L'adulto con sindrome di Down: un paziente geriatrico?

Graziano Onder
Centro Medicina Invecchiamento
Università Cattolica Sacro Cuore
Policlinico A. Gemelli

UNIVERSITÀ CATTOLICA del Sacro Cuore

Progerie

Patologia	Frequenza	Gene
Hutchinson–Gilford	1/6 milioni	LMNA

Laminina

1. componente della lamina nucleare;
2. organizzazione della cromatina, regolazione epigenetica, replicazione, trascrizione e riparazione del DNA

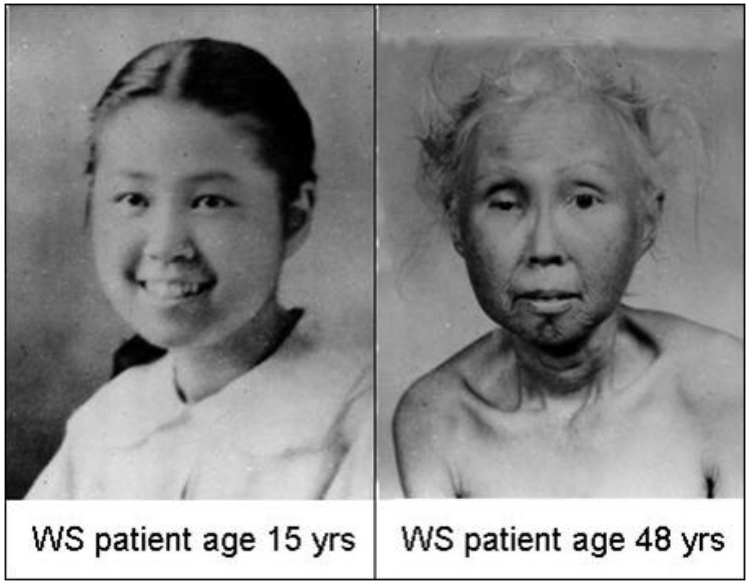
Progerie

Patologia	Frequenza	Gene
Hutchinson–Gilford	1/6 milioni	LMNA
Werner	1/1 milione	WRN

***WRN* gene**

1. Elicasi mantiene la stabilità del genoma (‘caretaker of the genome’)

2. replicazione e riparazione del DNA e di mantenimento della lunghezza dei telomeri



Progerie

Patologia	Frequenza	Gene
Hutchinson–Gilford	1/6 milioni	LMNA
Werner	1/1 milione	WRN
Bloom	1/1 milione	BLM

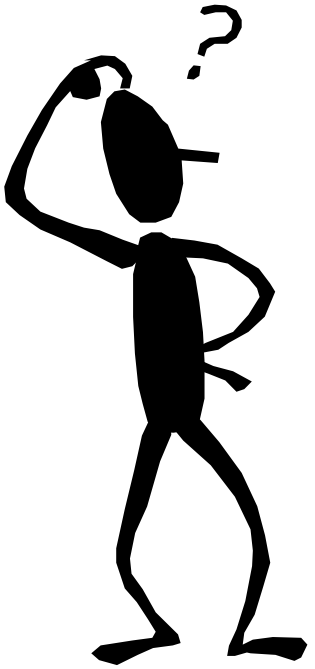
BLM

1. Elicasi che stabilizza il processo di svolgimento del DNA
2. Errori di copiatura, rottura e risaldatura dei cromosomi.

Progerie

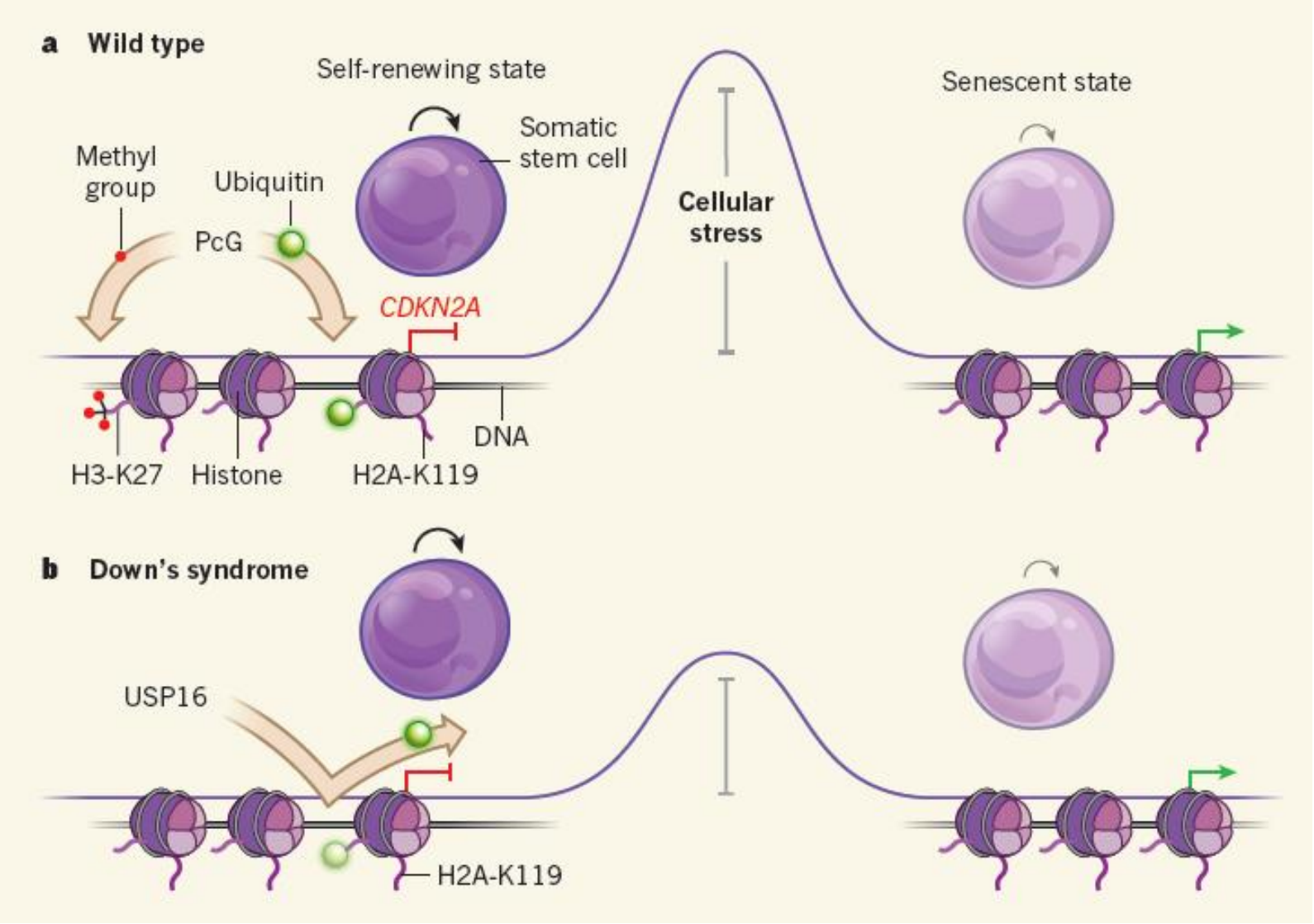
Patologia	Frequenza	Gene	Cancro
Hutchinson–Gilford	1/6 milioni	LMNA	-
Werner	1/1 milione	WRN	↑↑
Bloom	1/1 milione	BLM	↑↑

La sindrome di Down è una progeria?



Sindrome di Down - Stess ossidativo

Symbol	Name
BTG3	BTG family, member 3
MRPL39	Mitochondrial ribosomal protein L39
ATP5J	Mitochondrial coupling factor 6
GABPA	GA binding protein transcription factor, alpha subunit 60kDa
BACH1	BTB and CNC homology 1, basic leucine zipper transcription factor 1
SOD1	Superoxide dismutase 1, soluble
CRYZL1	Crystallin, zeta (quinone reductase)-like
ATP5O	ATP synthase H+ transporting, mitochondrial F1 complex
MRPS6	Mitochondrial ribosomal protein S6
DSCR1	Down syndrome critical region 1
CBR1	Carbonyl reductase 1
CBR3	Carbonyl reductase 3
SH3BGR	SH3 domain binding glutamic acid-rich protein
NDUFV3	NADH dehydrogenase (ubiquinone) flavoprotein 3, 10kDa
SNF1LK	SNF1-like kinase
C21orf2	Chromosome 2 open reading frame (mitochondrial protein)



Triplication of the enzyme USP16 in models of Down's syndrome creates defects in the stem cells resident in adult tissues.

Souroullas et al Nature 2013

nature

Sindrome di Down - Geni

Gene	Patologia
APP	Demenza di Alzheimer
ERG, TAM e AML1	Leucemia
DFNB10 e Claudin 14	Sordità
NCAM	Sviluppo cerebrale
Cristallina α	Cataratta
Interferon α e β, ω receptors 1 e 2, ϒ receptor 2 (integrina β2)	Patologie autoimmuni
BACE (Beta Amyloid site cleaving enzyme)	Demenza di Alzheimer (?)
S100Beta	Sviluppo cerebrale – Demenza di Alzheimer ?

