



# Comorbidità emergenti

**Domenico Mannino**



- Il sottoscritto Domenico Mannino negli ultimi due anni ha ricevuto compensi per la propria attività professionale come componente di Board scientifici o per attività congressuali da:
  - Lilly
  - Novo Nordisk
  - MSD
  - GSK

*Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).*

Donna di 79 anni  
affetta da:

- artrosi
- ipertensione
- diabete
- osteoporosi
- BPCO

| Time      | Medications†                                                                                                                                         | Other                                                                                                                                                                                                               |
|-----------|------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 7:00 AM   | ipratropium metered dose inhaler<br>70 mg/wk of alendronate                                                                                          | Check feet<br>Sit upright for 30 min on day when<br>alendronate is taken<br>Check blood sugar                                                                                                                       |
| 8:00 AM   | 500 mg of calcium and 200 IU<br>of vitamin D<br>12.5 mg of hydrochlorothiazide<br>40 mg of lisinopril<br>10 mg of glyburide<br>81 mg of aspirin      | Eat breakfast<br>2.4 g/d of sodium<br>90 mmol/d of potassium<br>Low intake of dietary saturated fat and<br>cholesterol<br>Adequate intake of magnesium and calcium                                                  |
| 12:00 PM  | 500 mg of calcium and 200 IU<br>of vitamin D                                                                                                         | Low intake of dietary saturated fat and<br>cholesterol<br>Adequate intake of magnesium and calcium                                                                                                                  |
| 1:00 PM   | ipratropium metered dose inhaler<br>500 mg of metformin<br>500 mg of calcium and 200 IU<br>of vitamin D<br>40 mg of lisinopril<br>250 mg of naproxen | Est dinner<br>2.4 g/d of sodium<br>90 mmol/d of potassium<br>Low intake of dietary saturated fat and<br>cholesterol<br>Adequate intake of magnesium and calcium<br>Medical nutrition therapy for diabetes‡<br>DASH‡ |
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| 11:00 PM  | ipratropium metered dose inhaler                                                                                                                     |                                                                                                                                                                                                                     |
| As needed | Albuterol metered dose inhaler                                                                                                                       |                                                                                                                                                                                                                     |

**13 diverse molecole**  
**18 somministrazioni**  
**+ terapia al bisogno**

Boyd, CM et al. JAMA 2005

## CASO CLINICO

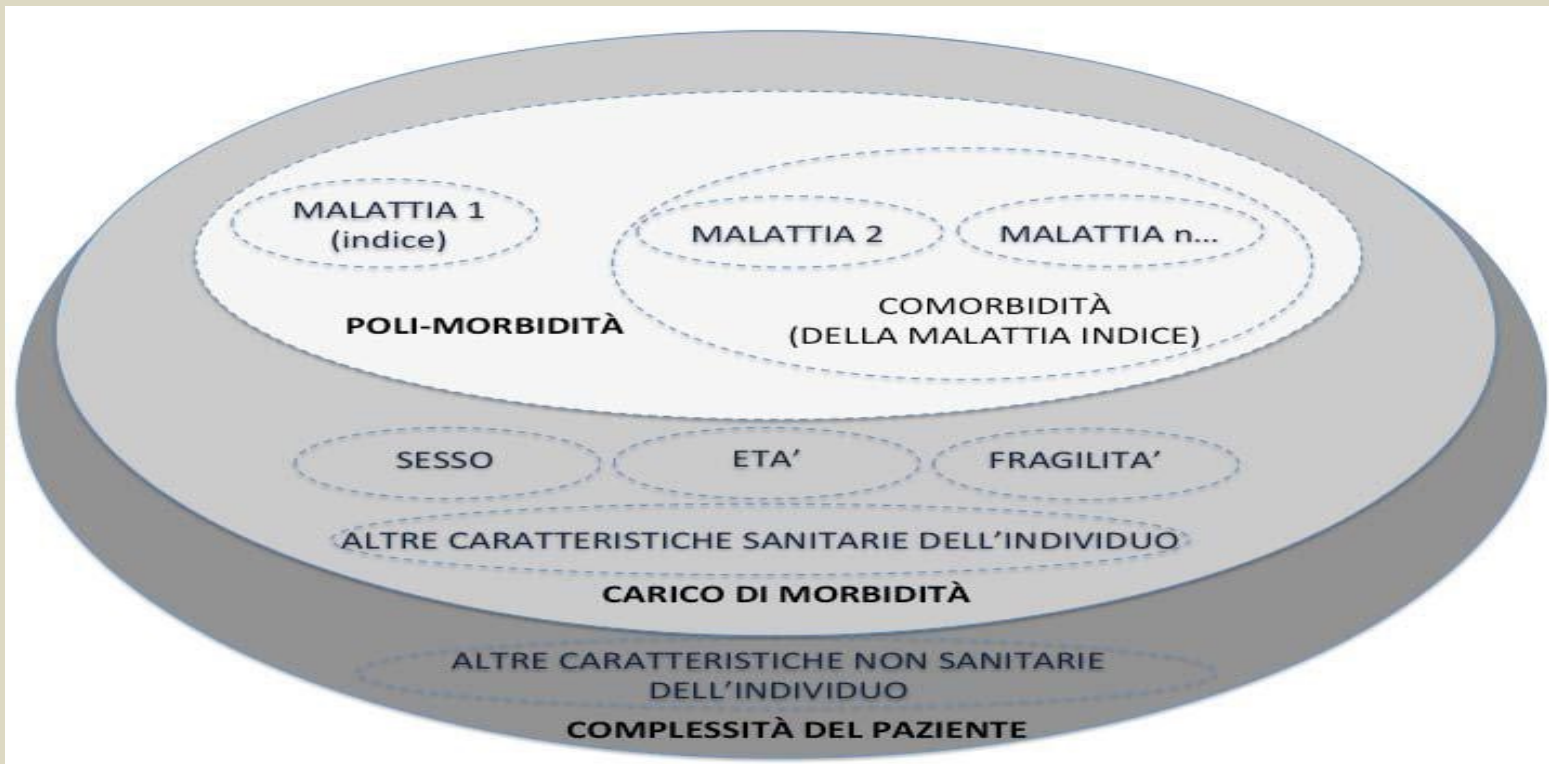
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**13 diverse molecole**  
**18 somministrazioni**  
**+ terapia al bisogno**

