



UNIVERSITÀ DEGLI STUDI DI NAPOLI FEDERICO II  
Dipartimento di Medicina Clinica e Chirurgia

Altogether  
to Beat  
Cushing's  
Syndrome



5ª Edizione

**Viaggio alla (ri)scoperta  
della Sindrome di Cushing**

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Coordinatori Scientifici

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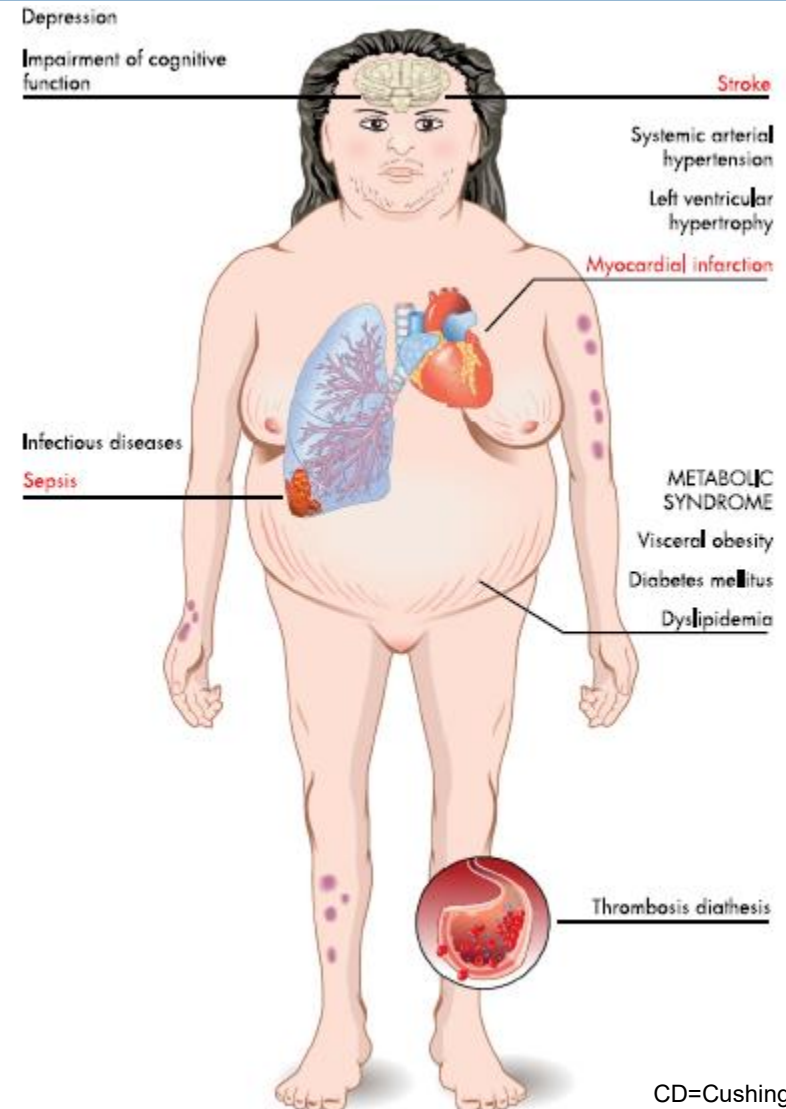
# Mortality in Cushing's syndrome: State of the art

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# Cushing's syndrome

CS is associated with excessive mortality mainly caused by cardiovascular or infectious disease, and their systematic consequences<sup>1,2</sup>.



CD=Cushing's disease

1. Pivonello et Al, *Endocrine Reviews*, 2015
2. Pivonello et Al, *Lancet Diabetes Endocrinol*, 2016

# Mortality in Cushing's syndrome

## Cushing's Disease

- 1) Overall SMR 0.98-9.3
- 2) Post-surgery Remission: SMR 0.31-8.3

**Main death causes:**  
Cardiovascular disease,  
Sepsis,  
Suicide

## Adrenal Cushing's syndrome

- 1) AA: SMR 1.35-7.5
- 2) BAH: SMR 1.14-12
- 3) AC: SMR up to 48

**Main death causes:**

- 1) Benign lesion: Cardio-/cerebrovascular disease, thromboembolism, sepsis, suicide
- 2) Malignant lesion: neoplastic progression or pulmonary thromboembolism