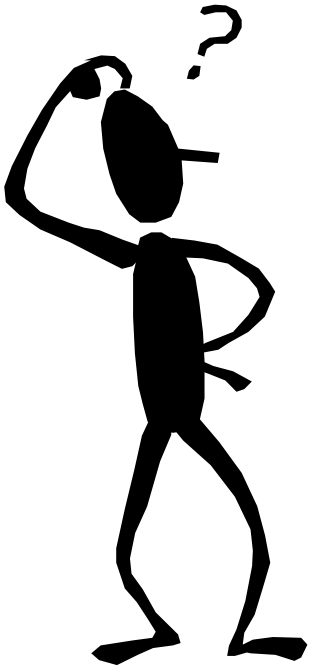
Standardised mortality odds ratios (SMORs) of selected medical disorders in people with Down's syndrome

	SMOR (95% CI)
Disorder	
Aspiration, pneumonia or influenza	7·61 (7·36–7·87)
Congenital heart defects	29·10 (27·8–30·4)
Seizure disorder	7·80 (7·39–8·23)
Infectious and parasitic diseases	1·14 (1·08–1·20)
Ischaemic heart disease	0·42 (0·40–0·45)
Diseases of pulmonary circulation	3·83 (3·60–4·07)
Dementia	21·10 (19·6–22·7)
Other congenital anomalies	0·92 (0·85–1·01)
Hypothyroidism	20·30 (18·5–22·3)
Diabetes	0·63 (0·58–0·69)
Leukaemia	1·57 (1·41–1·75)
Other malignancy	0·07 (0·06–0·08)
Obesity	1·87 (1·63–2·15)
Protein/calorie malnutrition	1·41 (1·20–1·65)
Viral hepatitis	3·30 (2·81–3·89)
Intestinal obstruction	1·29 (1·06–1·58)
Sudden infant death syndrome.	0·08 (0·06–0·11)

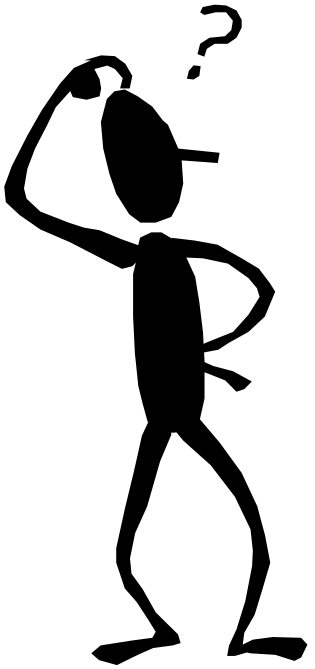
Yang et al Lancet 2002 THE LANCET

La sindrome di Down è una progeria?

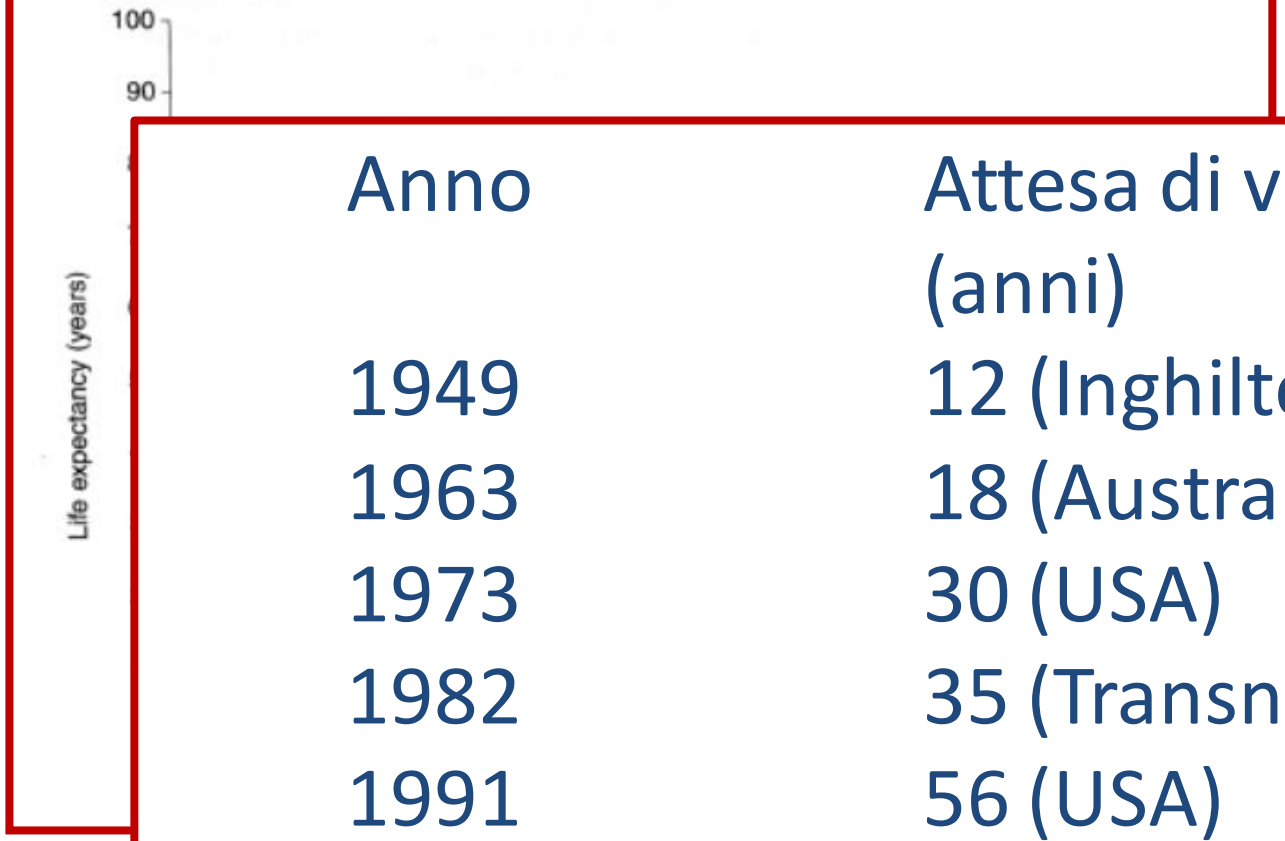
Non da un punto di vista biologico



Deve essere il geriatra a farsene carico?



Attesa di vita – Sindrome di Down



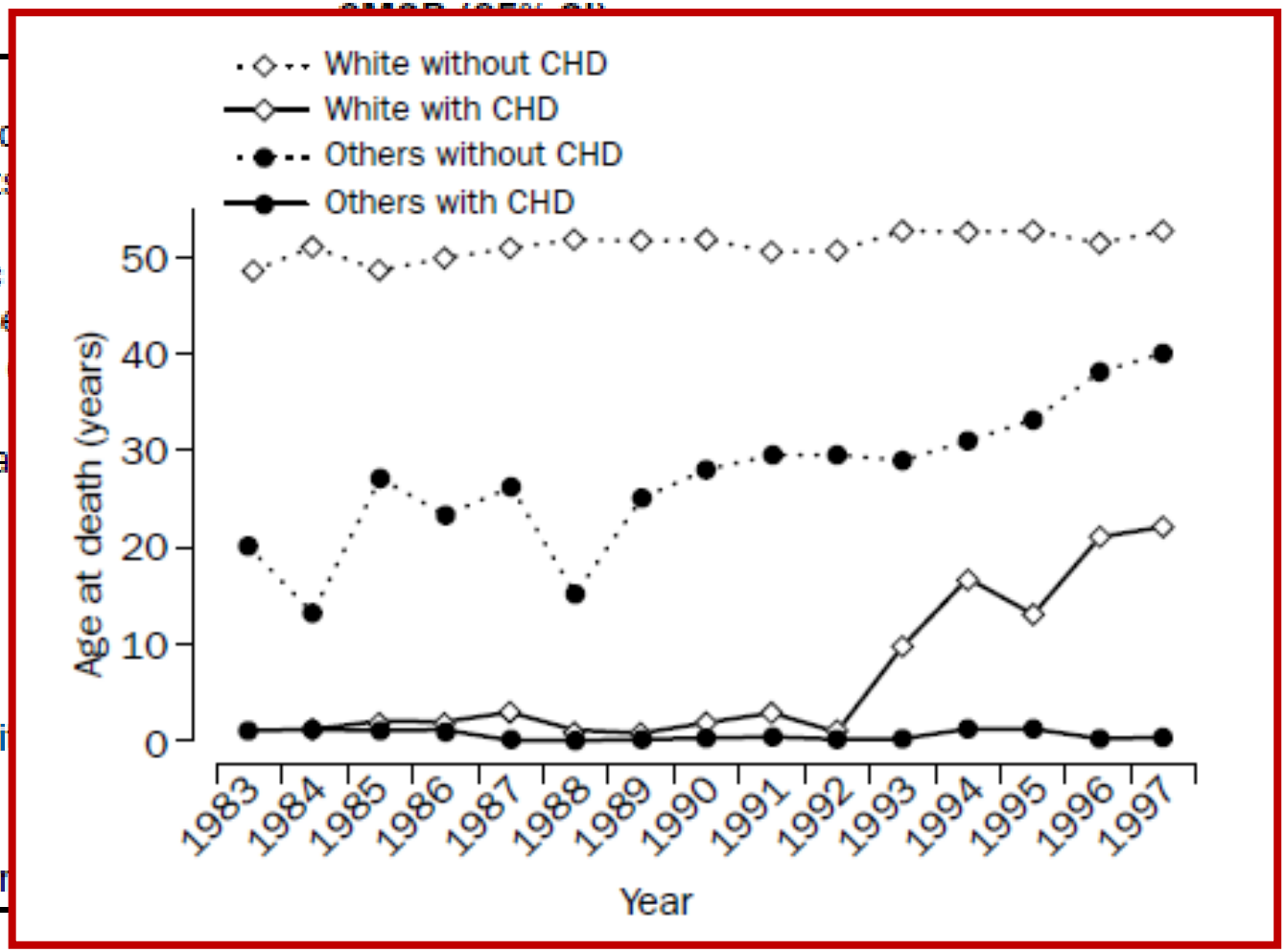
Anno	Attesa di vita media (anni)
1949	12 (Inghilterra)
1963	18 (Australia)
1973	30 (USA)
1982	35 (Transnational)
1991	56 (USA)
2002	60 (Australia)

- In

Down di cui il 61% ha più di 25 anni.

