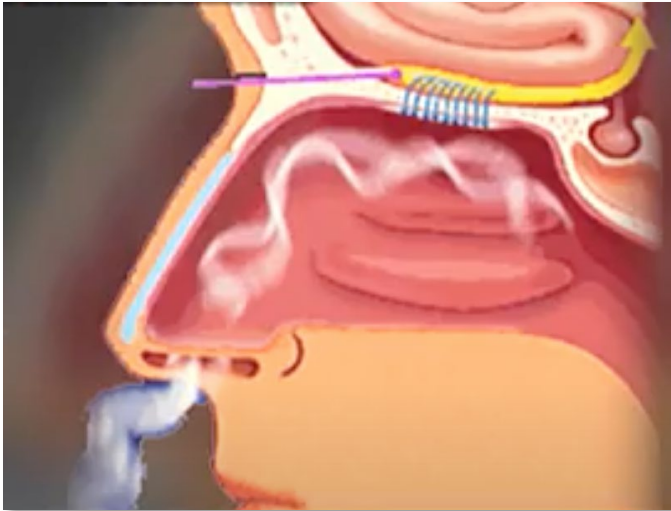
Suzanne Craft, PhD; Sanjay Asthana, MD; John W. Newcomer, MD; Charles W. Wilkinson, PhD; Iris Tio Matos, MD; Laura D. Baker, PhD; Monique Cherrier, PhD; Cassin Lofgreen, RN; Shawn Latendresse; Andreana Petrova; Stephen Plymate, MD; Murray Raskind, MD; Karla Grimwood, MS; Richard C. Veith, MD



Conclusions: ...elevated insulin without hyperglycemia enhances memory in adults with AD....

INSULINA, Cervello e Malattia di Alzheimer

Insulina Intranasale



Nervo Olfattivo

Seconda branca del Trigemino

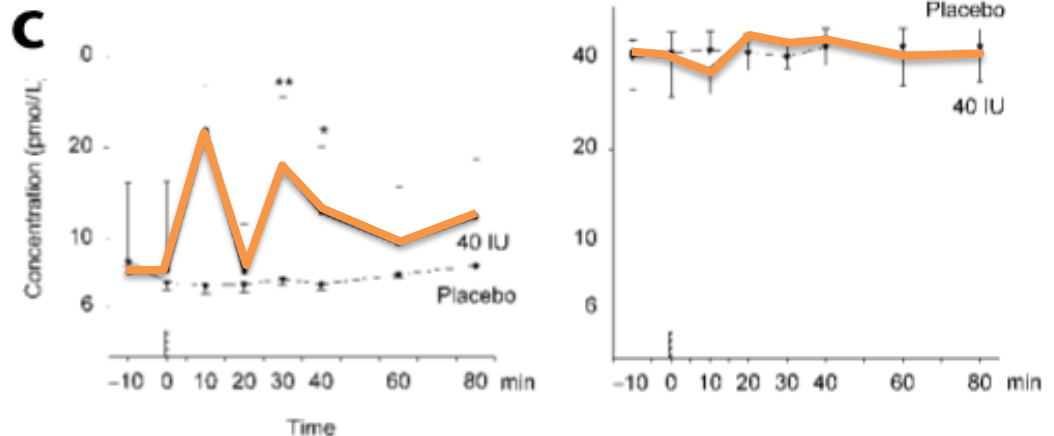
Sniffing neuropeptides: transnasal approach to the human brain

Jan Born¹, Tanja Lange², Werner Kern²,
Gerard P. McGregor³, Ulrich Bickel⁴ and Horst L. Fehr

Insulin Concentration

CSF

Serum



INSULINA, Cervello e Malattia di Alzheimer

Insulina Intranasale – Effetti Cognitivi

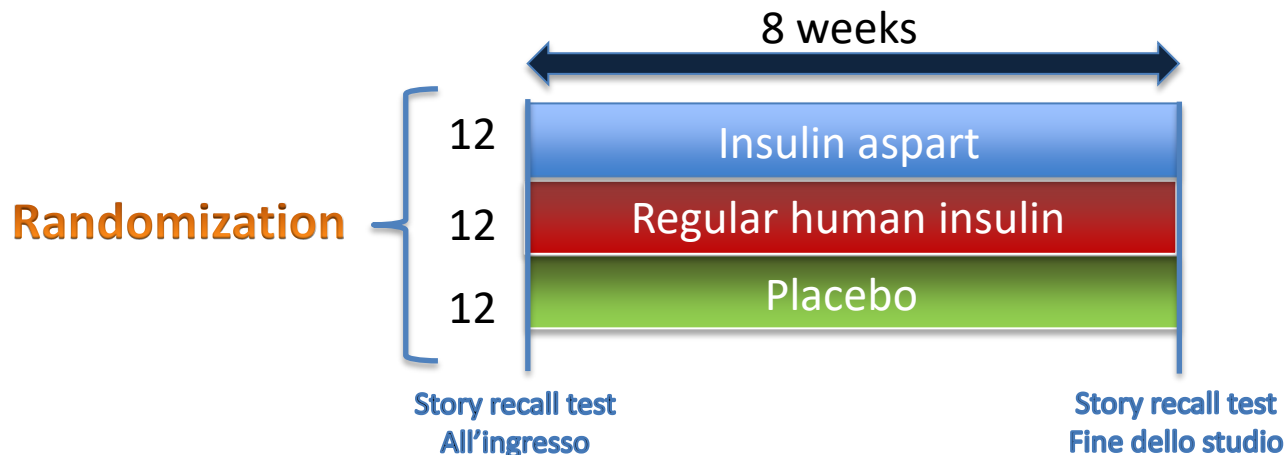
Intranasal Insulin Improves Memory in Humans: Superiority of Insulin Aspart

Christian Benedict^{*1}, Manfred Hallschmid¹, Katrin Schmitz¹, Bernd Schultes², Frank Ratter³,
Horst L Fehm⁴, Jan Born¹ and Werner Kern⁴

¹Department of Neuroendocrinology, University of Lübeck, Lübeck, Germany; ²Obesity Centre, Spitalregion St Gallen-Rorschach, Switzerland;

³Novo Nordisk Germany, Mainz, Germany; ⁴Department of Internal Medicine I, University of Lübeck, Lübeck, Germany