- Alterazione della abitudini quotidiane
- ↓ compliance/aderenza
- ↑ Interaz. farmacologiche
- ↑ reazioni avverse
- “prescribing cascade”

Boyd, CM et al. JAMA 2005

# Polimorbilità e Complessità



# Comorbidità, comorbilità, comorbosità

**DEFINIZIONE:** compresenza di patologie diverse in uno stesso individuo

Più precisamente, la comorbidità è un fenomeno per cui un paziente (**per lo più anziano**), che è in cura per una patologia (**generalmente cronica**), presenta anche un'altra o più malattie, non direttamente causate dalla prima, che condizionano la terapia, gli esiti della patologia principale, la qualità di vita del paziente, la durata di un eventuale ricovero in ospedale.

Secondo la letteratura medica, il primo a usare e definire il termine *co-morbidity* è stato l'epidemiologo americano Alvan R. Feinstein in un articolo pubblicato nel 1970 (*The pre-therapeutic classification of co-morbidity in chronic disease*, "Journal of Chronic Diseases", Vol. 23, Issue 7, pp. 455-468).

# Comprehensive Medical Evaluation and Assessment of Comorbidities: Standards of Medical Care in Diabetes

- Autoimmune Diseases
- *Cancer*
- *Cognitive Impairment/Dementia*
- Fatty Liver Disease
- Pancreatitis
- Fractures
- Hearing Impairment
- HIV
- Low Testosterone in Men
- *Obstructive Sleep Apnea*
- Psychosocial/Emotional Disorders
- Anxiety Disorders
- *Depression*
- Disordered Eating Behavior
- Serious Mental Illness

**Gli studi di epidemiologia clinica indicano che il diabete si accompagna ad un aumento del rischio di cancro**

*- aumento dell'incidenza di cancro*

*- aumento della mortalità per cancro*

# Diabetes: Relative Risk for Cancer (*RR & 95% C.I.*)

|                                   |                          |                         |
|-----------------------------------|--------------------------|-------------------------|
| <b>Liver</b>                      | <b>13 cohort studies</b> | <b>2.01 (1.61-2.51)</b> |
| <b>Pancreas</b>                   | <b>35 cohort studies</b> | <b>1.94 (1.66-2.27)</b> |
| <b>Endometrium</b>                | <b>23 cohort studies</b> | <b>1.61 (1.51-1.71)</b> |
| <b>Kidney</b>                     | <b>11 cohort studies</b> | <b>1.39 (1.09-1.78)</b> |
| <b>Colon-Rectum</b>               | <b>8 cohort studies</b>  | <b>1.21 (1.02-1.42)</b> |
| <b>Bladder</b>                    | <b>19 cohort studies</b> | <b>1.35 (1.12-1.62)</b> |
| <b>Non-Hodgkin's<br/>Lymphoma</b> | <b>11 cohort studies</b> | <b>1.21 (1.02-1.45)</b> |
| <b>Breast</b>                     | <b>20 cohort studies</b> | <b>1.23 (1.12-1.34)</b> |
| <b>Prostate</b>                   | <b>29 cohort studies</b> | <b>0.87 (0.80-0.94)</b> |

# **L' associazione tra tumori e diabete riguarda per lo più il DMT2**

**PAF (Population Attributable Factor) calcolato su : 3.727.500  
casi / 175 nazioni / 12 tumori / anni: 2002-12**

**Per i 12 tumori esaminati, dovuto ad obesità e/o  
diabete tipo 2 : 5.6%  
(circa 20.000 casi/anno in Italia)**

**24.5% di tutti i tumori del fegato**

**38.4% di tutti i tumori dell' endometrio**

# Diabetes and risk of cancer incidence: results from a population-based cohort study in northern Italy

BMC Cancer (2017) 17:703

P. Ballotari, M. Vicentini, V. Manicardi, M. Gallo, S. Chiatamone Ranieri, M. Greci and P. Giorgi Rossi

**Table 3** Population, No. of cancer, Incidence Rate Ratios (IRR) and 95% Confidence Intervals (95% CI) for type of diabetes, treatment (only for type 2 diabetes), and diabetes duration vs subjects without diabetes