## Ectopic Cushing's syndrome

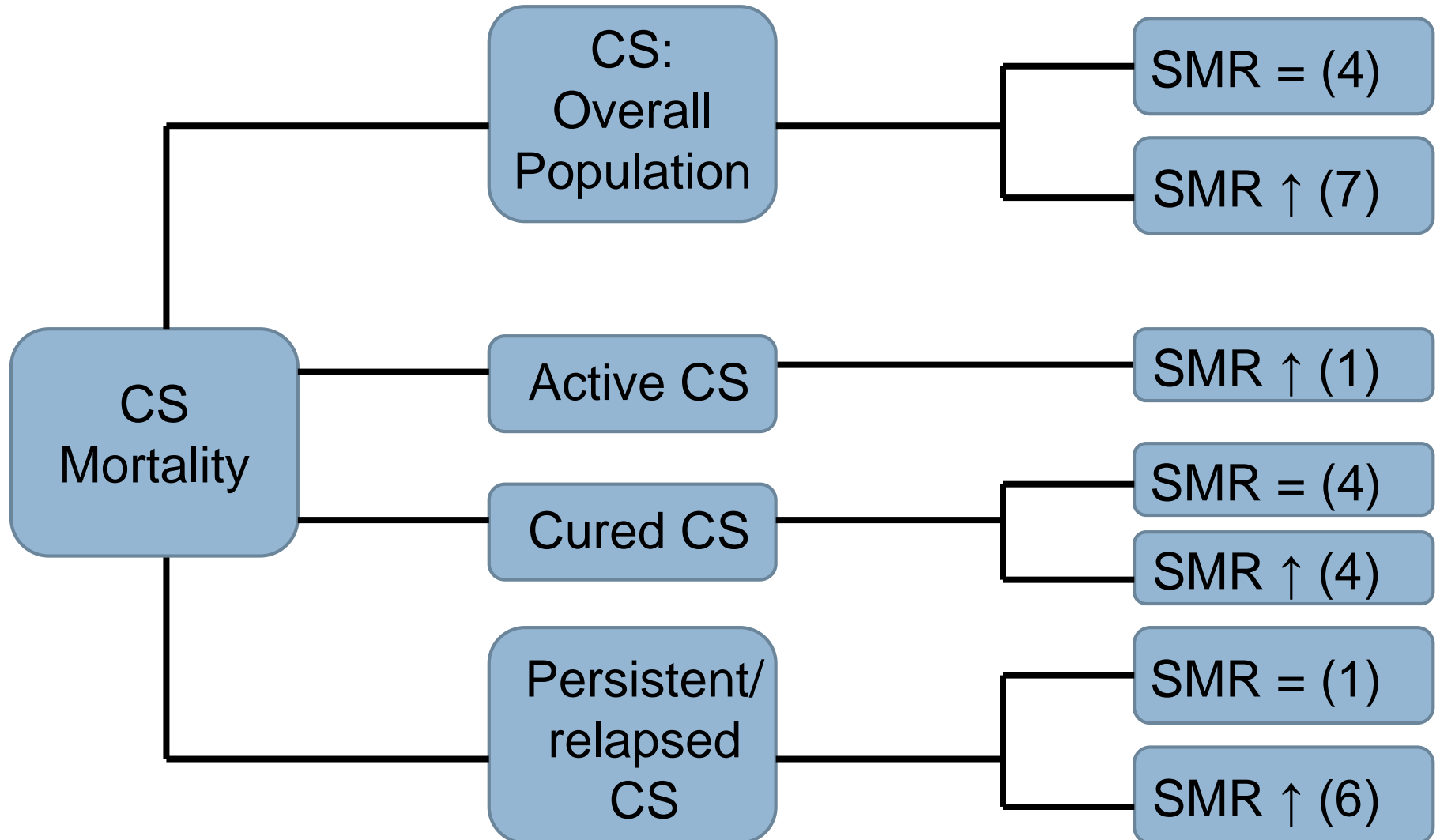
SMR: 13.3-68.5

**Main death causes:**  
Neoplastic progression,  
Sepsis

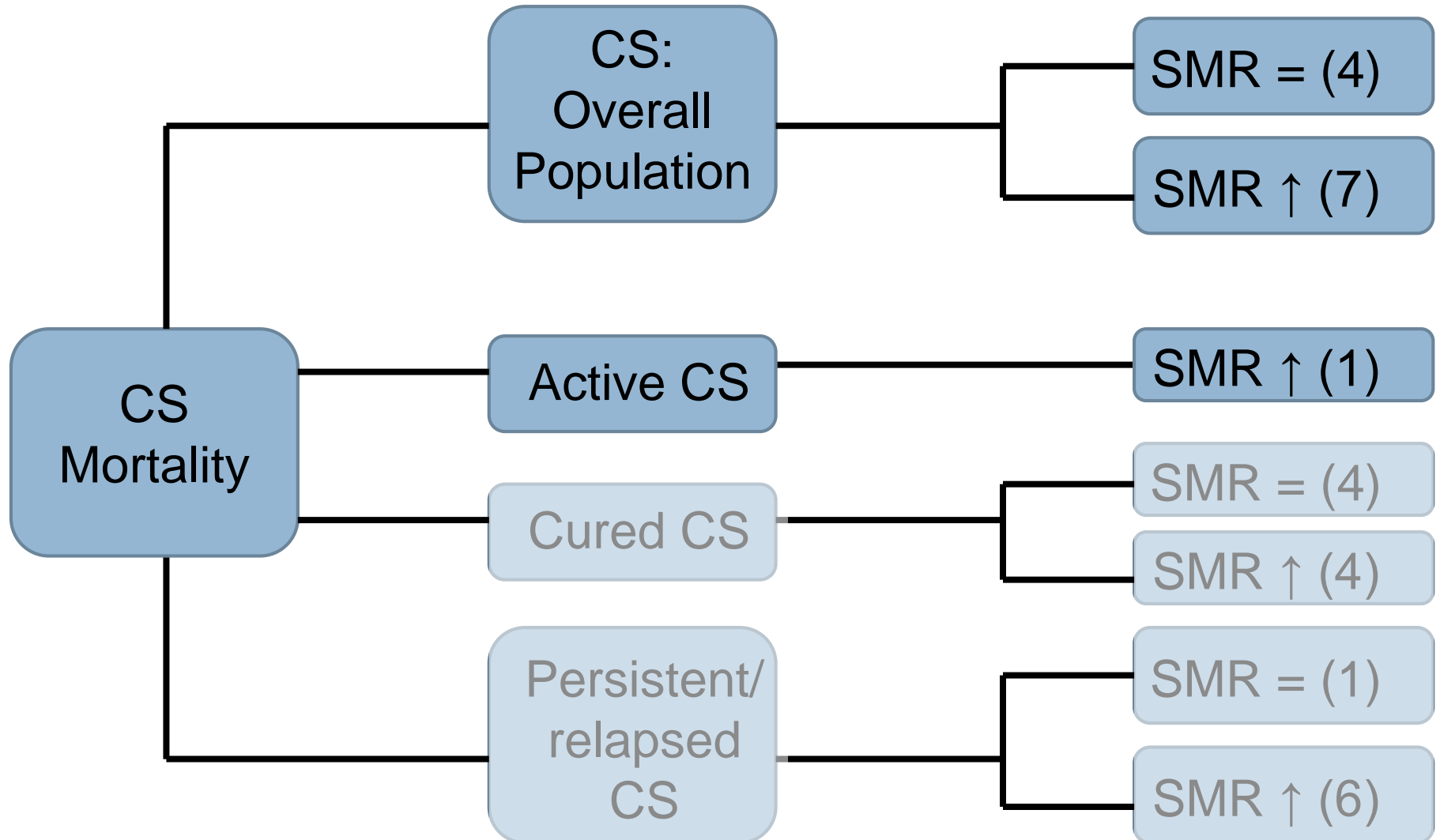
### Mortality Predictive Factors:

- Age at diagnosis (old>young)
- Presence and duration of active disease
- Comorbidities (mainly hypertension and diabetes)

# Literature overview



# Literature overview



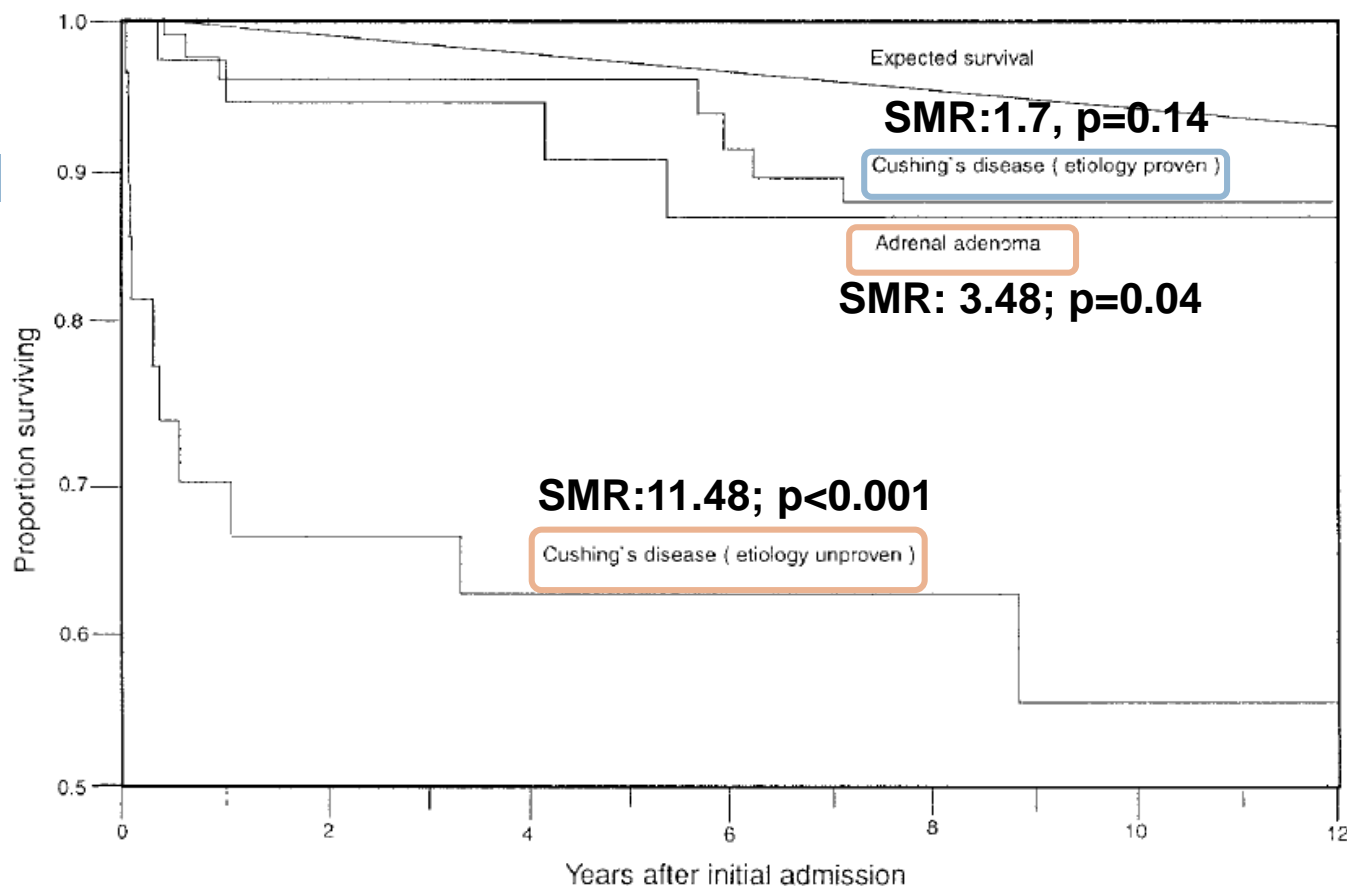
# Studies showing similar SMR in overall CS