Soggetti SANI di età inferiore a 40 anni Obesi o normopeso



INSULINA, Cervello e Malattia di Alzheimer

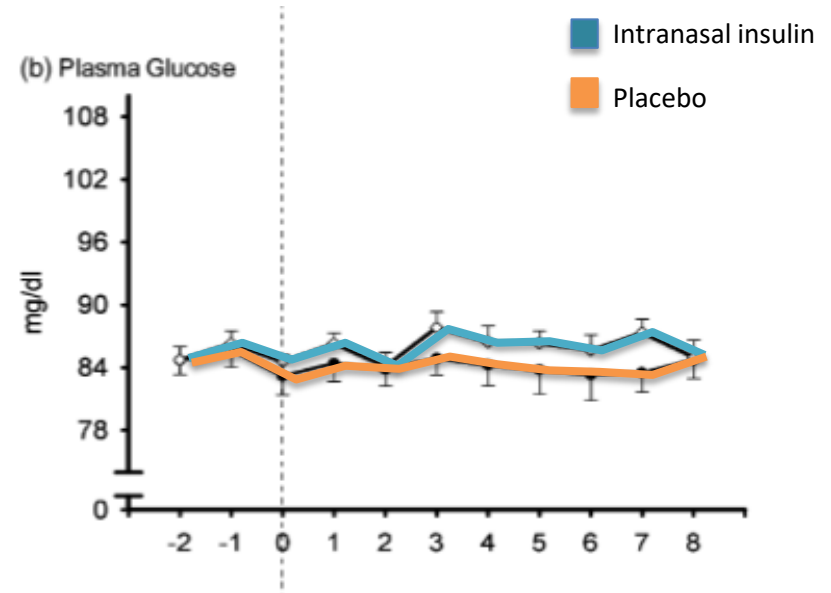
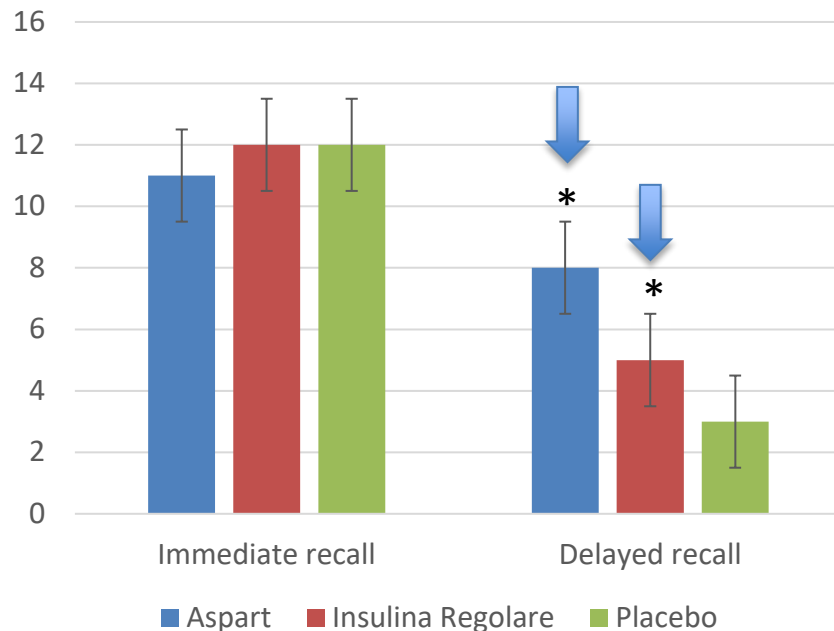
Insulina Intranasale – Effetti Cognitivi

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INSULINA, Cervello e Malattia di Alzheimer

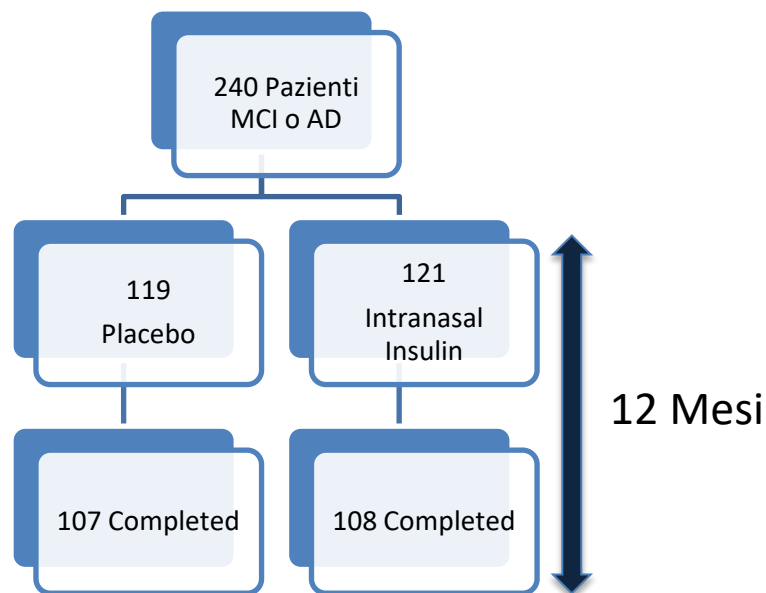
Insulina Intranasale – Effetti Cognitivi

JAMA Neurology | Original Investigation

Safety, Efficacy, and Feasibility of Intranasal Insulin for the Treatment of Mild Cognitive Impairment and Alzheimer Disease Dementia A Randomized Clinical Trial

Suzanne Craft, PhD; Rema Raman, PhD; Tiffany W. Chow, MD; Michael S. Rafii, MD; Chung-Kai Sun, MS; Robert A. Rissman, PhD; Michael C. Donohue, PhD; James B. Brewer, MD, PhD; Cecily Jenkins, PhD; Kelly Harless, BS; Devon Gessert, BS; Paul S. Aisen, MD

Studio Randomizzato 1:1



Primary Outcome: Alzheimer disease assessment scale somministrato al basale e ogni 3 mesi

Alzheimer Disease Assessment Scale – Cognitive Subscale	
	Score Range
Memory and new learning	0-35
Word Recall	0-10
Orientation	0-8
Word recognition	0-12
Remembering test instructions	0-5
Language	0-25
Commands	0-5
Spoken language ability	0-5
Naming objects/fingers	0-5
Word finding difficulty	0-5
Comprehension	0-5
Praxis	0-10
Constructional Praxis	0-5
Ideational praxis	0-5
Total	0-70