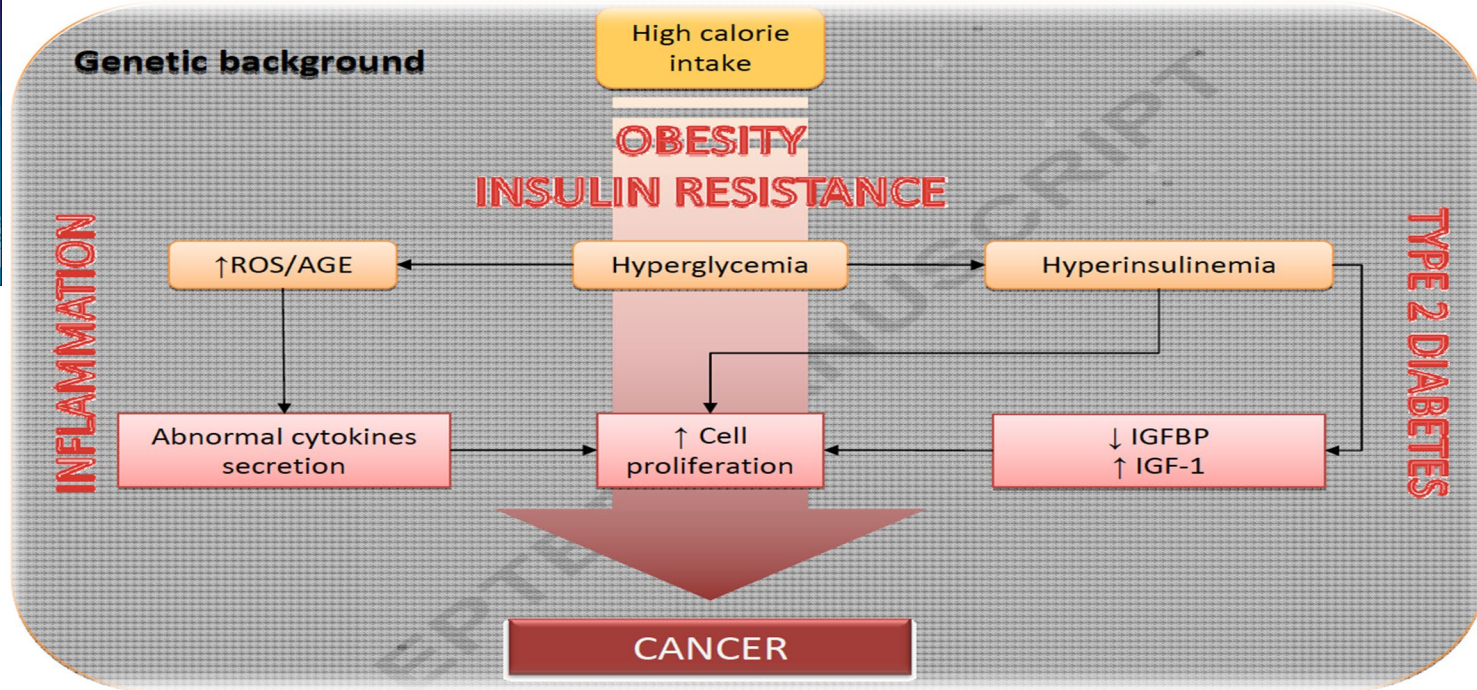
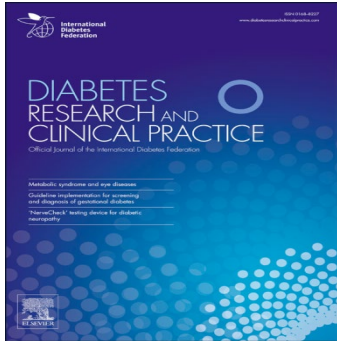
|                                 | Person-years | N cancer | IRR  | 95% CI    |
|---------------------------------|--------------|----------|------|-----------|
| Without diabetes                | 1,499,890    | 9858     | 1.00 | –         |
| With diabetes                   | 85,953       | 1464     | 1.22 | 1.15–1.29 |
| By type of diabetes:            |              |          |      |           |
| Type 1 diabetes                 | 3017         | 15       | 0.88 | 0.53–1.47 |
| Secondary diabetes <sup>a</sup> | 393          | 10       | 2.04 | 1.10–3.80 |
| Type 2 diabetes                 | 82,542       | 1439     | 1.22 | 1.15–1.29 |
| By treatment:                   |              |          |      |           |
| Diet only                       | 22,900       | 349      | 1.10 | 1.00–1.23 |
| OHIAs only                      | 44,637       | 792      | 1.22 | 1.14–1.32 |
| Insulin only                    | 7738         | 161      | 1.32 | 1.13–1.54 |
| OHIAs + insulin                 | 7267         | 137      | 1.37 | 1.16–1.62 |
| By diabetes duration (years):   |              |          |      |           |
| 0–1                             | 24,553       | 361      | 1.10 | 0.99–1.23 |
| 2–5                             | 24,710       | 403      | 1.23 | 1.11–1.36 |
| 6–10                            | 17,033       | 337      | 1.44 | 1.29–1.61 |
| 11+                             | 19,658       | 363      | 1.15 | 1.04–1.30 |

IRR = calculated using Poisson model, adjusted for age, foreign status, and sex. People without diabetes were used as reference. <sup>a</sup>diseases of the exocrine pancreas and drug-induced diabetes

This observational study, .....found an overall **15–30% higher cancer incidence among subjects with diabetes in comparison to those without diabetes**. Excess cancer risk persisted, when we restricted our analysis to patients with at least 2-years of diabetes duration. Cancer sites driving the overall increased risk were: liver, pancreas, bladder, and colon-rectum, corpus uteri for females, regardless of diabetes duration. There was also suggestion for an increased risk for kidney cancer in women and a decreased risk for prostate cancer. Compared to non-diabetic population, the excess risk was appreciable for **Type 2 diabetes**. Insulin, monotherapy or combined therapy (per se or as indication of poor blood glucose control) and diabetes duration may play a role in the association between diabetes and cancer.

# Diabetes and cancer: pathophysiological fundamentals of a 'dangerous affair'

A. Cignarelli, V.A. Genchi, I. Caruso, A. Natalicchio, S. Perrini, L. Laviola, F. Giorgino



*Diabetes Research and Clinical Practice (2018)*



## Obesity, Diabetes & Cancer

| Type of cancer           | Relative risk with BMI $\geq 30$ Kg/m <sup>2</sup> |           | Relative risk with Diabetes |           |
|--------------------------|----------------------------------------------------|-----------|-----------------------------|-----------|
|                          | Incidence                                          | Mortality | Incidence                   | Mortality |
| All types                | 1.2                                                | 1.2       | 1.3                         | 1.3       |
| Breast (post-menopausal) | 1.4                                                | 1.5       | 1.2                         | 1.5       |
| Endometrium              | 2.7                                                | 1.8       | 2.1                         | 1.8       |
| Liver                    | 1.5                                                | 1.8       | 2.5                         | 1.3       |
| Colon                    | 1.5                                                | 1.0       | 1.3                         | 1.3       |

modified by Khandekar MJ et al., Nat.Rev.Cancer 2011; Renehan A et al., The Lancet 2010; Reeves GK et al., BMJ 2007; Ohkuma et al., Diabetologia 2018