First Author	Patient type (n) Cured/remission (%)	Study design	SMR total population	Main death causes
Swearingen, 1999	CD (161) <b>87%</b>	Retrospective study	0.98 (0.44-2.2)	Cardiovascular disease, stroke
Pikkarainen, 1999	CS (74), CD (43) <b>NA</b>	Retrospective single-center study	•CS=1.68 (0.81-3.09) •CD=2.67 (0.89-5.25)	Cardiovascular disease, pancreatitis
Lindholm, 2001	CS (166), CD (73) <b>81%</b>	National registry study	•CS=3.68 (2.34-5.33) •CD=1.7 (0.68-3.5)	Stroke, sepsis, aortic aneurysm rupture
Hammer 2004	CD (289) <b>84%</b>	Retrospective single-center study	1.42 (0.95-2.1)	Cardiovascular disease,

1. Pivonello et Al, *Endocrine Reviews*; 2015;
2. Pivonello et Al, *Lancet Diabetes Endocrinol*, 2016

NA: not available,

# Survival rate of patients with CS according to etiology



Time after 1 <sup>o</sup> admission	No. of pts	No. Of deaths	Time at risk (yr)	Expected no. deaths	SMR (95% CI)	P
First yr	139	13	130.3	0.64	<b>20.27 (10.8-34.7)</b>	<0.001
Following yr	126	10	863.6	5.6	<b>1.79 (0.86-3.28)</b>	0.08

# Mortality in patients with more than 5 yrs from the first operation

Group	No. of pts	M/F ratio	No.	Cause of death	Time at	Expected	SMR (95% CI)	P
A	45						1.1 (0.1-2.2)	>0.05
B	25						1.5 (0.1-5)	>0.05
C	20						1.6 (0.6-3.0)	<0.05

**LIMITATIONS**

- Retrospective study
- Small sample size
- No focus on active disease
- Different types and number of treatments were not considered separately
- Hormonal deficiencies were not considered

Group A: cured after initial transphenoidal neurosurgery.  
 Group B: cured by unilateral adrenalectomy because of benign adenoma.  
 Group C: not cured at initial pituitary surgery.



# Studies showing increased SMR in overall CS

First Author	Patient type (n) Cured/rem (%)	Study design	SMR total population	Main death causes
<b>Extabe, 1994</b>	<b>CD (49) 88%</b>	<b>Population based study</b>	<b>3.8 (2.5-17.9)</b>	<b>Cardiovascular &amp; Infectious disease</b>
Dekkers,2007	CD (74) <b>93%</b>	Retrospective single center study	2.39 (1.22-3.9)	Cardiovascular disease, malignancy, infectious disease
Clayton, 2011	CD (60) <b>90%</b>	Retrospective single center study	4.8 (2.8-8.3)	Cardio-cerebrovascular disease, malignancy, aortic aneurysm rupture
Bolland, 2011	CS (253),CD(188) <b>89%; 91%</b>	Nationwide retrospective survey	CS=4.1 (2.9-5.6) CD=Macro:3.5 (1.3-7.8), micro: 3.2 (2-4.8)	Malignancy, cardiovascular disease, stroke, sepsis, pulmonary embolism
Hassan-Smith, 2012	CD (80) <b>65%</b>	Retrospective single center study	3.17 (1.7-5.43)	Cardiovascular disease, malignancy, infectious disease
Ntali, 2013	CS(209),CD(182) <b>79%; 77%</b>	Retrospective multicenter study	CD=9.3 (6.2-13.4) AC=5.3 (0.3-26) ECS=68.5 (21.5-151.8)	Cardiovascular diseases, infectious disease & sepsis, malignancy
<b>Yaneva, 2013</b>	<b>CS(386),CD (240) NA;79%</b>	<b>Retrospective single center study</b>	<b>CS=4.05 (2.5-5.8) CD=1.88 (0.69-4.08)</b>	<b>Cardio- &amp; cerebrovascular disease, infectious disease &amp; sepsis</b>

NA: not available  
ACS=Adrenal CS  
ECS=ectopic CS

# Mortality and predictive factors in CD patients

	Standardized Mortality Ratio (SMR)	95% CI
<b>Men</b>		
Total	0.48	(0.48-100)
<b>Women</b>		
Cardiovascular disease	0.36	(0.36-75)
Infectious disease		
Post adrenal		
Total		
<b>Total population</b>		