INSULINA, Cervello e Malattia di Alzheimer

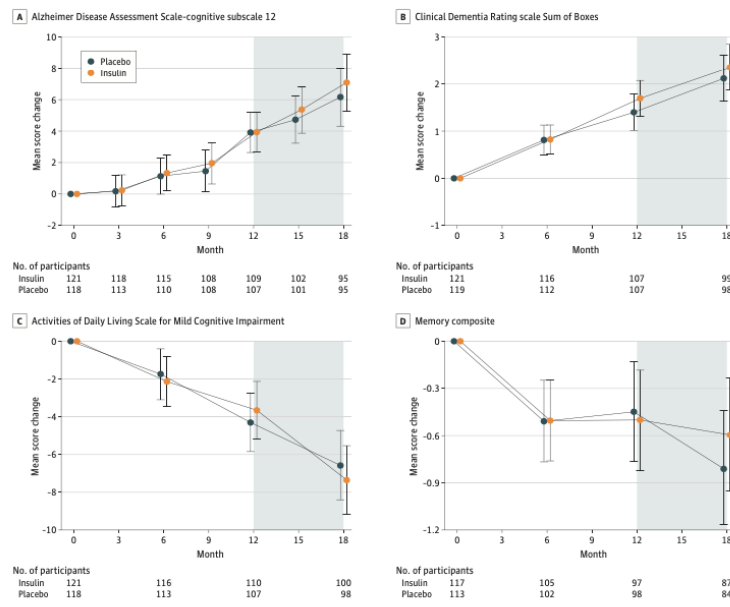
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Figure 2. Mean Score Changes From Baseline to Month 18 for the Primary (Device 2) Cohort



The model used time as a categorical variable and included fixed effects for treatment, treatment-by-time interactions, baseline outcome, sex, age, baseline score on the Mini-Mental State Examination, and apolipoprotein E ε4 allele carriage status. The shaded region indicates the open-label phase. A, Alzheimer

Disease Assessment Scale-cognitive subscale 12. B, Clinical Dementia Rating scale Sum of Boxes. C, Activities of Daily Living Scale for Mild Cognitive Impairment. D, Memory composite. Error bars indicate 95% CIs.

INSULINA, Cervello e Malattia di Alzheimer

Insulina Intranasale – Effetti Cognitivi

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Usato nei Trial precedenti

Accensione/spegnimento automatico

Dispensazione farmaco automatica per 20 secondi per narice



Non testato in studi di pazienti con AD

Accensione/spegnimento e dispensazione manuali

INSULINA, Cervello e Malattia di Alzheimer

CONCLUSIONI

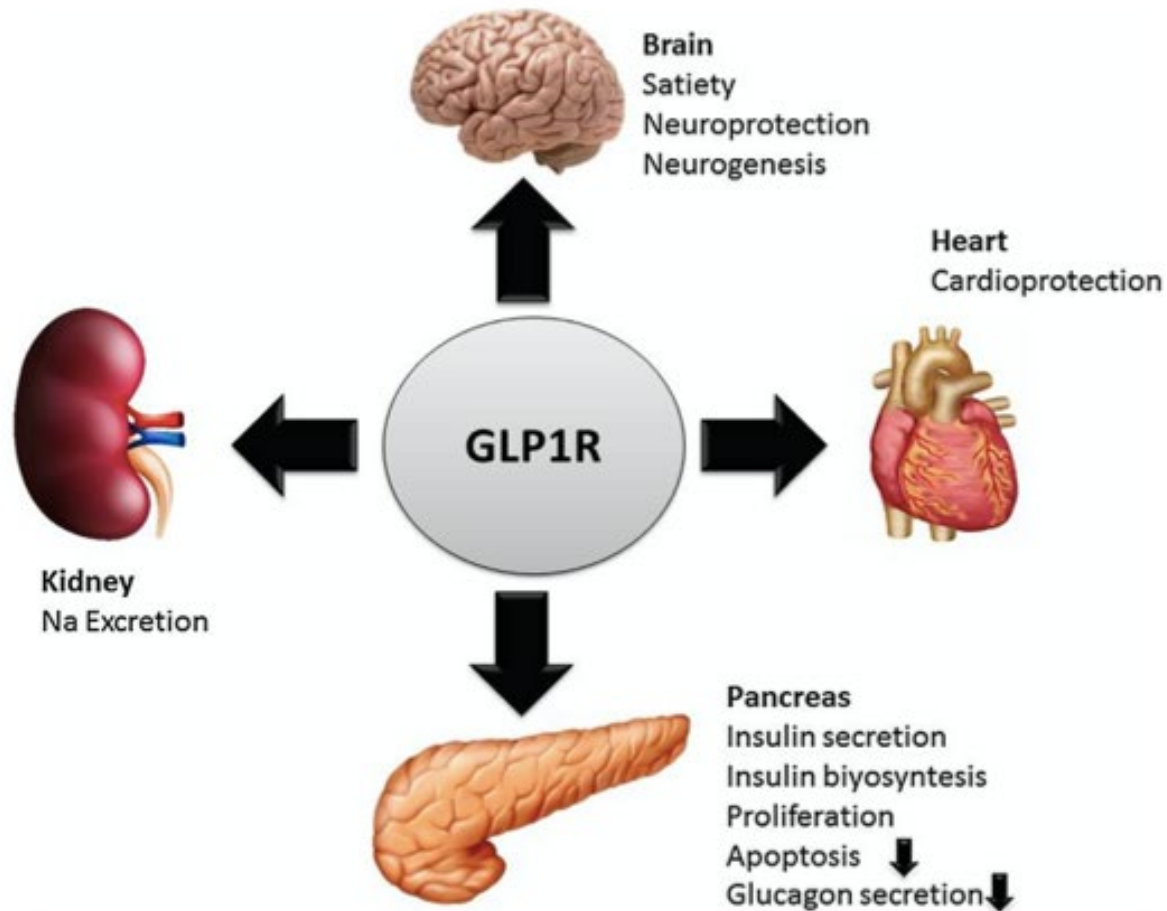
L'insulina è il link fisiopatologico che lega la malattia di Alzheimer al Diabete

L'insulina intranasale è una valida opzione che raggiunge concentrazioni elevate a livello encefalico