↑ Metastasis

↓ Response to therapy

*Il cancro deve essere considerato una complicanza cronica del diabete, anche se il rischio oncologico è molto inferiore al rischio cardiovascolare*

***Cosa fare?***

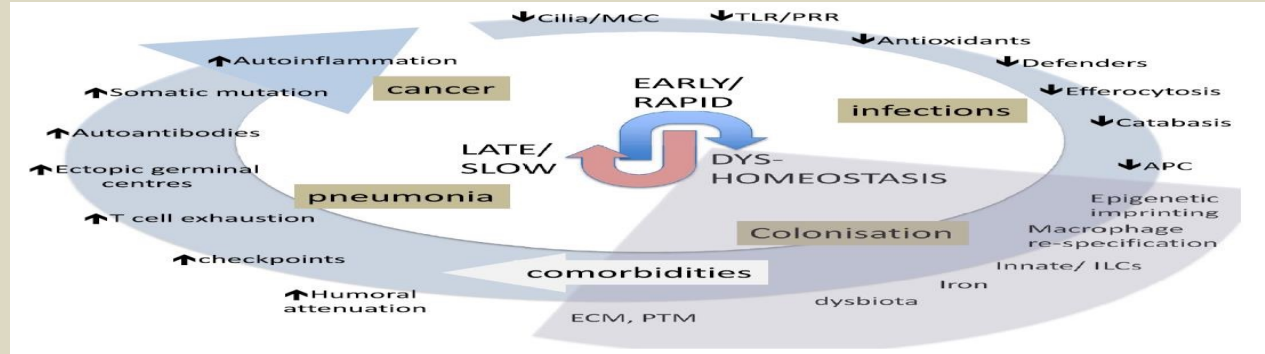
***Ridurre il rischio !***

***Pertanto...***

- ***Mantenere buon compenso metabolico ed evitare iperinsulinemia: obesità, stile di vita, metformina, dosi non troppo alte di insulina***
- ***Attenzionare la diagnosi precoce di tumore : screening oncologici specie nei soggetti a rischio più alto (familiarità, fumo, obesità, etc.)***

# Diabete e ...

BPCO



Declino  
cognitivo



## Diabete e apparato respiratorio Associazione diabete-BPCO

**Paolo Ruggeri**  
**Umberto Alecci\***  
**Giuseppe Girbino**

Dipartimento di Scienze  
Cardiovascolari e Toraciche, Clinica  
Malattie Respiratorie, Università  
di Messina; \* Medico di Medicina  
Generale, SIMG Messina

### Riassunto

La BPCO e il diabete mellito costituiscono, sotto il profilo epidemiologico, due entità nosologiche in costante e significativo incremento. Coinvolgono più frequentemente adulti in età avanzata e risultano spesso associate. Lo studio di tale associazione risulta di fondamentale importanza nel comprendere da un lato le possibili connessioni sotto il profilo eziopatogenetico, e dall'altro, sotto il profilo clinico, le ripercussioni in termini di diagnosi e modificazioni dell'approccio terapeutico specialmente per ciò che concerne la possibilità di utilizzare la terapia con corticosteroidi per via inalatoria nella fase di stabilità della BPCO e sistemica in corso di gravi riacutizzazioni. Il link patogenetico tra queste due patologie sembra essere rappresentato dall'inflammatione sistemica, oggi sempre meglio caratterizzata in corso di BPCO, che mediante l'azione di specifiche citochine (TNF- $\alpha$  e IL-6) potrebbe spiegare la più probabile comparsa di diabete in corso di BPCO. Le linee guida attuali delle due patologie non tengono in debito conto la possibilità di tale associazione, sebbene sempre maggiore interesse venga oggi rivolto al ruolo delle comorbidità nella BPCO che, si è visto,



- .....Excess weight, in particular central obesity, is also the strongest risk factor for the development of OSA.
- OSA affects about 4% of men and 2% of women in the general population, but the prevalence rate is significantly higher in the obese population.
- An increasing number of studies also show that OSA is independently associated with insulin resistance and type 2 diabetes.
- The prevalence of some form of sleep disturbance among people with diabetes is very high and can reach 58%.8.
- Both impaired glucose tolerance and diabetes have a high prevalence among people with sleep apnoea.
- Additionally, increasing insulin resistance has been correlated with increasing severity of OSA.

# Obstructive sleep apnoea syndrome in patients living with diabetes: Which patients should be screened?

A.L. Borel, R. Tamisier, P. Bohme, P. Priou, A. Avignon P.Y. Benhamou, H. Hanaire, J.L. Pépin, L. Kessler, P. Valensi, P. Darmon, F. Gagnadoux