Aumento attesa di vita

Disorder
Aspiration, pneumonia c
Congenital heart defect
Seizure disorder
Infectious and parasitic
Ischaemic heart disease
Diseases of pulmonary
Dementia
Other congenital anoma
Hypothyroidism
Diabetes
Leukaemia
Other malignancy
Obesity
Protein/calorie malnutri
Viral hepatitis
Intestinal obstruction
Sudden infant death syr



Yang et al Lancet 2002 THE LANCET

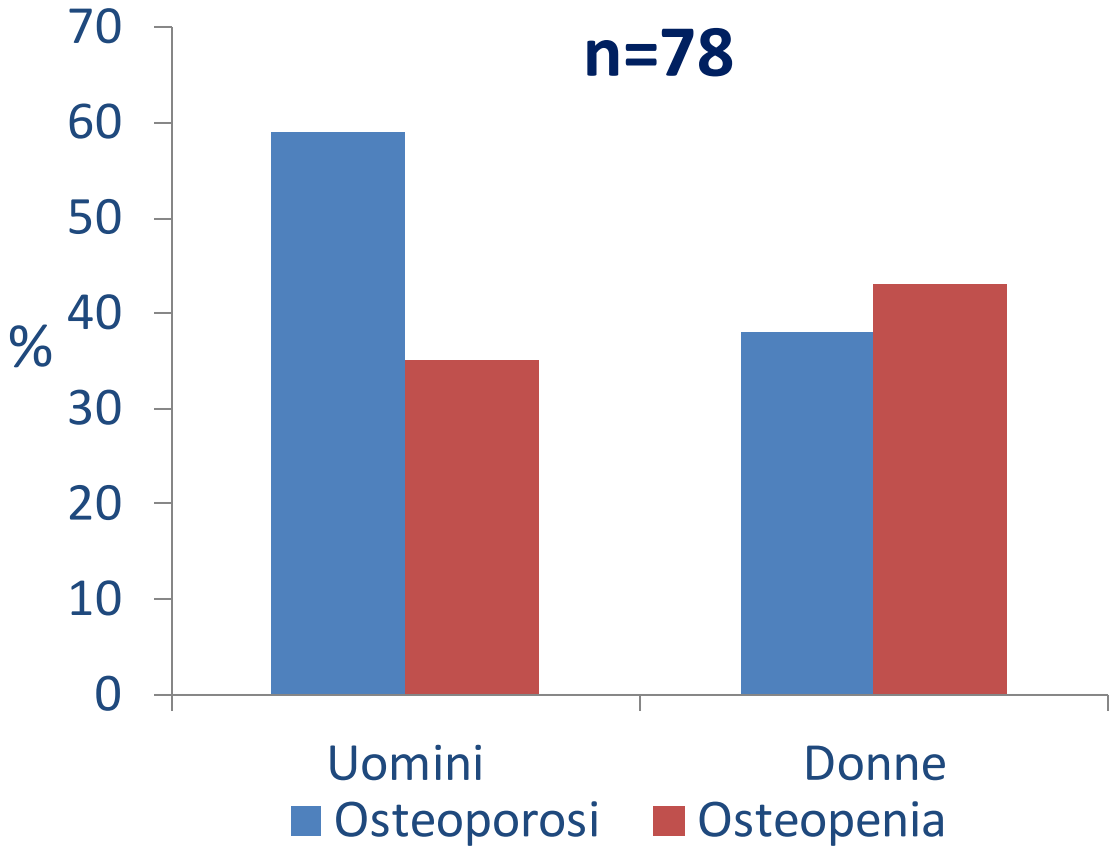
Sindrome di Down - Adulto

Dati letteratura + campione 78 Persone con SD adulti (età media 41 aa; range 21 -75 aa) afferenti al DH di Geriatria, Policlinico A. Gemelli

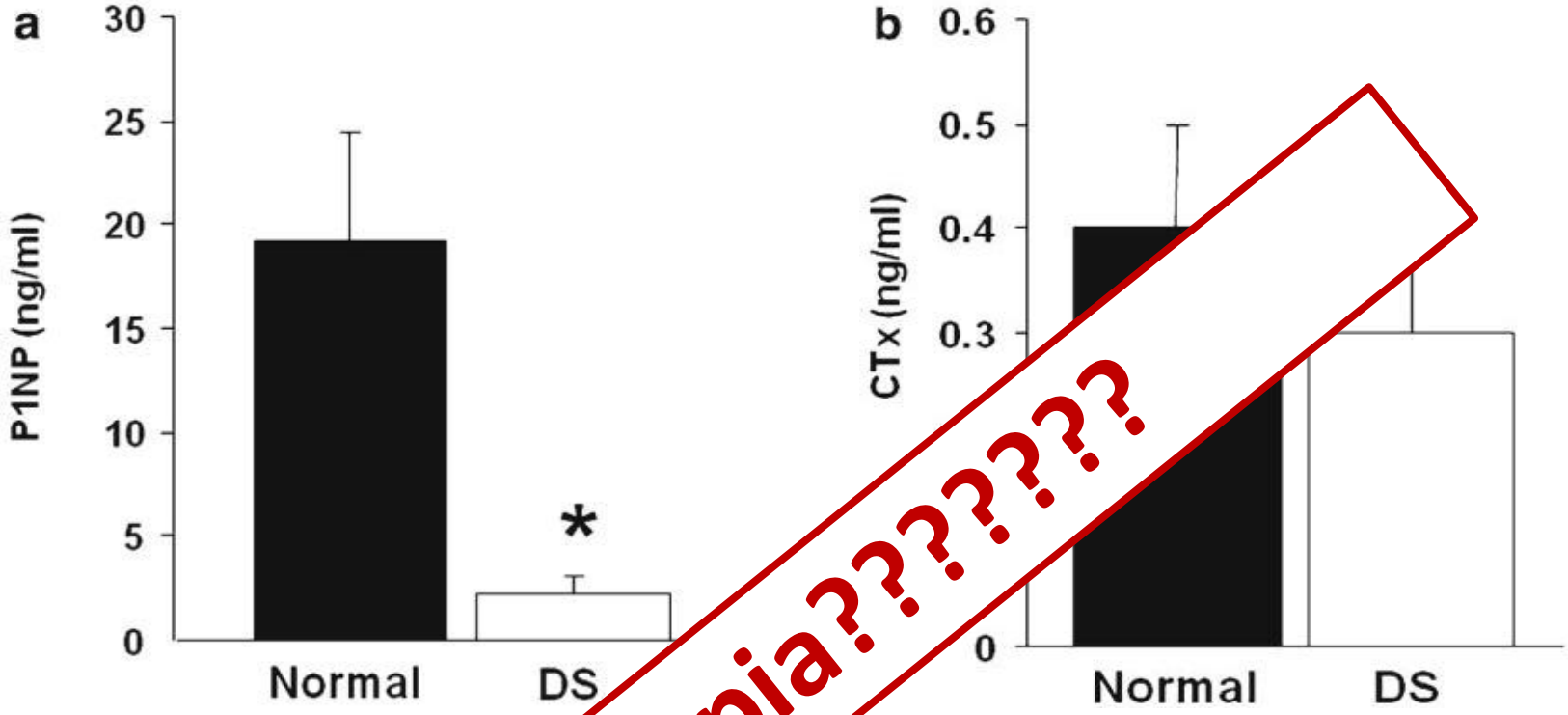
Patologie

- **Osteoporosi**

Sindrome di Down - Osteoporosi



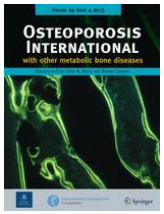
Cause	%
Deficit vit D	86.4%
Celiachia*	4.1%
Antiepilettici	17.1%
Problemi tiroidei	63.4%
Ipomobilità	10.4%
Ormoni	???



Terapia???????