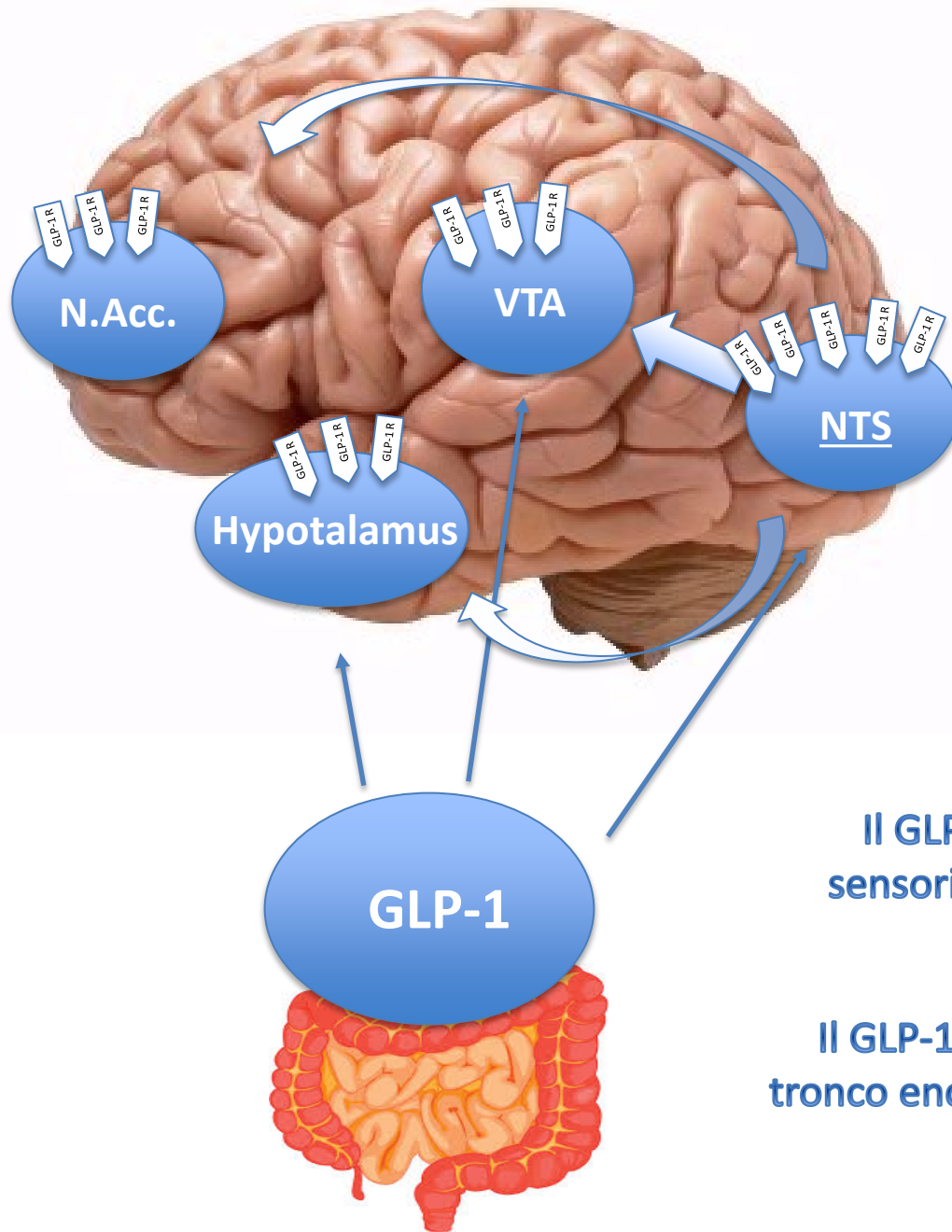
Studi condotti nell'uomo hanno dato risultati discordanti, soprattutto in pazienti che avevano una MCI o AD

GLP-1, Cervello e Malattia di Alzheimer

Il recettore del GLP-1 è distribuito in molti tessuti dell'organismo.



GLP-1 e Cervello



Il GLP-1 proietta attraverso i neuroni sensoriali presenti a livello dell'intestino.

Il GLP-1 viene prodotto anche a livello del tronco encefalico in particolare a livello del NTS

IL GLP-1 POTREBBE BYPASSARE L'INSULINO-RESISTENZA CEREBRALE

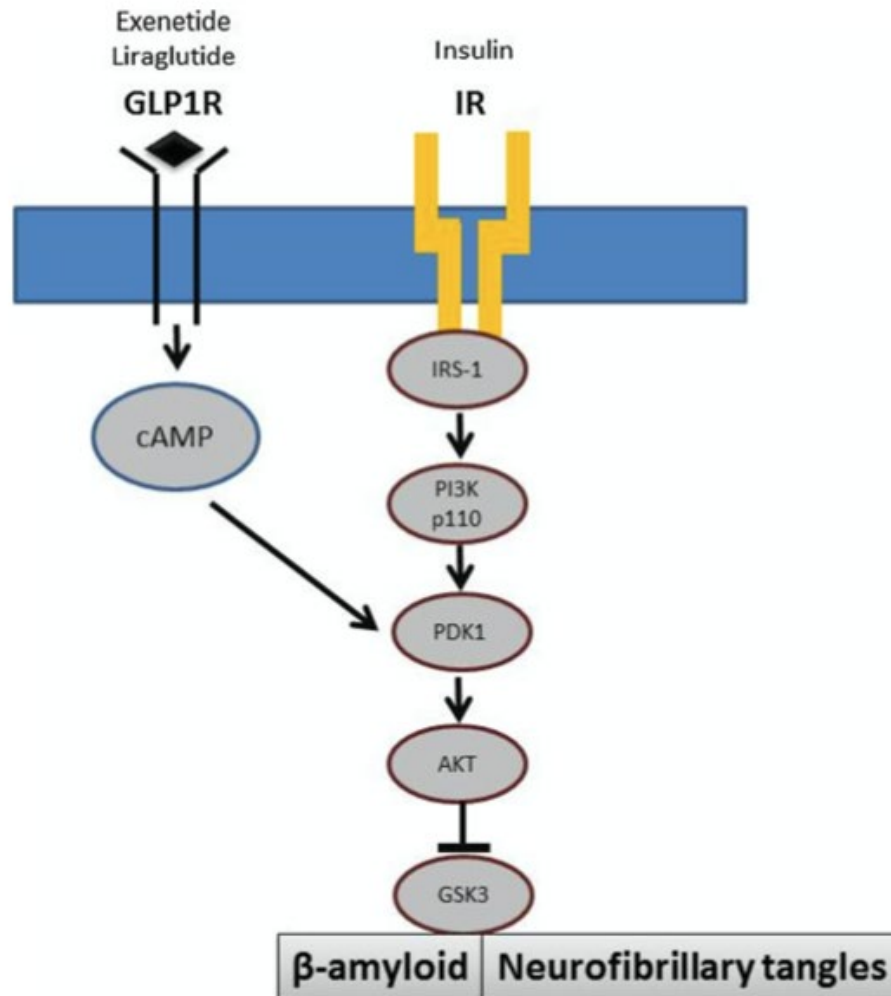


Fig. 5. The IRS-1 → AKT pathway in AD. Restoring signaling through this pathway may be of particular benefit in AD.