### LIMITATIONS

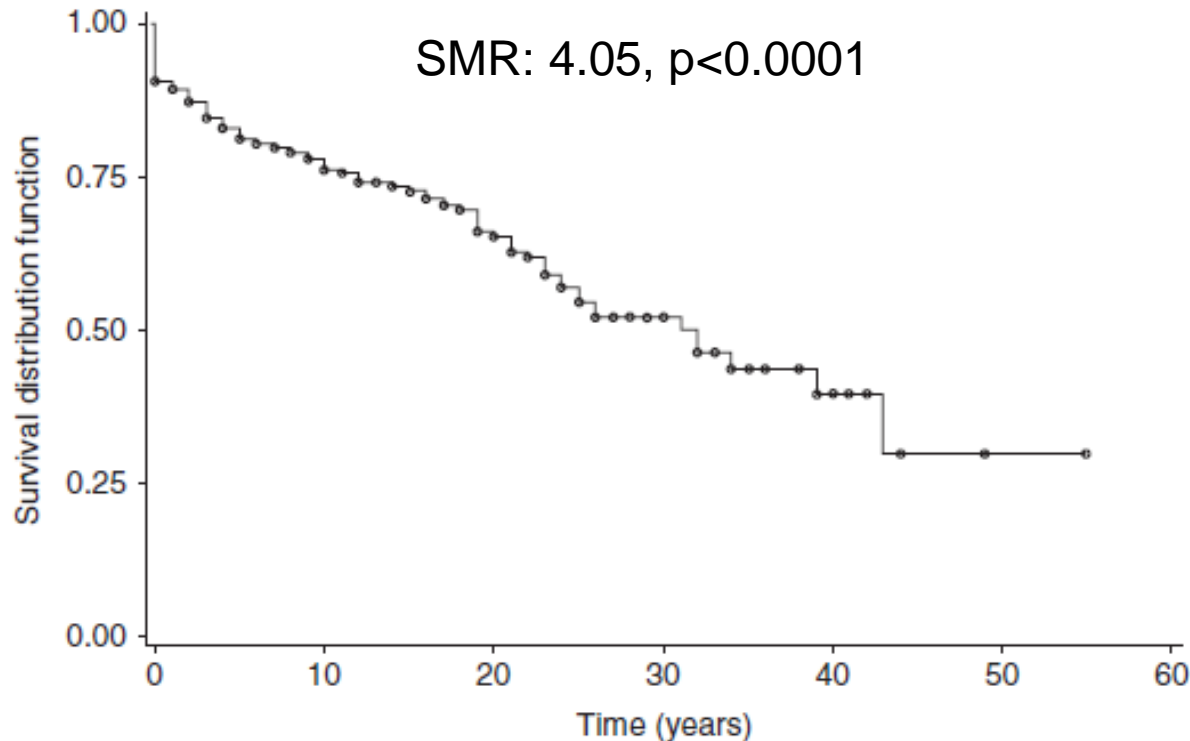
- Small sample size
- No separate evaluation of active, cured and relapsed CD
- Different types and number of treatments were not considered separately
- Hormonal deficiencies were not considered

• Mortality was significantly higher in women (SMR 0.36) especially in those with cardiovascular disease (<math>P</math> <math><0.01</math>).

- Independent risk factors for mortality:**
- Older age
  - Persistence of hypertension
  - Persistence of glucose abnormalities after treatment

especially in those with cardiovascular disease (<math>P</math> <math><0.01</math>).

# Survival rate of the entire cohort of CS



In active CS was 2.4  
( $p=0.013$ )

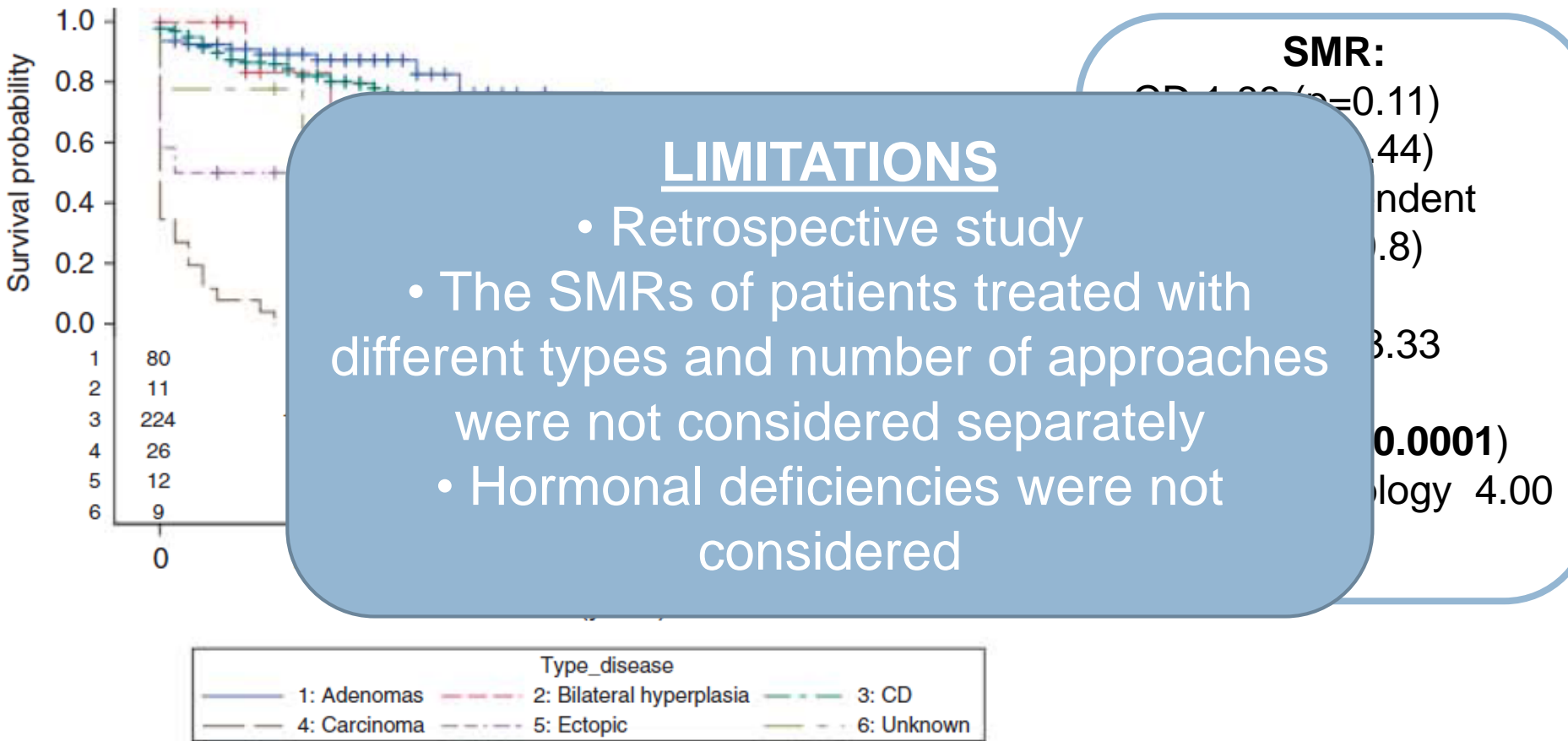
In CS after remission SMR  
was 1.67 ( $p>0.05$ )