Low BMD in adu[illegible] DS is correlated with a significant d[illegible]n bone formation markers and is **indepe[illegible]of gender** … **diminished osteobla[illegible]bone formation**, with no significant differences in bone resorption…

McKelvey et al. Osteoporosis Int 2013



Sindrome di Down - Adulto

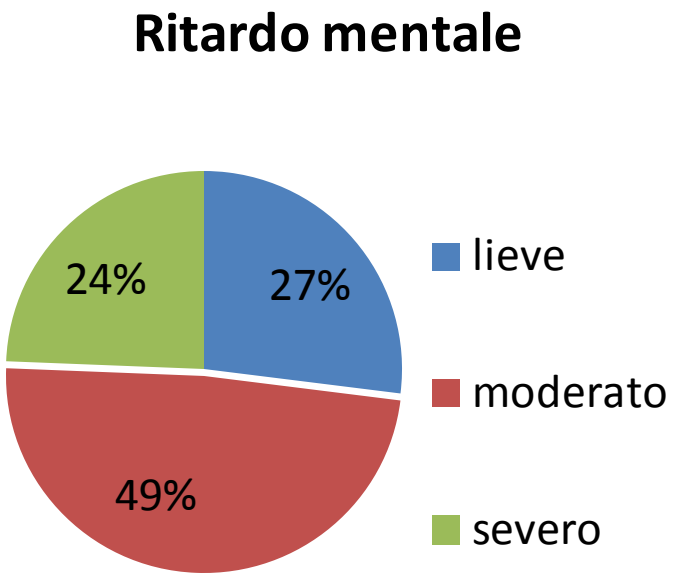
Patologie

- Osteoporosi
- **Demenza**

Demenza – Diagnosi clinica

- Complessità di valutazione: deficit di sviluppo + patologia degenerativa

Cause (n=78)	%
Deficit vitaminici	22.4%
Psicofarmaci	30.1%
Deficit sensoriali	25.6%
Problemi tiroidei	63.4%



Demenza - Trattamento

To date there is only one small randomised controlled study on the effect of **donepezil**. This shows, at best, **a modest, non statistically significant trend in favour of people with Down syndrome and Alzheimer's dementia who are able to tolerate donepezil**. This study does not provide good evidence on which to base practice…

Cochrane Database Syst Rev, 1 (2009), p. CD007178

Demenza - Trattamento

	Memantine group	Placebo group	Difference (95% CI)	p value
Mean change in total DAMES				
No dementia	−4·6 (39·2); n=52	−0·8 (19·8); n=49	−3·7 (−15·5 to 8·1)	0·53*
Dementia	−8·4 (18·3); n=20	−4·0 (19·1); n=25	−4·5 (−16·1 to 7·2)	0·44*
Mean change in total DAMES, excluding zero values				
No dementia	−5·6 (41·9); n=43	−1·7 (21·5); n=39	−4·8 (−18·8 to 9·3)	0·50*
Dementia	−9·3 (27·5); n=7	−1·2 (22·7); n=15	−8·0 (−31·9 to 15·8)	0·49*
Mean change in ABS part I				
No dementia	−4·4 (33·6); n=53	1·4 (37·0); n=48	−3·2 (−16·4 to 10·0)	0·63*
Dementia	−25·7 (41·5); n=22	−7·6 (31·0); n=25	−18·8 (−40·6 to 3·1)	0·09*
Median change in ABS part II				
No dementia	0 (−11·0 to 13·0); n=53	1·5 (−11·5 to 8·5); n=48	1·6 (−7·3 to 10·5)	0·91†
Dementia	3 (−33·0 to 24·0); n=22	−1 (−13·0 to 20·0); n=25	5·3 (−7·2 to 11·3)	0·93†

Data are mean (SD) or median (IQR) unless otherwise stated. ABS=adaptive behaviour scale. DAMES=Down's syndrome attention, memory and executive function scale. *Analysis of covariance with baseline score fitted as covariate. †Quantile regression with baseline score fitted as covariate.

Table 4: **Primary outcome measures at 52 weeks, stratified by dementia status at randomisation**

Hanney et al. Lancet 2012 THE LANCET

Sindrome di Down - Adulto

Patologie

- Osteoporosi
- Demenza
- **Problemi cardiaci**

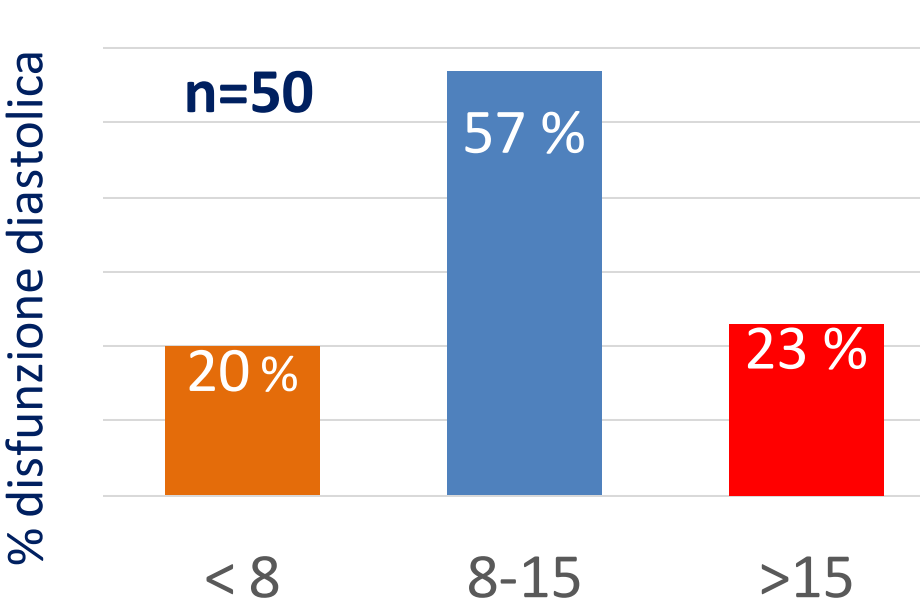
Standardised mortality odds ratios (SMORs) of selected medical disorders in people with Down's syndrome

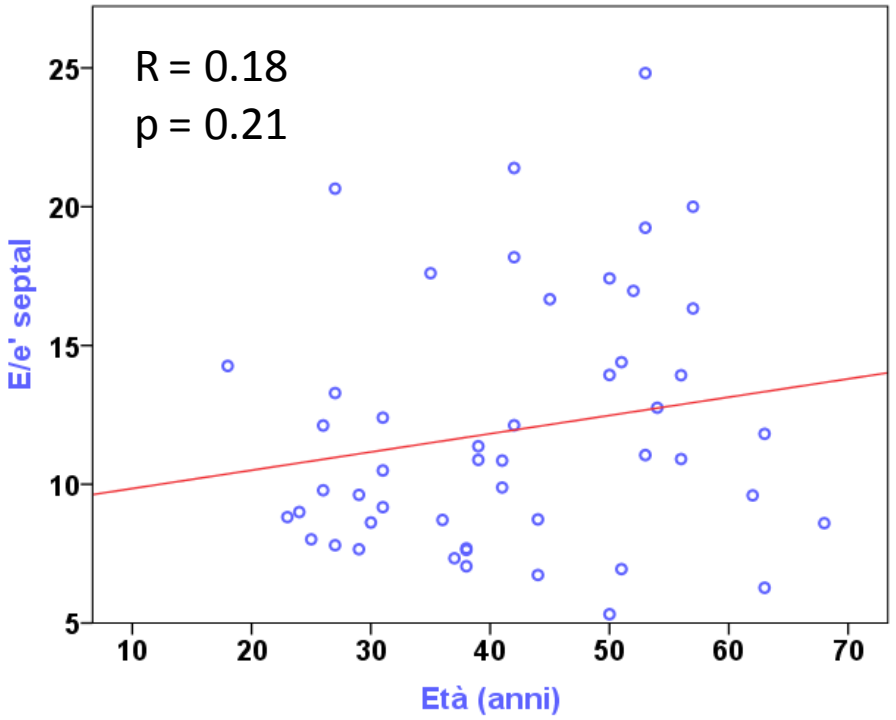
Disorder	SMOR (95% CI)
Aspiration, pneumonia or influenza	7·61 (7·36–7·87)
Congenital heart defects	29·10 (27·8–30·4)
Seizure disorder	7·80 (7·39–8·23)
Infectious and parasitic diseases	1·14 (1·08–1·20)
Ischaemic heart disease	0·42 (0·40–0·45)
Diseases of pulmonary circulation	3·83 (3·60–4·07)
Dementia	21·10 (19·6–22·7)
Other congenital anomalies	0·92 (0·85–1·01)
Hypothyroidism	20·30 (18·5–22·3)
Diabetes	0·63 (0·58–0·69)
Leukaemia	1·57 (1·41–1·75)
Other malignancy	0·07 (0·06–0·08)
Obesity	1·87 (1·63–2·15)
Protein/calorie malnutrition	1·41 (1·20–1·65)
Viral hepatitis	3·30 (2·81–3·89)
Intestinal obstruction	1·29 (1·06–1·58)
Sudden infant death syndrome.	0·08 (0·06–0·11)

Yang et al Lancet 2002

THE LANCET

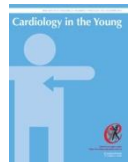
Disfunzione Diastolica (E/e' septal)





Children with Down syndrome had significantly higher … left ventricular diastolic dysfunction detected by tissue Doppler than observed in the controls.