GLP-1, Cervello e Malattia di Alzheimer

GLP-1 RAs e Protezione Cerebrale

In Alzheimer's Disease, 6-Month Treatment with GLP-1 Analog Prevents Decline of Brain Glucose Metabolism: Randomized, Placebo-Controlled, Double-Blind Clinical Trial

Michael Gejl^{1,2}, Albert Gjedde^{2,3}, Lærke Egeffjord^{1,2}, Arne Møller², Søren B. Hansen², Kim Vang², Anders Rodell², Hans Brændgaard⁴, Hanne Gottrup⁴, Anna Schacht², Niels Møller⁵, Birgitte Brock^{1,6} and Jørgen Rungby^{1,7*}

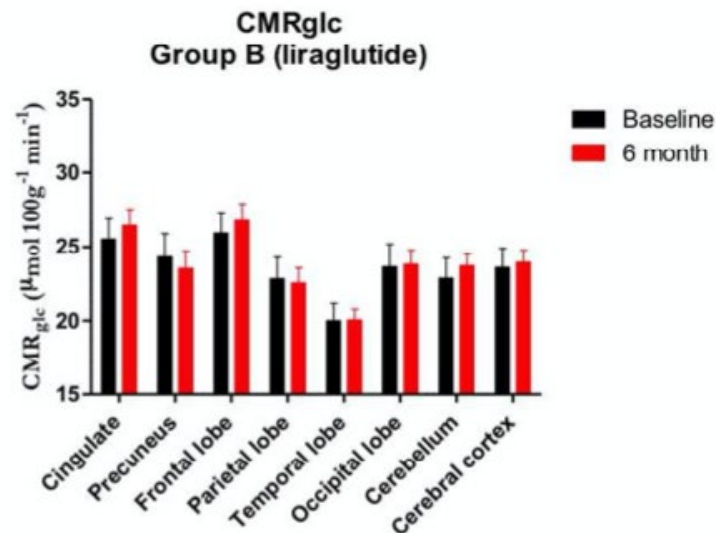
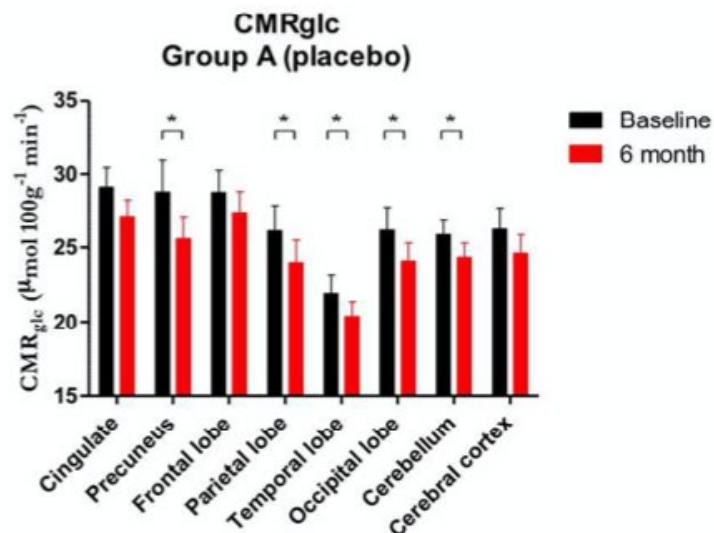
Trial randomizzato della durata di 6 mesi

38 Pazienti Liraglutide/Placebo

Primary Outcome

Metabolismo del glucosio a livello cerebrale (CMR_{glc})

B



GLP-1, Cervello e Malattia di Alzheimer

GLP-1 RAs e Protezione Cerebrale

STUDY PROTOCOL

Open Access

Evaluating the effects of the novel GLP-1 analogue liraglutide in Alzheimer's disease: study protocol for a randomised controlled trial (ELAD study)



Grazia Daniela Femminella^{1†}, Eleni Frangou^{2†}, Sharon B. Love², Gail Busza¹, Clive Holmes³, Craig Ritchie¹, Robert Lawrence⁴, Brady McFarlane³, George Tadros⁵, Basil H. Ridha⁶, Carol Bannister⁷, Zuzana Walker⁸, Hilary Archer⁹, Elizabeth Coulthard⁹, Ben R. Underwood¹⁰, Aparna Prasanna¹¹, Paul Koranteng¹², Salman Karim¹³, Kehinde Junaid¹⁴, Bernadette McGuinness¹⁵, Ramin Nilforooshan¹⁶, Ajay Macharouthu¹⁷, Andrew Donaldson¹⁸, Simon Thacker¹⁹, Gregor Russell²⁰, Naghma Malik²¹, Vandana Mate²², Lucy Knight²³, Sajeev Kshemendran²⁴, John Harrison^{25,26}, David J. Brooks^{1,27}, Anthony Peter Passmore¹⁵, Clive Ballard⁷ and Paul Edison^{1,28*} 

Trial randomizzato della durata di 12 mesi

206 Pazienti Liraglutide/Placebo

Primary Outcome

Metabolismo del glucosio a livello cerebrale (CMRglc)

GLP-1, Cervello e Malattia di Alzheimer

GLP-1 RAs e Protezione Cerebrale

A Pilot Study of Exenatide Actions in Alzheimer's Disease

Roger J. Mullins¹, Maja Mustapic¹, Chee W. Chia², Olga Carlson², Seema Gulyani¹, Joyce Tran¹, Yazhou Li³, Mark P. Mattson¹, Susan Resnick⁴, Josephine M. Egan², Nigel H. Greig³, Dimitrios Kapogiannis^{1,*}

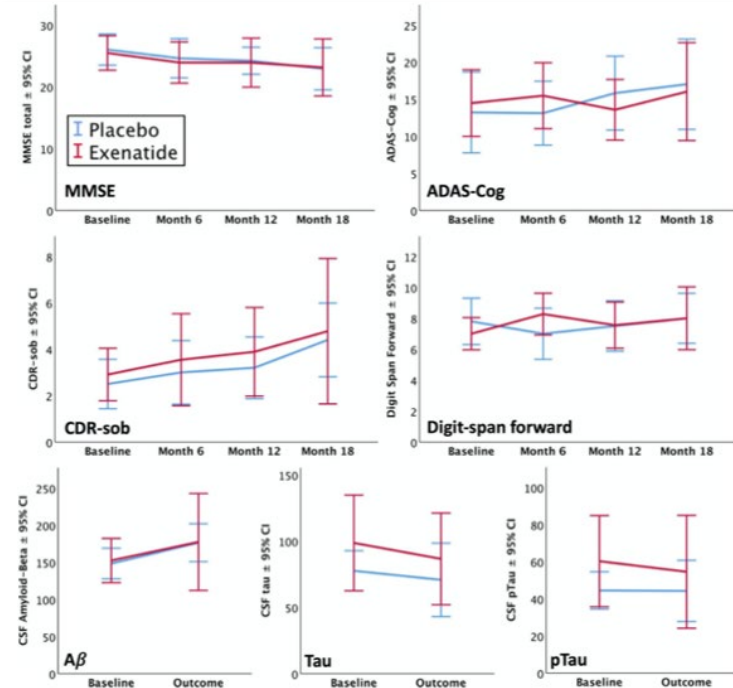
Trial randomizzato della durata di 18 mesi