Diabetes &  
Metabolism sept  
2018

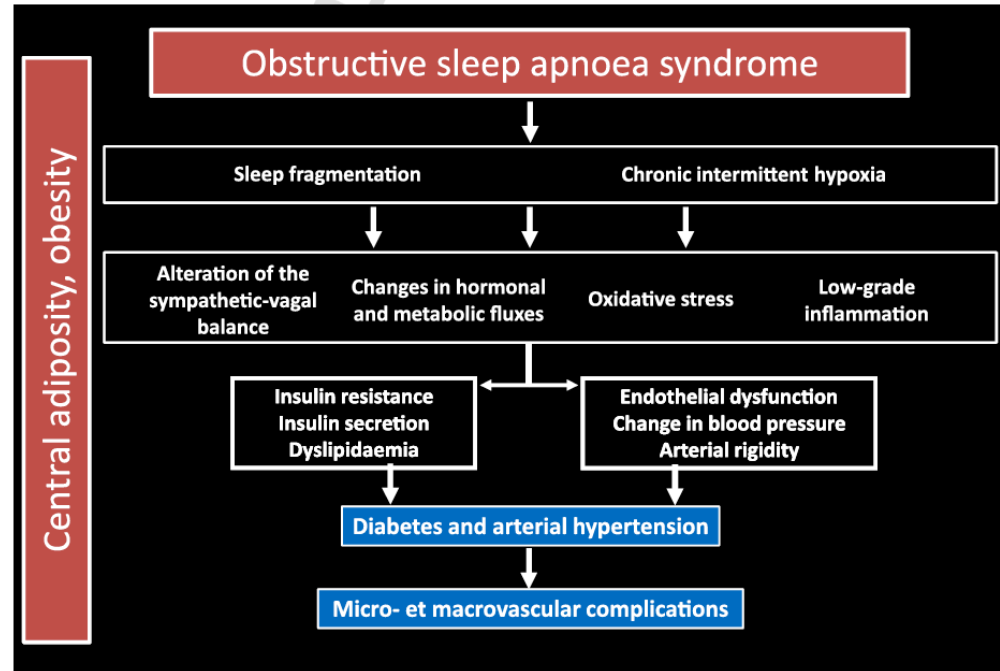
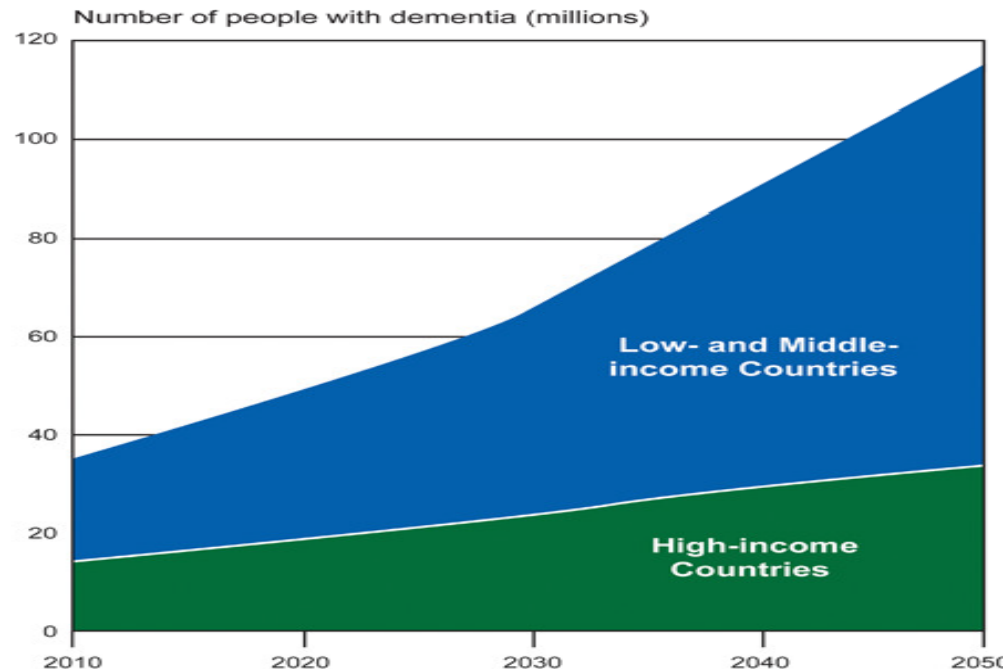


Fig. 1. Summary of the metabolic effects of obstructive sleep apnoea syndrome (OSAS).