Al-Biltagi et al. Cardiol Young. 2013

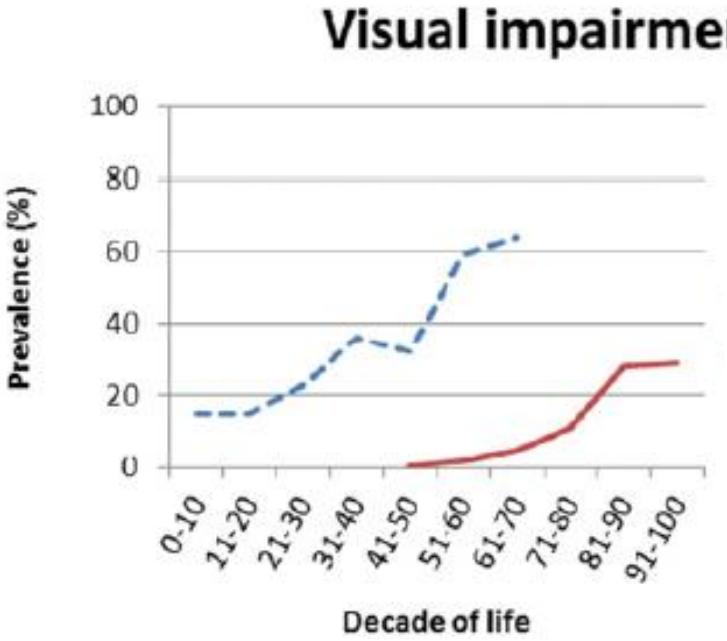


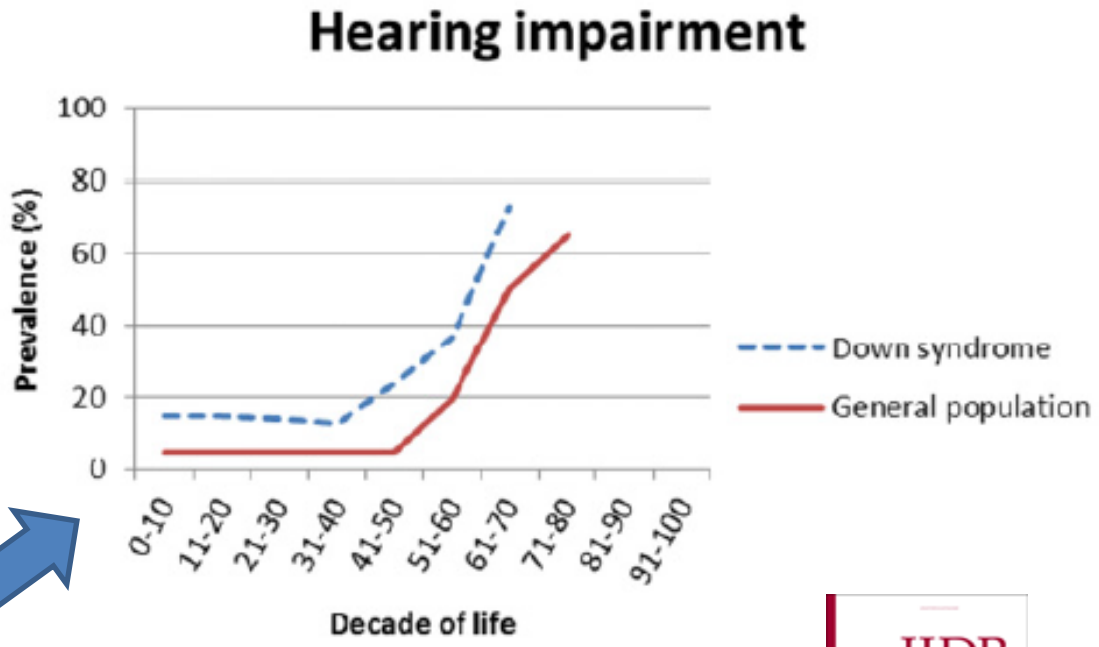
Sindrome di Down - Adulto

Patologie

- Osteoporosi
- Demenza
- Problemi cardiaci
- **Deficit sensoriali**

Deficit sensoriali e sindrome Down





Screening con esame audioimpedenziometrico

Ipoacusia 20/78 (25.6%)

Glasson EJ et al. JIDR 2013

Sindrome di Down - Adulto

Patologie

- Osteoporosi
- Demenza
- Problemi cardiaci
- Deficit sensoriali

OSAS	88%
Anemia	17%
Leucopenia	47%
Tiroidite	58%
Epilessia	22%

Sindrome di Down - Adulto

Patologie

- Osteoporosi
- Demenza
- Problemi cardiaci
- Deficit sensoriali

Condizioni geriatriche

- **Problemi nutrizionali**

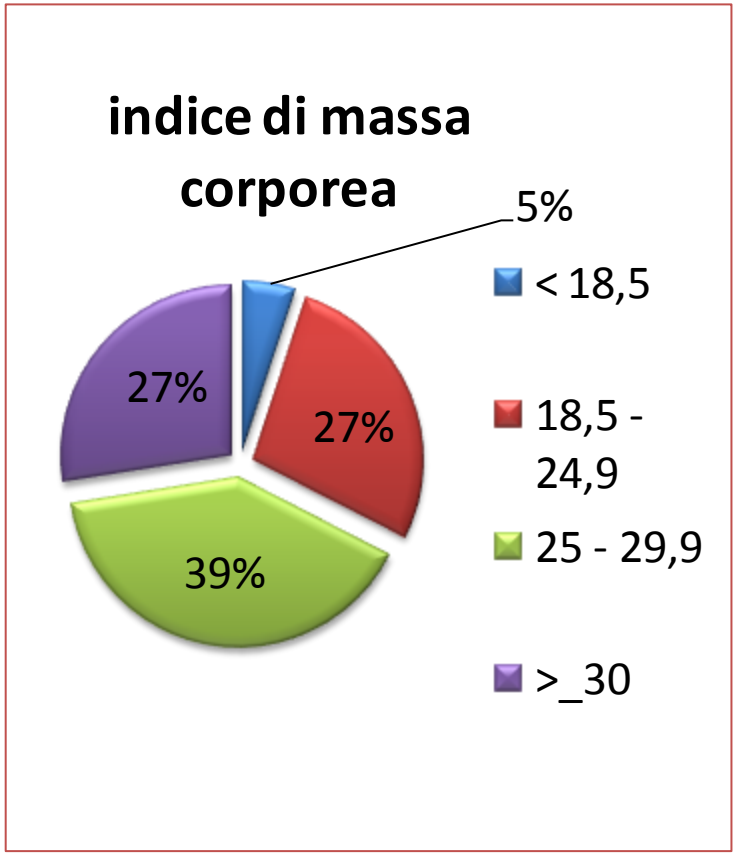
Valutazione nutrizionale

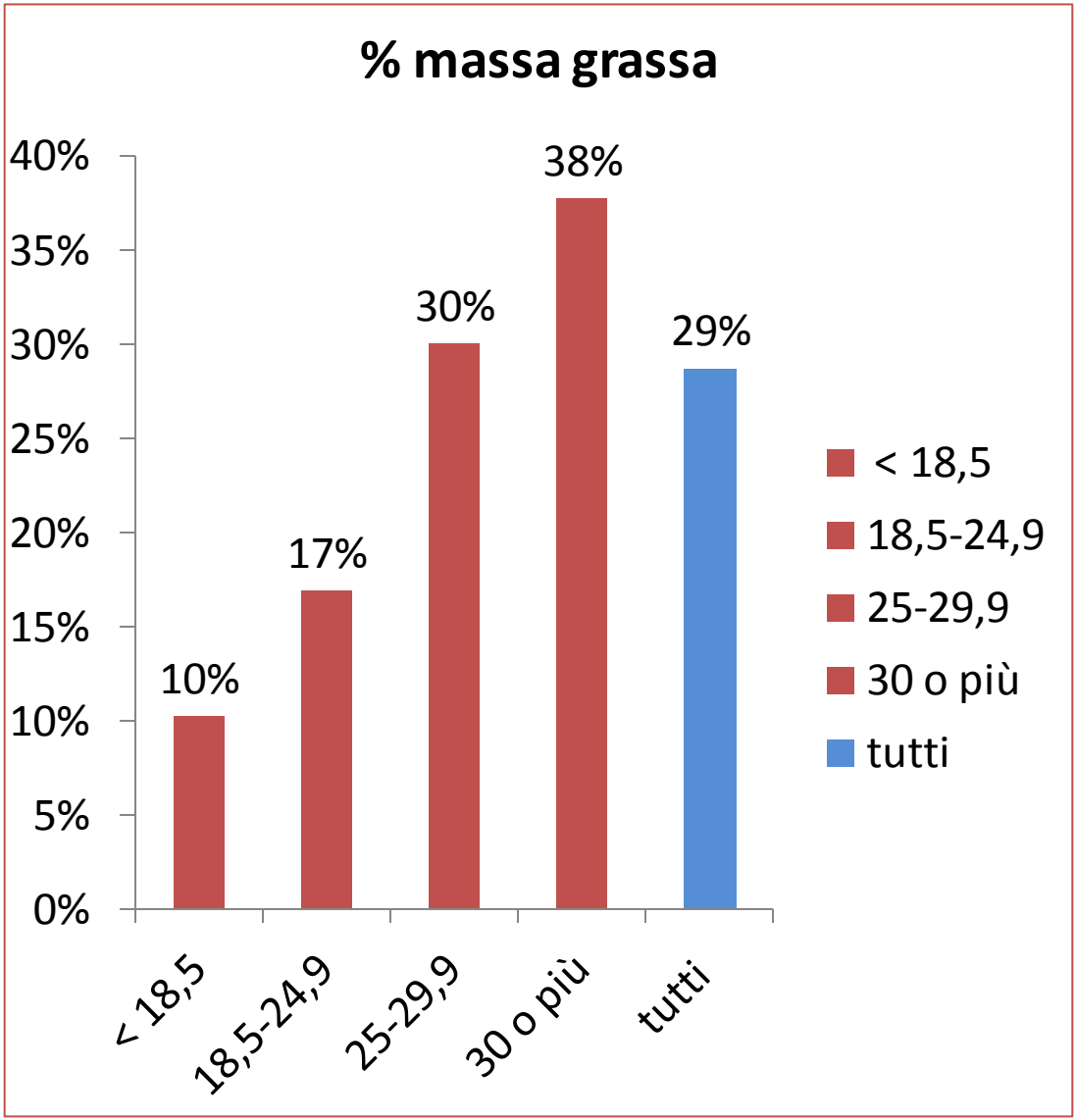
Il campione: 41 adulti affetti da sindrome di Down, 20 uomini e 21 donne, tra i 20 e i 64 anni (media 39 anni), reclutati al Day Hospital di geriatria del Policlinico A. Gemelli, Università Cattolica del Sacro Cuore.