21 Pazienti exenatide/placebo

Trial interrotto prematuramente

Primary Outcomes: MMSE, ADAs-cog

Secondary Outcomes: Markers CSF



GLP-1, cervello e malattia di Alzheimer

DPP-4i e Protezione Cerebrale

Effect of Linagliptin on Cognitive Performance in Patients With Type 2 Diabetes and Cardiorenal Comorbidities: The CARMELINA Randomized Trial

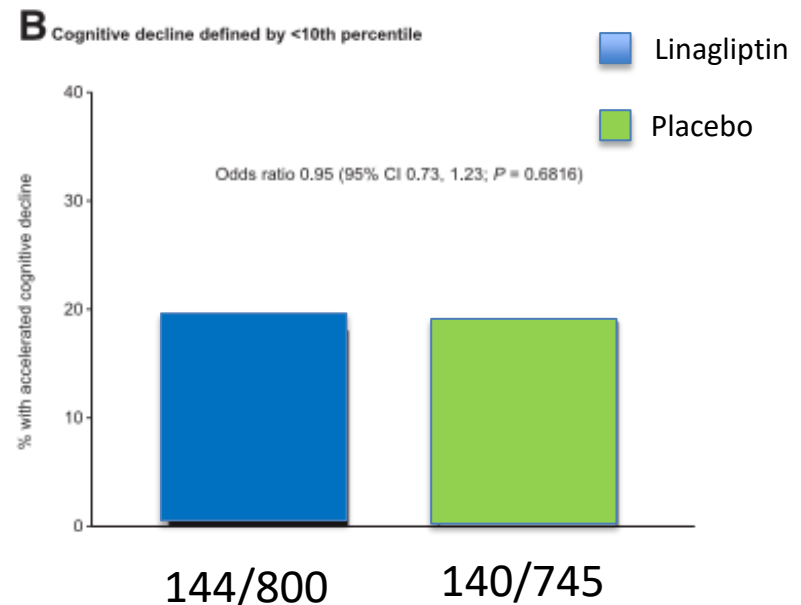
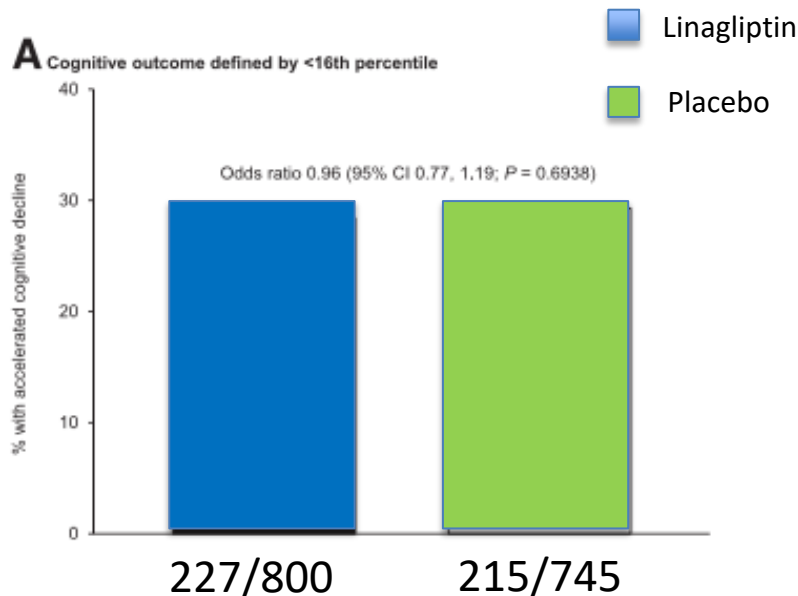
Diabetes Care 2019;42:1930–1938 | <https://doi.org/10.2337/dc19-0783>

Geert Jan Biessels,¹ Chloë Verhagen,¹
Jolien Janssen,^{1,2} Esther van den Berg,^{1,3}
Bernard Zinman,⁴ Julio Rosenstock,⁵
Jyothis T. George,⁶ Anna Passera,⁷
Sven Schnaidt,⁸ and Odd Erik Johansen,⁹ on
behalf of the CARMELINA Investigators

- Trial Randomizzato 1:1 Linagliptin/Placebo
- 1545 pazienti in prevenzione secondaria seguiti per 2,5 anni

PRIMARY OUTCOME COGNITIVO

Incidenza di declino cognitivo al di sotto del 16 percentile del MMSE



GLP-1, cervello e malattia di Alzheimer

DPP-4i e Protezione Cerebrale



Effects of Linagliptin Versus Glimepiride on Cognitive Performance in Type 2 Diabetes Mellitus: The CAROLINA® COGNITION Sub-Study

Geert J. Biessels,¹ Chloë Verhagen,¹ Jolien Janssen,^{1,2} Esther van den Berg,^{1,3} Anna Passera,⁴ Gudrun Wallenstein,⁵ Bernard Zinman,⁶ Mark A. Espeland,⁷ Odd Erik Johansen⁸

¹Department of Neurology, UMC Utrecht Brain Center, University Medical Center Utrecht, Netherlands; ²Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Netherlands; ³Department of Neurology, Erasmus MC – University Medical Center, Rotterdam, Netherlands; ⁴Biostatistics and Programming Department, HMS Analytical Software, Sulzbach, Germany; ⁵Biostatistics and Data Sciences, Boehringer Ingelheim, Ingelheim, Germany; ⁶Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada;

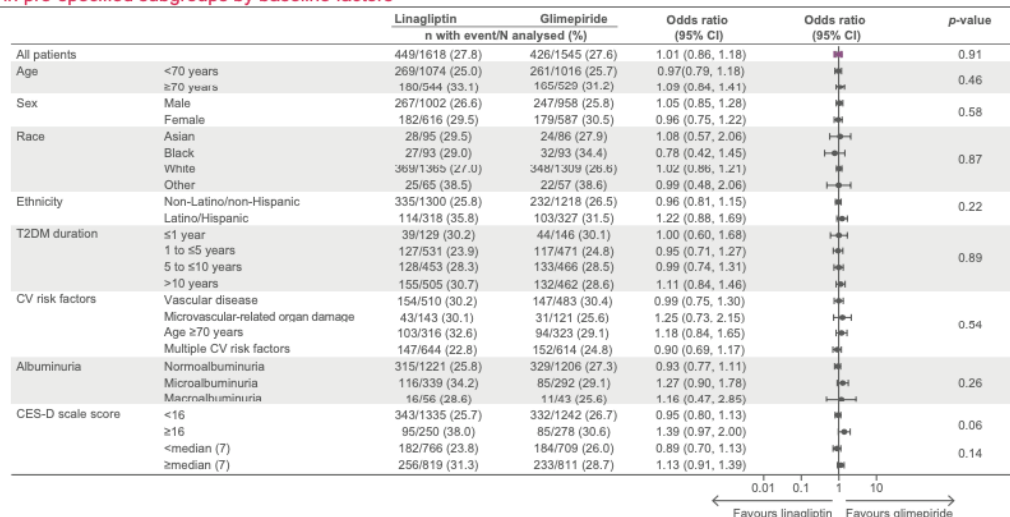
Trial Randomizzato 1:1 Linagliptin/Glimepiride

3163 pazienti seguiti per 5 anni

PRIMARY OUTCOME COGNITIVO

Incidenza di declino cognitivo al di sotto del 16 percentile del MMSE

Figure 2. Effect on accelerated cognitive decline with linagliptin versus glimepiride at end of treatment: overall effect and in pre-specified subgroups by baseline factors



CES-D, Center for Epidemiological Studies Depression Scale; CV, cardiovascular; T2DM, type 2 diabetes mellitus.