In overall CD was 1.88  
( $p>0.05$ )

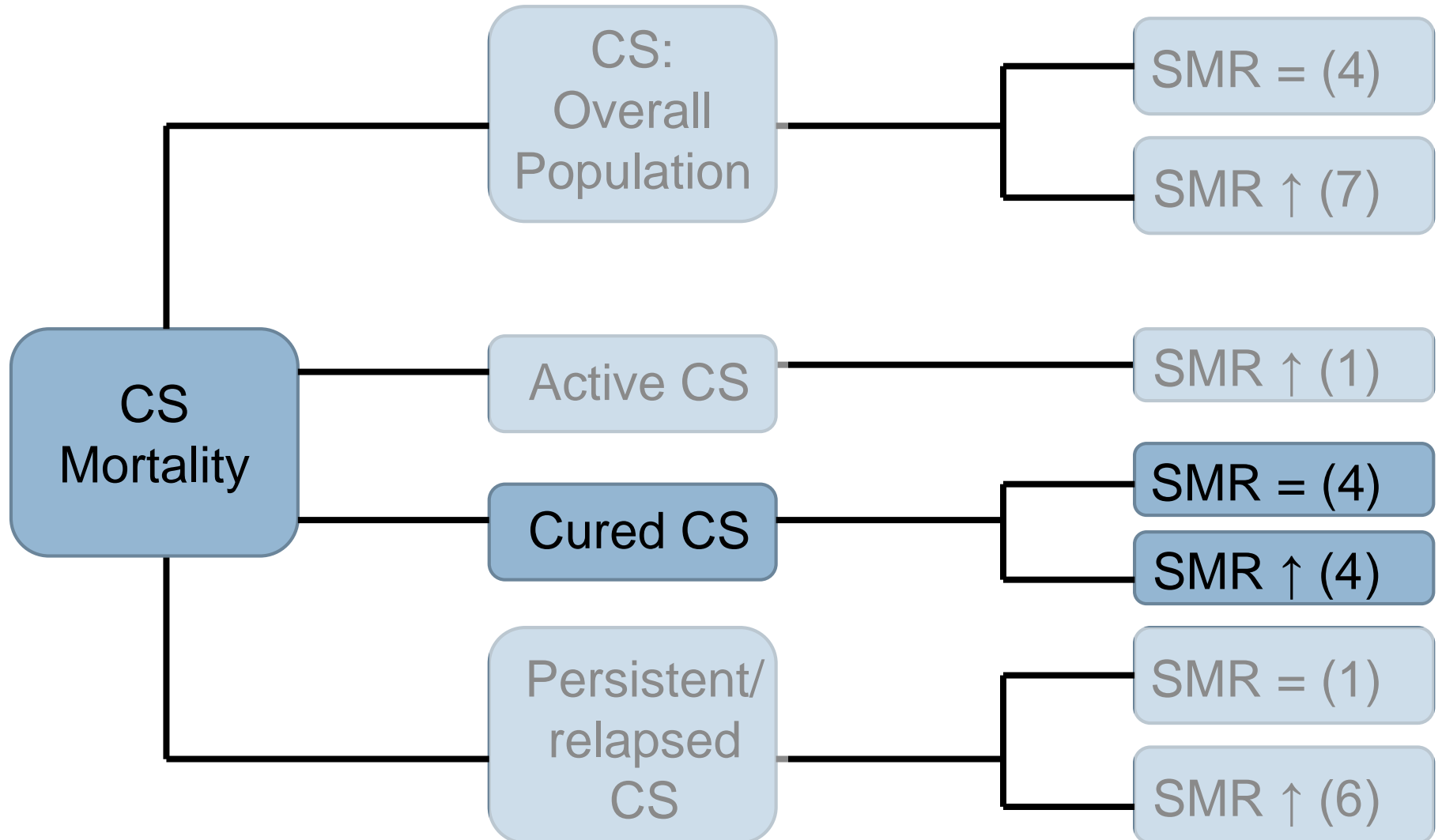
In CD without initial  
remission after TSA was  
2.8,  $p=0.005$ .