# Dementia Prevalence Worldwide is increasing



Alzheimer's Disease  
International, *World  
Alzheimer Report, 2010.*

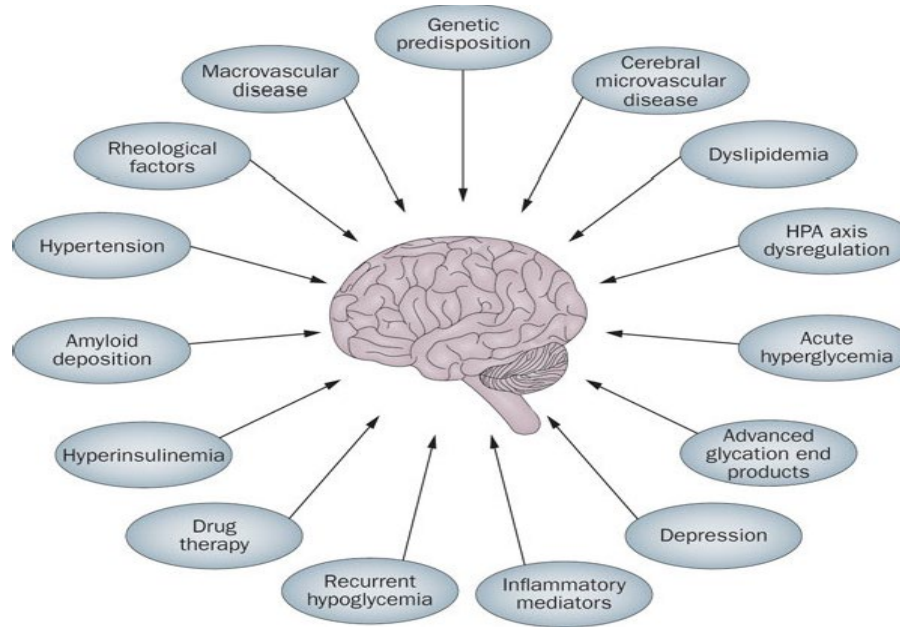
Available

at: <http://www.alz.co.uk/research/files/WorldAlzheimerReport2010>

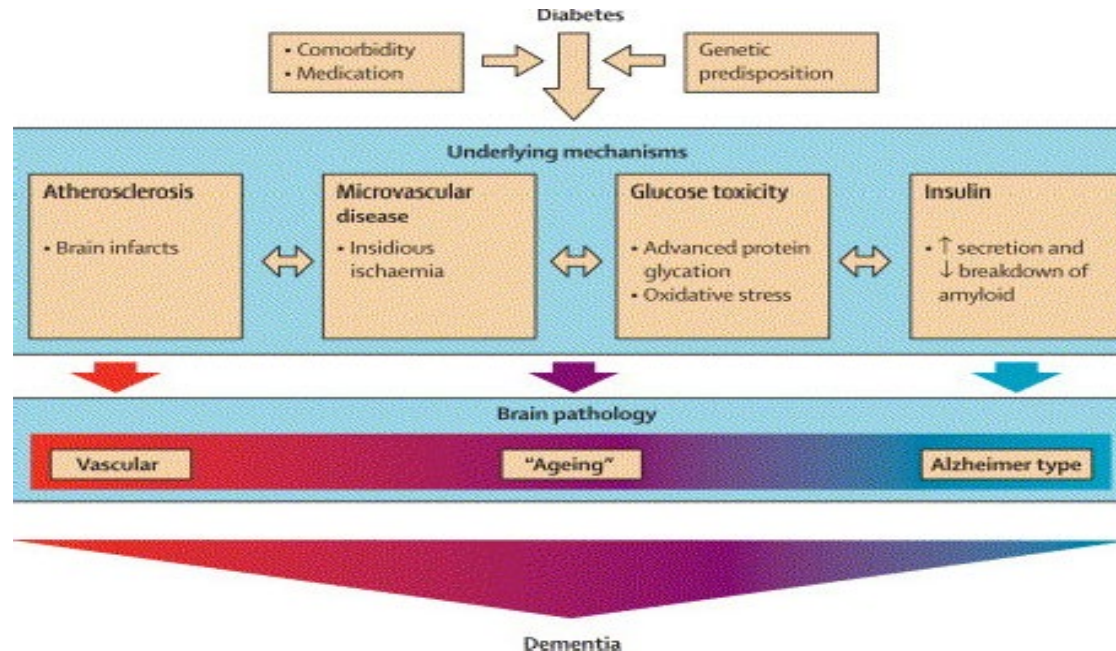
# Diabetes and Dementia

- " **Type 1 Diabetes:** mild to moderate slowing of mental speed and diminished mental flexibility
- " **Type 2 Diabetes:** cognitive changes affect *learning*, *memory*, mental flexibility and mental speed
- " The rate of cognitive decline is accelerated in elderly people with type 2 diabetes
- " T2 DM or impaired fasting glucose may be present in 80% of people with Alzheimer's disease

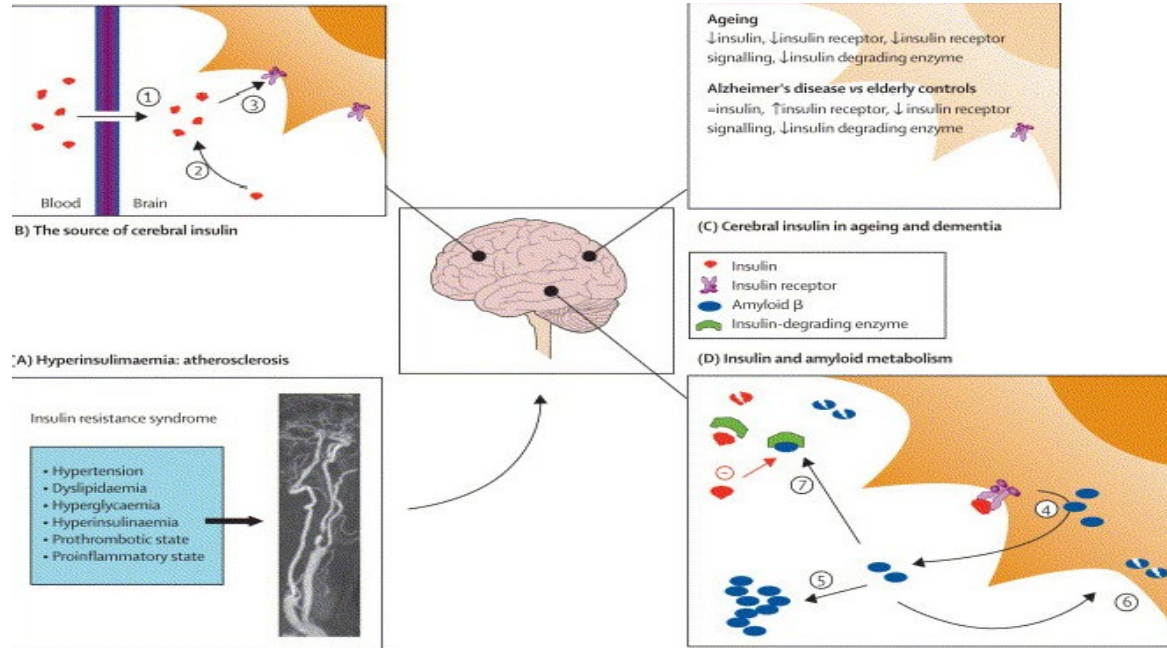
# Potential mediators of cognitive impairment in patients with type 2 diabetes mellitus.