GLP-1, Cervello e Malattia di Alzheimer

CONCLUSIONI

Gli effetti extraglicemici del GLP-1 sono numerosi anche a livello cerebrale; alcuni di questi potrebbero avere un possibile ruolo neuroprotettivo.

IDPP-4i hanno dimostrato effetto neutro su outcomes legati alla performance cognitiva

I GLP-1 RAs potrebbero modificare il metabolismo cerebrale del glucosio; tuttavia, i dati clinici su outcomes cognitivi sono pochi e discordanti

Diabete e demenza

- **Terapie ipoglicemizzanti e protezione cerebrale**
- **Ipoglicemia come fattore di rischio di demenza**

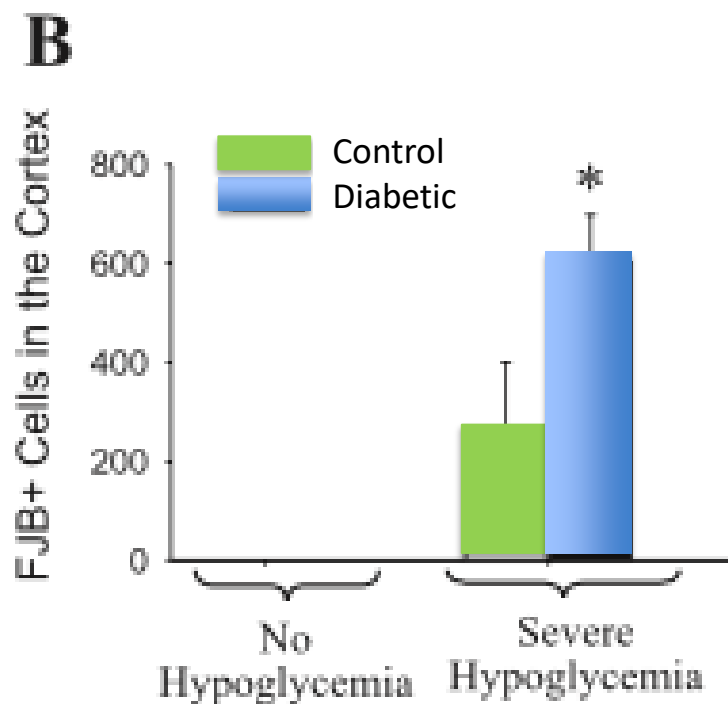
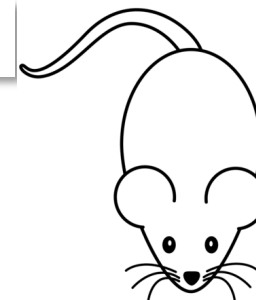
Ipoglicemia come fattore di rischio di demenza

Diabetes increases brain damage caused by severe hypoglycemia

Adam J. Bree,¹ Erwin C. Puente,¹ Dorit Daphna-Iken,¹ and Simon J. Fisher^{1,2}

¹Division of Endocrinology, Metabolism, and Lipid Research, Department of Medicine; and ²Department of Cell Biology and Physiology, Washington University, St. Louis, Missouri

Submitted 31 December 2008; accepted in final form 2 May 2009



Ipoglicemia come fattore di rischio di demenza

Hypoglycemic Episodes and Risk of Dementia in Older Patients With Type 2 Diabetes Mellitus

Rachel A. Whitmer, PhD

Andrew J. Karter, PhD

Kristine Yaffe, MD

Charles P. Quesenberry Jr, PhD

Joseph V. Selby, MD

16667 pazienti

Ipoglicemia da SDO o
da pronto soccorso.

Età media 65 anni

Follow up 1980-2007 (27 anni)

Hypoglycemia and Risk of Incident Dementia

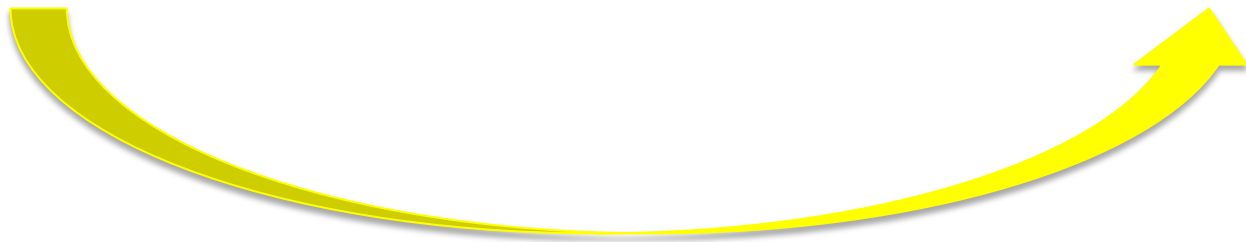
N° of Hypoglycemic Episodes	N° of Dementia Cases	HR (95%CI)*
3 or more	43	1.94
2	57	1.80
1	150	1.26

*Adjusted for Age, BMI, Race, Education, Sex, Diabetes Duration, Comorbidities, 7-years mean HbA1c, Diabetes treatment and Years of Insulin use.

Ipoglicemia come fattore di rischio di demenza

Ipoglicemia

Demenza



Ipoglicemia come fattore di rischio di demenza

Hypoglycemic Episodes and Risk of Dementia in Older Patients With Type 2 Diabetes Mellitus

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16667 pazienti

Ipoglicemia da SDO o
da pronto soccorso.