I dati raccolti :

- Peso
- Altezza
- Circonferenza polso, braccio, vita ,fianchi
- BIA
- Grip strenght
- Intervista alimentare
- Parametri ematochimici
- Velocità del passo

Valutazione nutrizionale





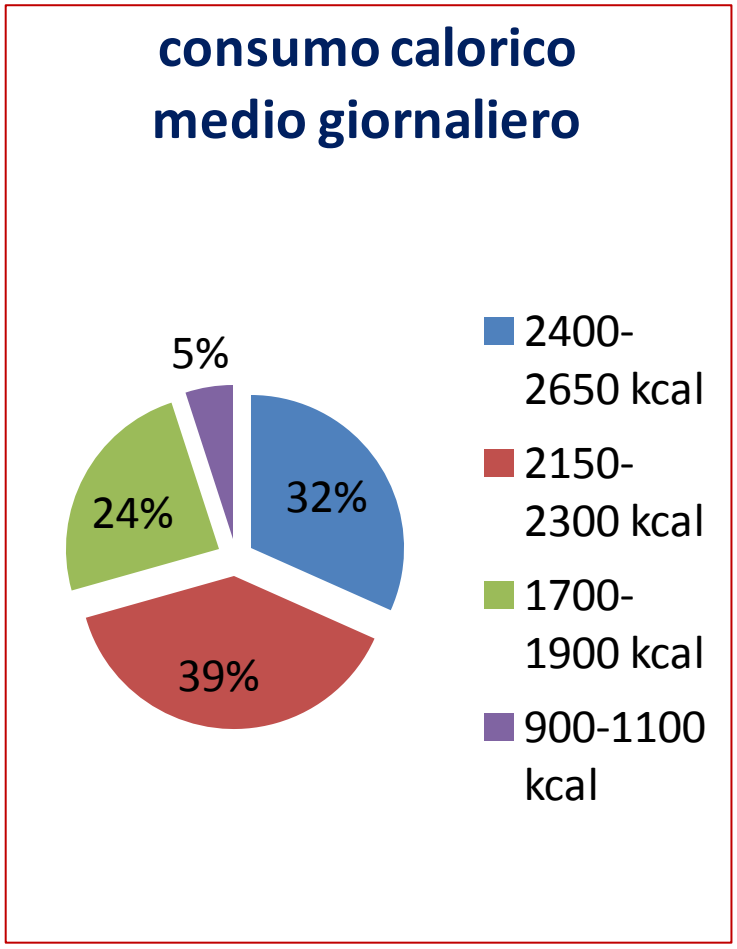
Valutazione nutrizionale

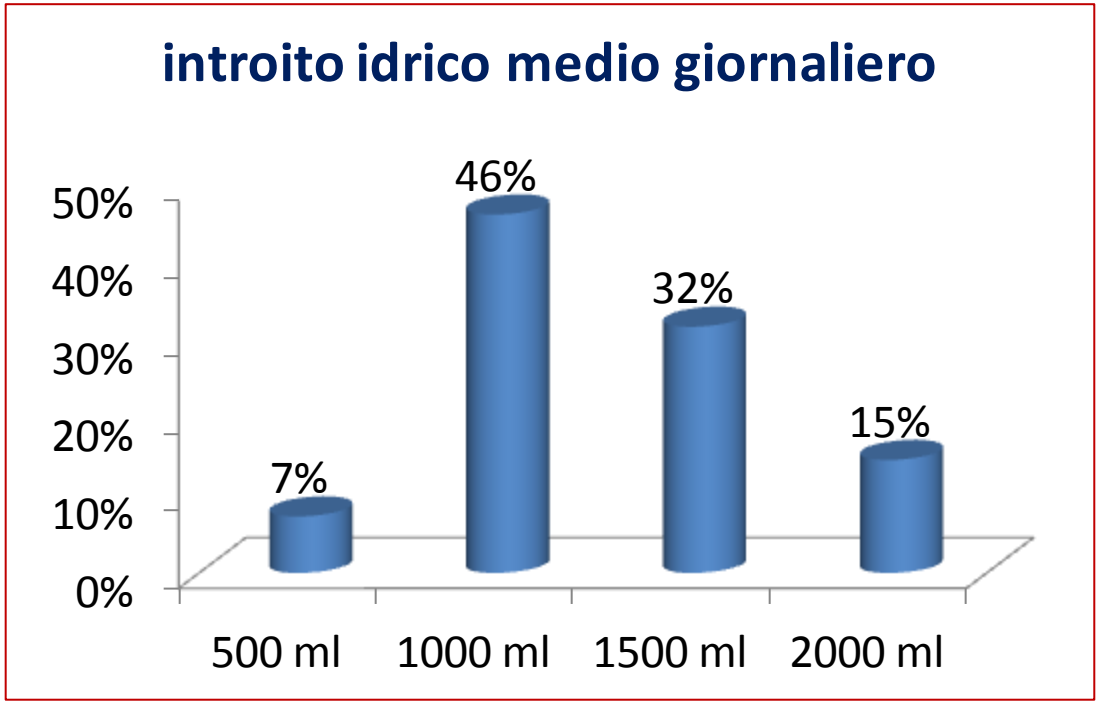
↓ Angolo di fase < 5,5 °	35 (85%)
↓ Skeletal muscle index	2 (5%)
↑ Rapporto vita fianchi > 0,95	16 (39%)
↑ Circonferenza vita > 95 cm	9 (22%)

↓ Folati	13 (32%)
↓ Vitamina B12	9 (22%)
↓ Vitamina D	36 (88%)

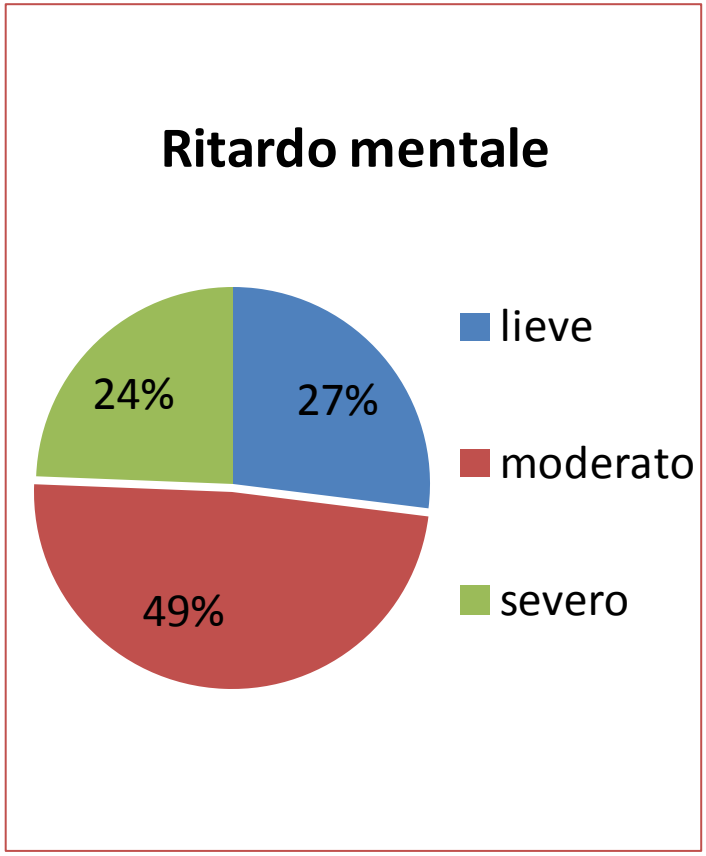
Risultati - Valutazione

Intervista alimentare





Problemi nutrizionali - Cause



Deficit funzionali	22 (53,7 %)
Uso antipsicotici	7 (17,1%)
Politerapia	10 (24,4%)
Problemi alla tiroide	26 (63,4%)
Diabete	1 (2,4%)
Celiachia	5 (9,8%)
Problemi sociali	12 (29,3%)