# Determinants of the risk of dementia in individuals with diabetes.



# The potential role of insulin in the pathogenesis of dementia



# Predictors of cognitive impairment and dementia in older people with diabetes

- " Surviving participants of the Fremantle Diabetes Study (FDS), who were aged 70 years
- " Of 302 participants, 28 (9.3%) had dementia (16 with probable Alzheimer's disease) and 60 (19.9%) had cognitive impairment without dementia
- " The major independent longitudinal predictors of dementia were
  - " **older age** (per decade; odds ratio 4.0)
  - " **diabetes duration** (for each 5 years; odds ratio 1.69)
  - " **peripheral arterial disease** (odds ratio 5.35)
  - " **exercise** (which was protective; odds ratio 0.26)
  - " For Alzheimer's disease, diabetes duration was an independent predictor in addition to age and diastolic blood pressure

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

JAMA. 2009;301(15):1565-1572. doi:10.1001/jama.2009.460

**Table 3.** Hypoglycemia and Risk of Incident Dementia<sup>a</sup>

| No. of Hypoglycemic Episodes <sup>b</sup> | No. of Dementia Cases | Hazard Ratio (95% Confidence Interval)                                                          |                                                      |                                                                                                             |
|-------------------------------------------|-----------------------|-------------------------------------------------------------------------------------------------|------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|
|                                           |                       | Adjusted for Age (as Time Scale), BMI, Race/Ethnicity, Education, Sex, and Duration of Diabetes | Additionally Adjusted for Comorbidities <sup>c</sup> | Additionally Adjusted for 7-Year Mean HbA <sub>1c</sub> Level, Diabetes Treatment, and Years of Insulin Use |
| 1 or more                                 | 250                   | 1.68 (1.47-1.93)                                                                                | 1.48 (1.29-1.70)                                     | 1.44 (1.25-1.66)                                                                                            |
| 1                                         | 150                   | 1.45 (1.23-1.72)                                                                                | 1.29 (1.10-1.53)                                     | 1.26 (1.10-1.49)                                                                                            |
| 2                                         | 57                    | 2.15 (1.64-2.81)                                                                                | 1.86 (1.42-2.43)                                     | 1.80 (1.37-2.36)                                                                                            |
| 3 or more                                 | 43                    | 2.60 (1.78-3.79)                                                                                | 2.10 (1.48-2.73)                                     | 1.94 (1.42-2.64)                                                                                            |

Abbreviations: BMI, body mass index; HbA<sub>1c</sub>, glycated hemoglobin.

<sup>a</sup>Analyses combined using Cox proportional hazard models.

<sup>b</sup>The 1 or more group was compared to 0 and 1, 2, and 3 or more groups were simultaneously compared to 0.

<sup>c</sup>Adjustment made using a comorbidity composite scale.

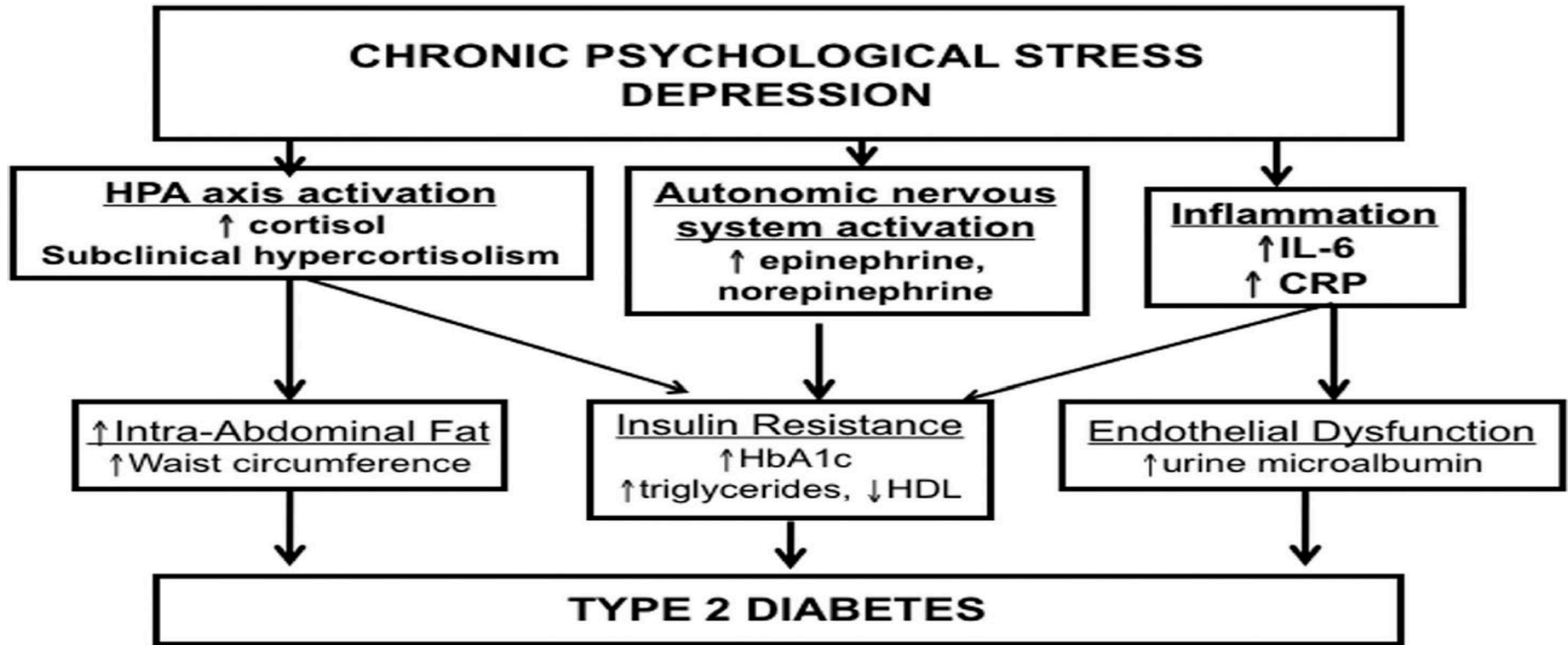
# Glucocorticoids and depression

- " Depression is a well-established risk factor for cognitive impairment
- " Depression is more common in people with DM
- " High cortisol levels and more depressive symptoms were associated with high blood glucose levels in people with DM
- " This effect was stronger in African American participants (who have a high incidence of both diabetes and depression) than in white individuals<sup>1</sup>
- " Is depression due to neurotransmitter changes from metabolic changes in DM, or due to cerebrovascular disease?
- " Relation between Type 2 DM and depression may be bidirectional; type 2 DM may develop from depression<sup>2</sup>

1. Boyle, S.H. et al. *Diabetes Care* 30, 2484-2488 (2007)

2. Myint, Aye Aye et al. *Science* 2.3, 114-121(2013)

# Cortisol dysregulation: the bidirectional link between stress, depression, and type



**Figure 1.**

A hypothesized relationship between stress, depression, cortisol, and diabetes.