Età media 65 anni

Follow up 1980-2007 (27 anni)

Frequency of Hypoglycemic Episodes by Dementia Status

Any Hypoglycemia	Excess of Attributable risk per Year (95%) CU
No	
Yes	2.39 

N° of Hypoglycemic episodes	Excess of Attributable risk per Year (95%) CI Vs No Dementia
3 or more	4.28
2	4.34
1	1.64
0	

Ipoglicemia come fattore di rischio di demenza

Original Investigation

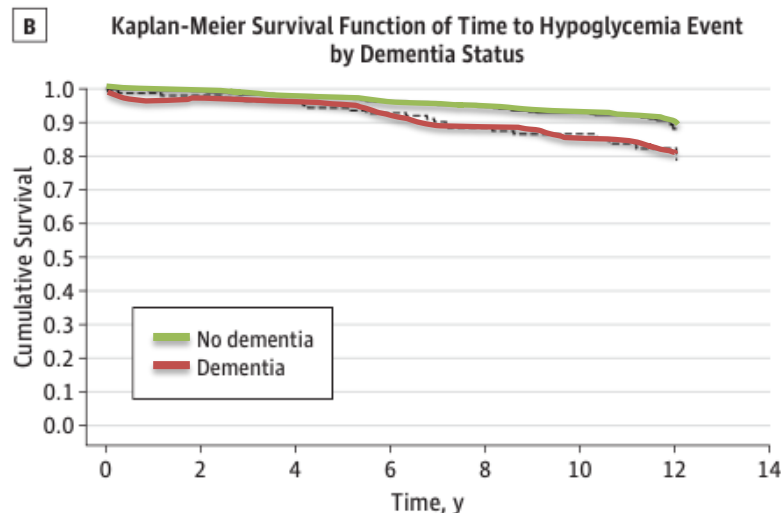
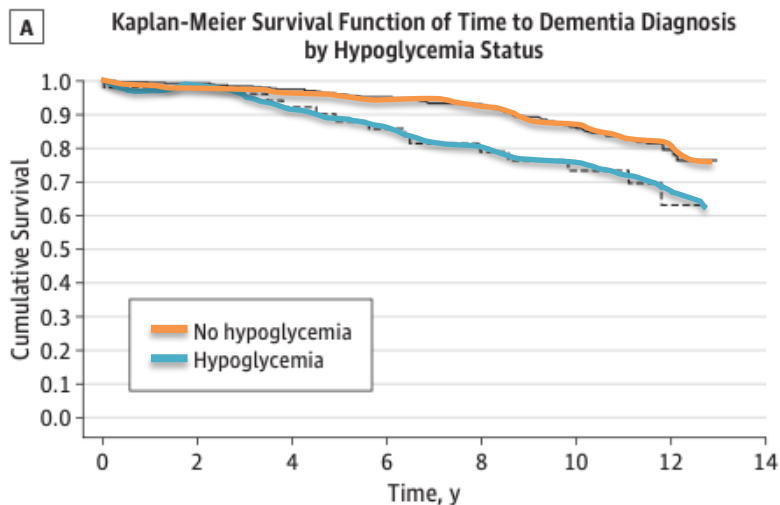
Association Between Hypoglycemia and Dementia in a Biracial Cohort of Older Adults With Diabetes Mellitus

Kristine Yaffe, MD; Cherie M. Falvey, MPH; Nathan Hamilton, MA; Tamara B. Harris, MD; Eleanor M. Simonsick, PhD; Elsa S. Strotmeyer, PhD, MPH; Ronald I. Shorr, MD, MS; Andrea Metti, MPH; Ann V. Schwartz, PhD, MPH; for the Health ABC Study

Studio condotto su 783 soggetti con diabete di tipo 2

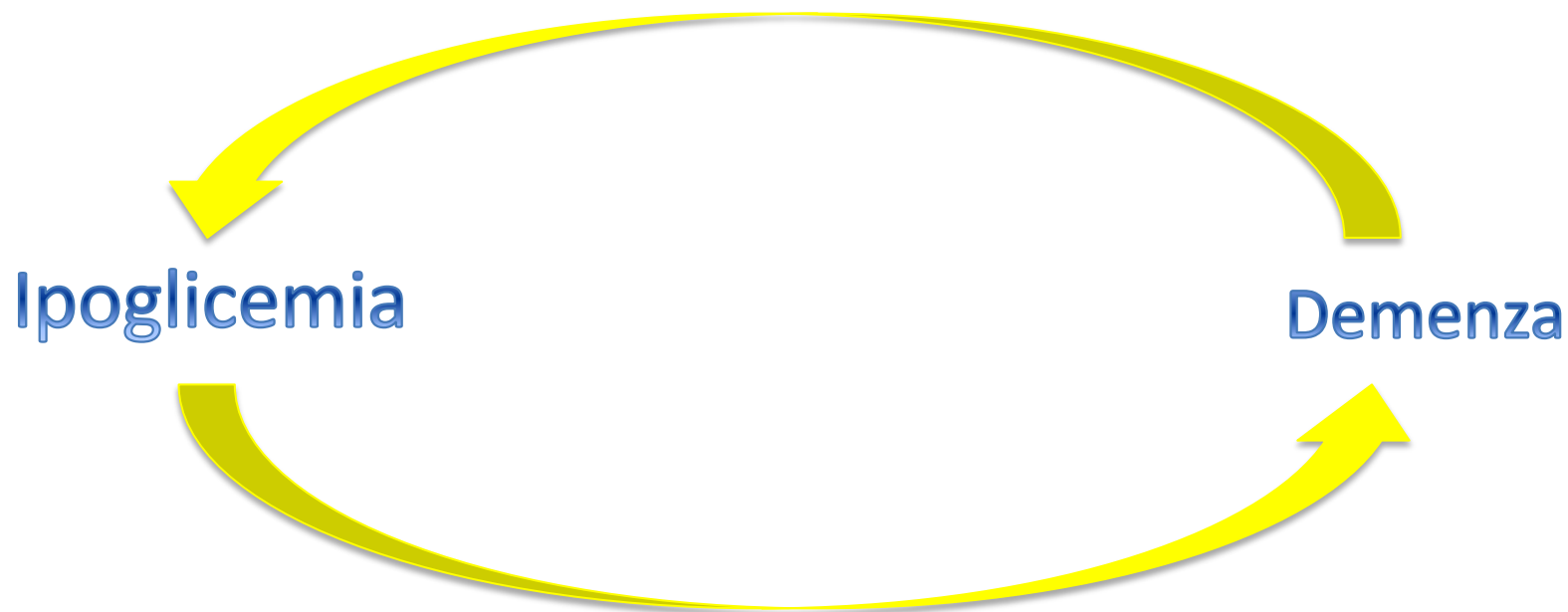
Età media 74 anni

Follow up 12 anni



Ipoglicemia come fattore di rischio di demenza

Relazione bidirezionale



Ipoglicemia come fattore di rischio di demenza

Conclusioni

Esiste un'associazione tra ipoglicemia e rischio di demenza

Tale relazione è probabilmente bidirezionale

Attenzione all'utilizzo di farmaci ad alto rischio di ipoglicemia
nella popolazione anziana