Sex (M/F OR=1.93), age at diagnosis, duration of disease activity, etiology and the current status at death (active or remission) correlated significantly with death

# Survival rate of patients with different CS etiologies



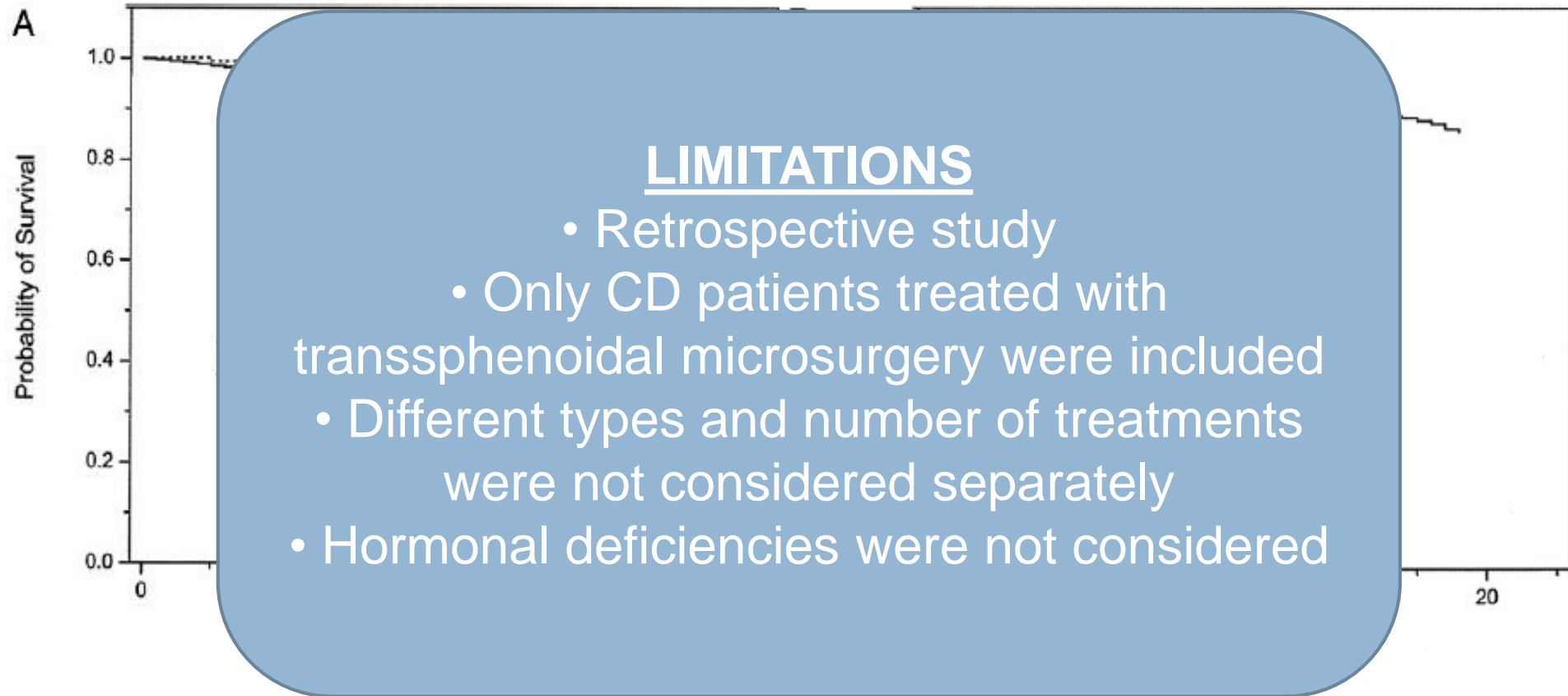
# Literature overview



# Studies showing similar SMR in cured CD

First Author	Patient type (n)	Study design	SMR cured disease	Main death causes
Lindholm, 2001	CS (166), CD (73)	National registry study	0.31 (0.01-1.72)	Stroke, sepsis, aortic aneurysm rupture
<b>Hammer, 2004</b>	<b>CD (289)</b>	<b>Retrospective single center study</b>	<b>1.18 (0.7-1.9)</b>	<b>Cardiovascular disease</b>
Dekkers, 2007	CD (74)	Retrospective single center study	1.8 (0.71-3.37)	Cardiovascular disease, malignancy, infectious disease
Yaneva, 2013	CS(386),CD (240)	Retrospective single center study	1.67 (0.61-3.62)	Cardio- & cerebrovascular disease, infectious disease & sepsis

# Mortality rate among patients in initial remission (A) or initial persistent disease (B)



# Studies showing increased SMR in cured CS

First Author	Patient type (n)	Study desing	SMR cured disease	Main death causes
<b>Bolland, 2011</b>	<b>CS (253),CD(188)</b>	<b>Nationwide restrospective survey</b>	<b>Macro:2.3 (0.4-7.5), micro: 3.1 (1.8-4.9)</b>	<b>Malignancy, cardiovascular disease, stroke, sepsis, pulmunity embolism</b>
Clayton, 2011	CD (60)	Retrospective single center study	3.3 (1.7-6.7)	Cardio-cerebrovascular disease, malignancy, aortic aneurysm rupture
Hassan-Smith, 2012	CD (80)	Retrospective single center study	2.47 (0.8-5.77)	Cardiovascular disease, malignancy, infectious disease
Ntali, 2013	CS(209),CD(182)	Retrospective multicenter study	8.3 (5.1-12.7)	Cardiovascular diseas, infectious disease & sepsis, malignancy