CENTRAL

PERIPHERAL

1. Hippocampal Receptors (GR + MR) and Hippocampal Function are impaired in T2DM

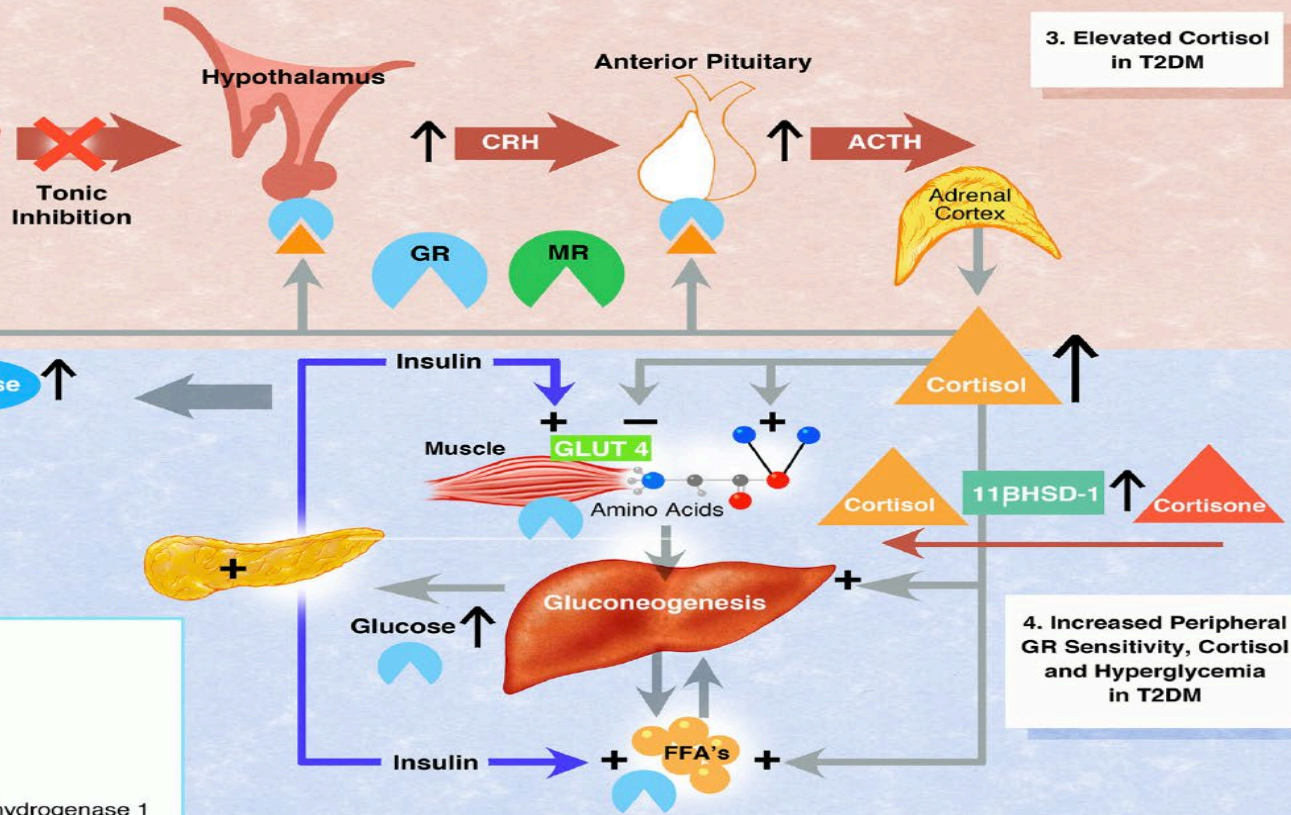
2. Impaired Anterior Pituitary GR in T2DM

3. Elevated Cortisol in T2DM

T2DM

5. Hyperglycemia and Hypercortisolism in T2DM result in a Vicious Cycle

GR = Glucocorticoid Receptor  
 GLU = Glucose  
 ACTH = Adrenocorticotropic Hormone  
 FFA = Free Fatty Acid  
 POMC = Pro-opiomelanocortin  
 Cortisol =   
 T2DM = Type 2 Diabetes Mellitus  
 11βHSD-1 = (11-beta) Hydroxysteroid Dehydrogenase 1  
 MR = Mineralocorticoid Receptor  
 CRH = Corticotropin-Releasing Hormone



# Medicina della complessità

Linee guida propongono riferimenti per pazienti affetti da una singola condizione morbosa, mentre l'esperienza clinica quotidiana ci propone assai frequentemente condizioni multiple.

# criticità e proposte

bisogno di integrazione e  
comunicazione

manca di percorsi condivisi

assenza di protocolli comuni

necessità di  
“strutturazioni di sistema”

limiti reciproci nelle conoscenze per  
l'altra branca

gestione frammentata

ambulatori condivisi / GIC  
team interdisciplinari

strumenti e protocolli operativi  
comuni

integrazione in rete

sistema informativo unico

formazione (individuale/di gruppo)

tavoli di lavoro e mod. organizzativi  
aziendali / PDTA

# Approccio Olistico

Presa in carico

- ORGANICA
- INTER-DISCIPLINARE
- TEMPESTIVA

Medicina personalizzata e persona-centrica

Approccio globale: concezione del paziente nella sua UNICITA' e COMPLESSITA' biologica;

Aumentata compliance alle terapie.



GRAZIE PER L'ATTENZIONE