Sindrome di Down - Adulto

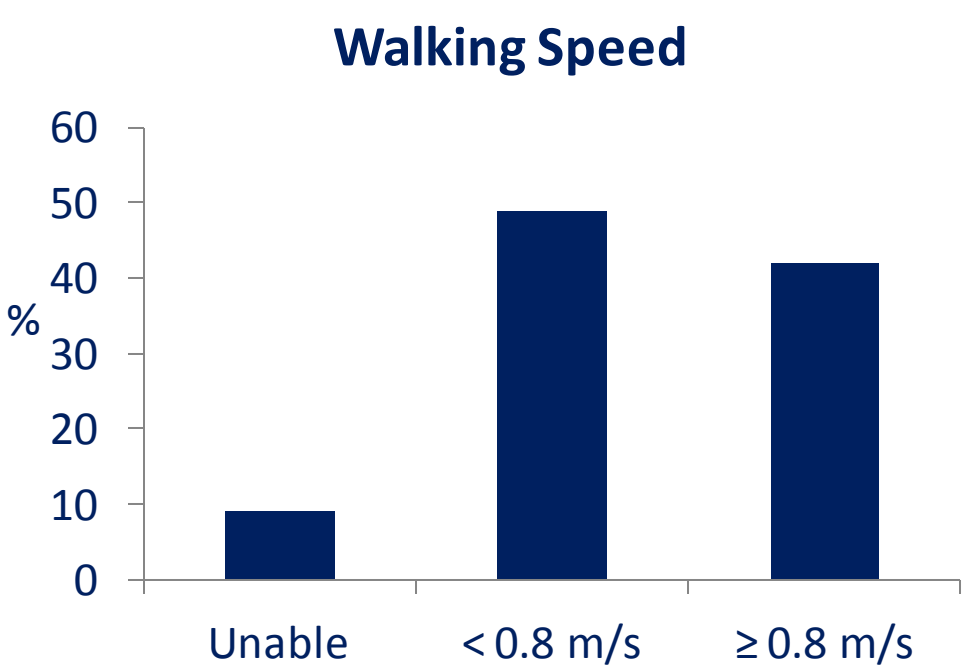
Patologie

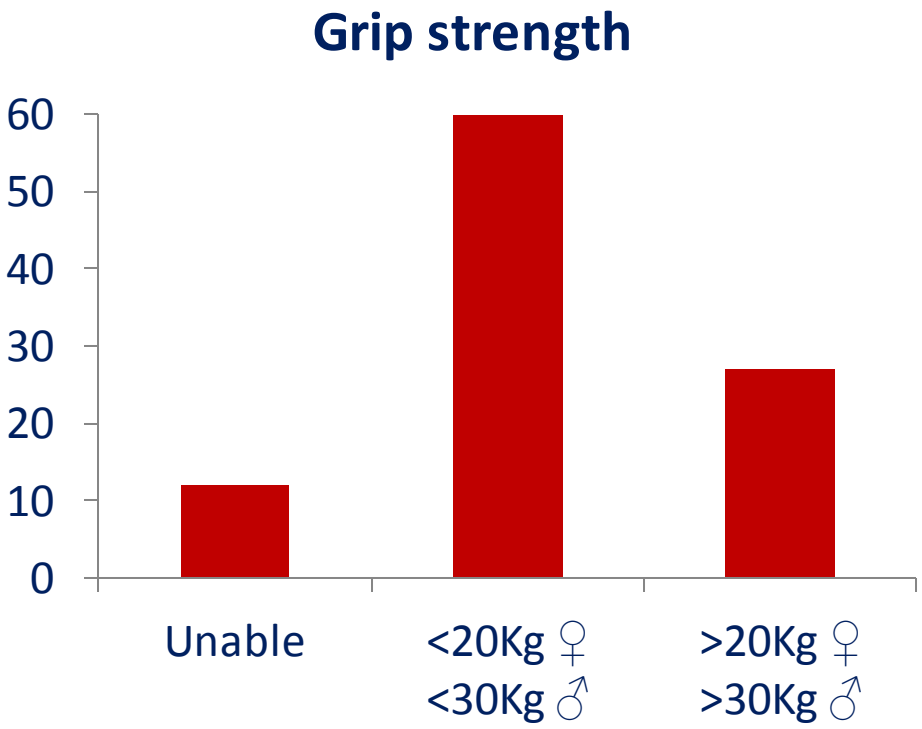
- Osteoporosi
- Demenza
- Problemi cardiaci
- Deficit sensoriali

Condizioni geriatriche

- Problemi nutrizionali
- **Funzione fisica**

Misure di Performance Fisica (n=78)





Sindrome di Down - Adulto

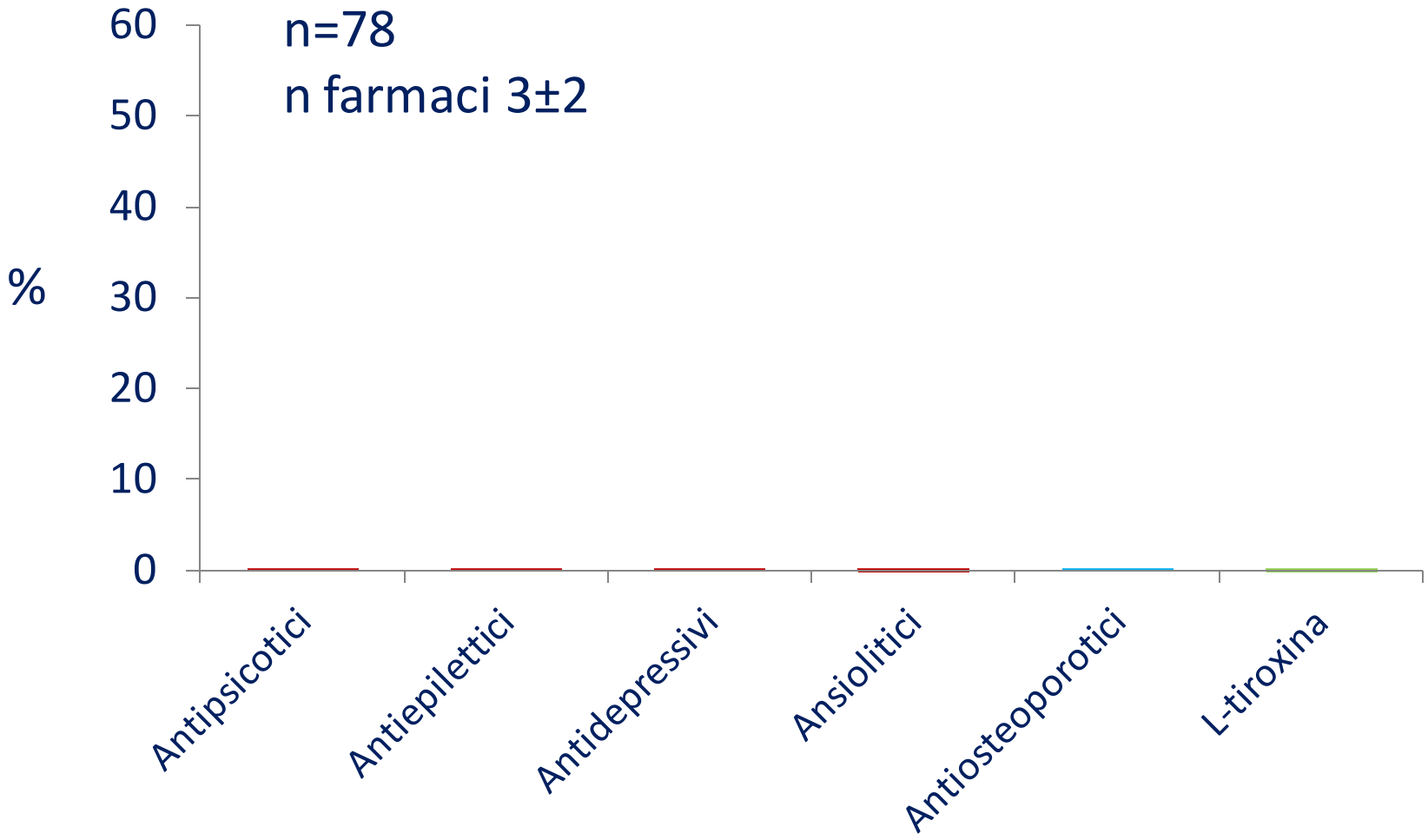
Patologie

- Osteoporosi
- Demenza
- Problemi cardiaci
- Deficit sensoriali

Condizioni geriatriche

- Problemi nutrizionali
- Funzione fisica
- **Terapia farmacologica**

Terapia farmacologica



Sindrome di Down - Adulto

Patologie

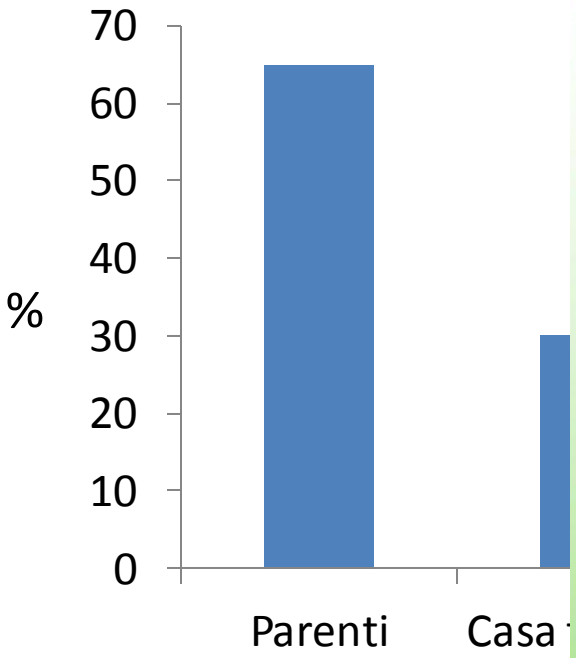
- Osteoporosi
- Demenza
- Problemi cardiaci
- Deficit sensoriali

Condizioni geriatriche

- Problemi nutrizionali
- Funzione fisica
- Terapia farmacologica
- **Problemi sociali**

Problemi sociali

Dove



FONDAZIONE ITALIANA
VERSO IL FUTURO

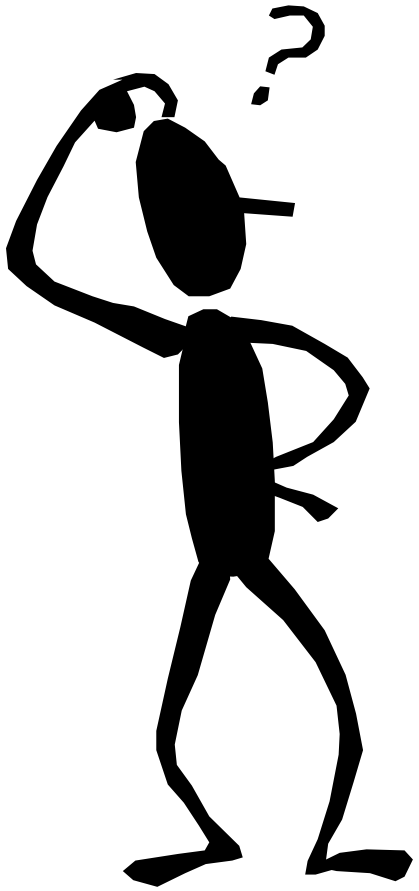
SIBLINGS
SORELLE E FRATELLI
DI PERSONE CON DISABILITA'

Conclusioni

- La SD non è una progeria da un punto di vista puramente biologico
- Molte patologie dell'adulto con SD sono simili a quelle dell'anziano
- Poco si conosce sul trattamento di queste patologie

Challenges

- Trattamento patologie (p.e. osteoporosi, demenza)
- Diagnostica (p.e. demenza)
- Fattori di rischio (reverse epidemiology?)



Conclusioni

- La SD non è una progeria da un punto di vista puramente biologico
- Molte patologie dell'adulto con SD sono simili a quelle dell'anziano
- Poco si conosce sul trattamento di queste patologie
- Condizioni geriatriche (problemi nutrizionali, sociali, funzionali, cognitivi) sono frequenti nell'adulto con SD

Rev Med Int Sindr Down. 2012;16(1):3-10

ELSEVIER DOYMA

INTERNATIONAL MEDICAL REVIEW ON DOWN'S SYNDROME

www.elsevier.es/sd

FUNDACIÓ CATALANA SÍNDROME DE DOWN
www.fcsd.org

ORIGINAL ARTICLE

Specific aspects of ageing in Down's syndrome

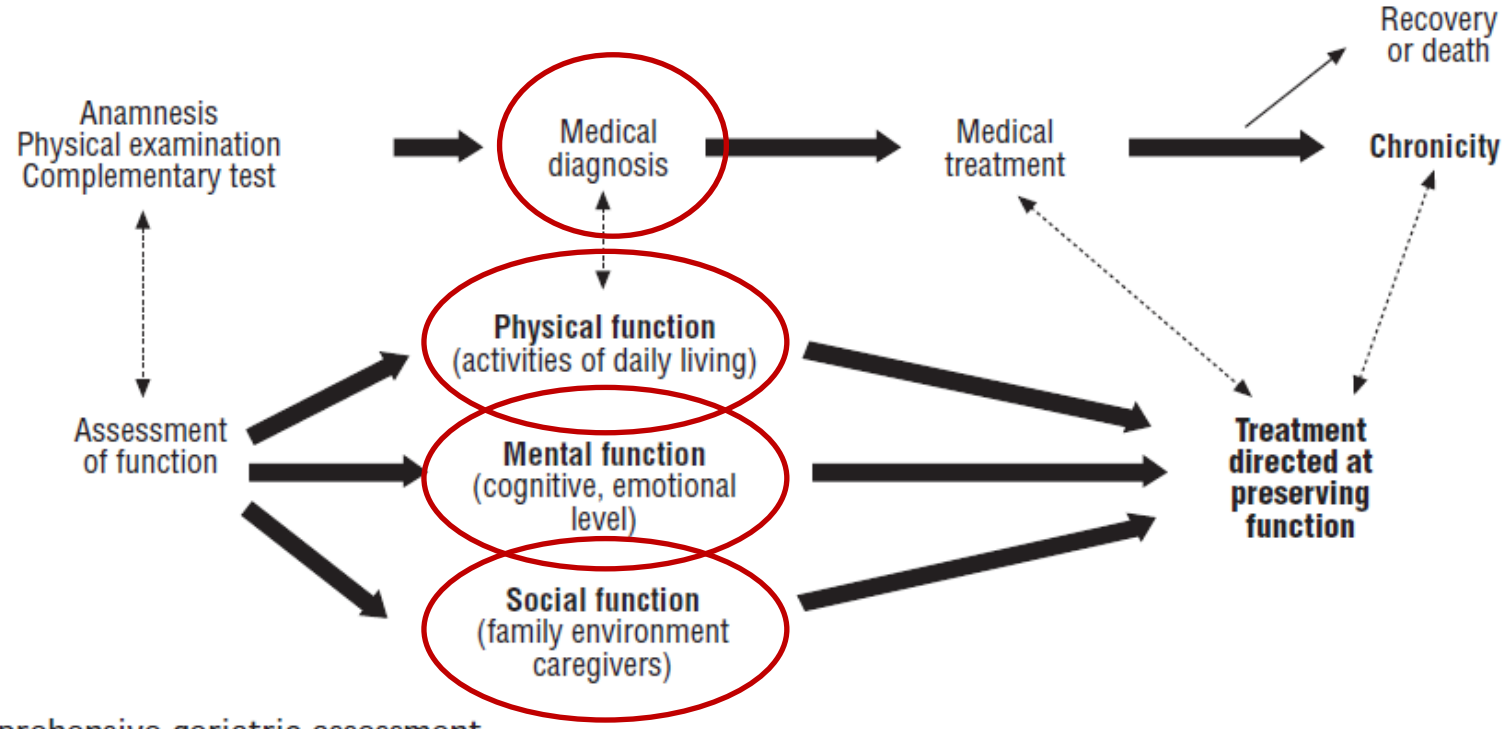
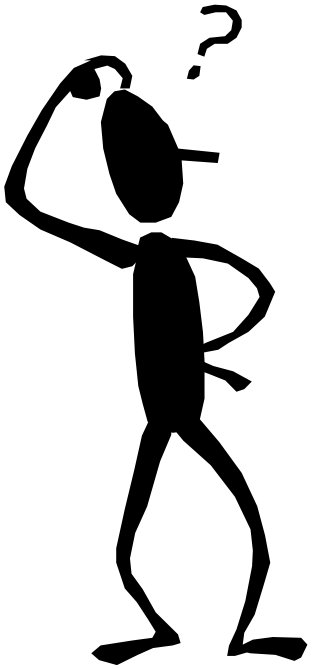


Figure 1 Comprehensive geriatric assessment.

Deve essere il geriatra a farsene carico?



Sì per la multidimensionalità delle problematiche

UNIVERSITÀ CATTOLICA del Sacro Cuore

ASSOCIAZIONE ITALIANA PERSONE DOWN onlus

FONDAZIONE ITALIANA VERSO IL FUTURO

Dietista: Dott.ssa Luparelli

ORL: Dott.ssa Picciotti

Pneumologo: Dott. Mormile

Neurologo: Dott.ssa Silveri

Gastroenterologo: Dott. De Vitis

Fisiatra: Dott. Specchia

Grazie per l'attenzione