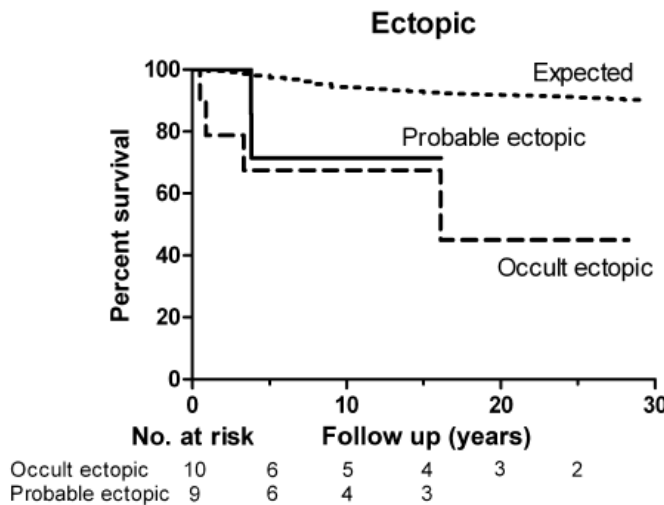
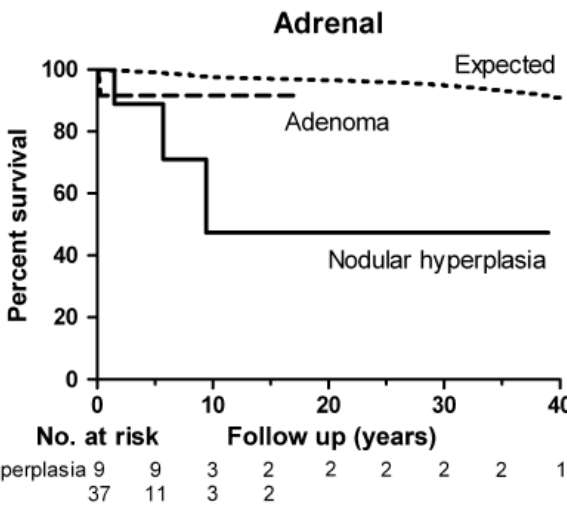
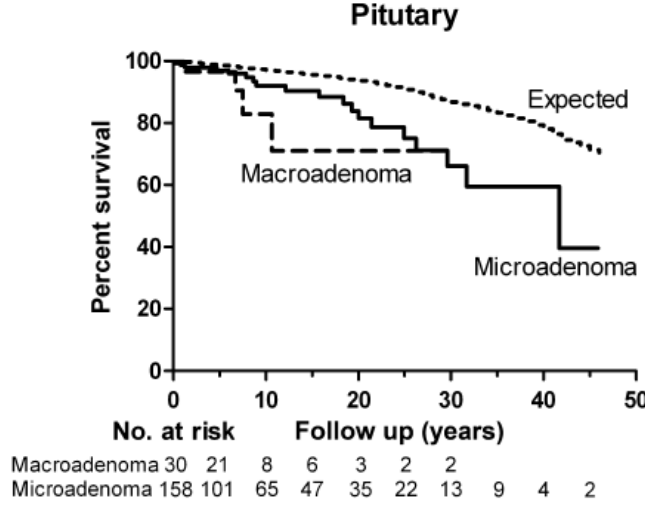
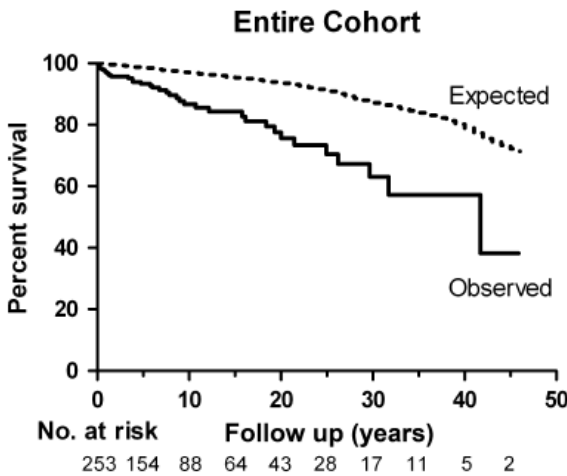


# Mortality data for the entire cohort and by diagnosis

	Biochemical Cure at last follow up (%)	SMR	p
Entire Cohort	89	4.1	<0.001
Adrenal adenoma	95	7.5	0.009
Bilateral nodular hyperplasia	56	14	0.001
Pituitary macroadenoma	93	3.5	0.018
Pituitary microadenoma	91	3.2	<0.001
Occult ectopic	70	27	<0.001
Probable ectopic	67	3.1	0.16

**The SMR was significantly increased in the entire cohort and in most of the individual subgroups of CS.**

# Mortality data for the entire cohort and by diagnosis



**Predictive factors of mortality**

in the entire cohort :

- biochemical cure
- hypertension at last follow-up.

In CD:

- age at diagnosis,
- diabetes mellitus at last follow-up
- type of treatment.

# Mortality was elevated regardless cure was achieved after the initial procedure

## LIMITATIONS

- Retrospective study
- Small sample size
- CD patients with microadenoma or macroadenoma were considered separately
- No focus on active disease
- Different types and number of treatments were not considered separately
- Hormonal deficiencies were not considered

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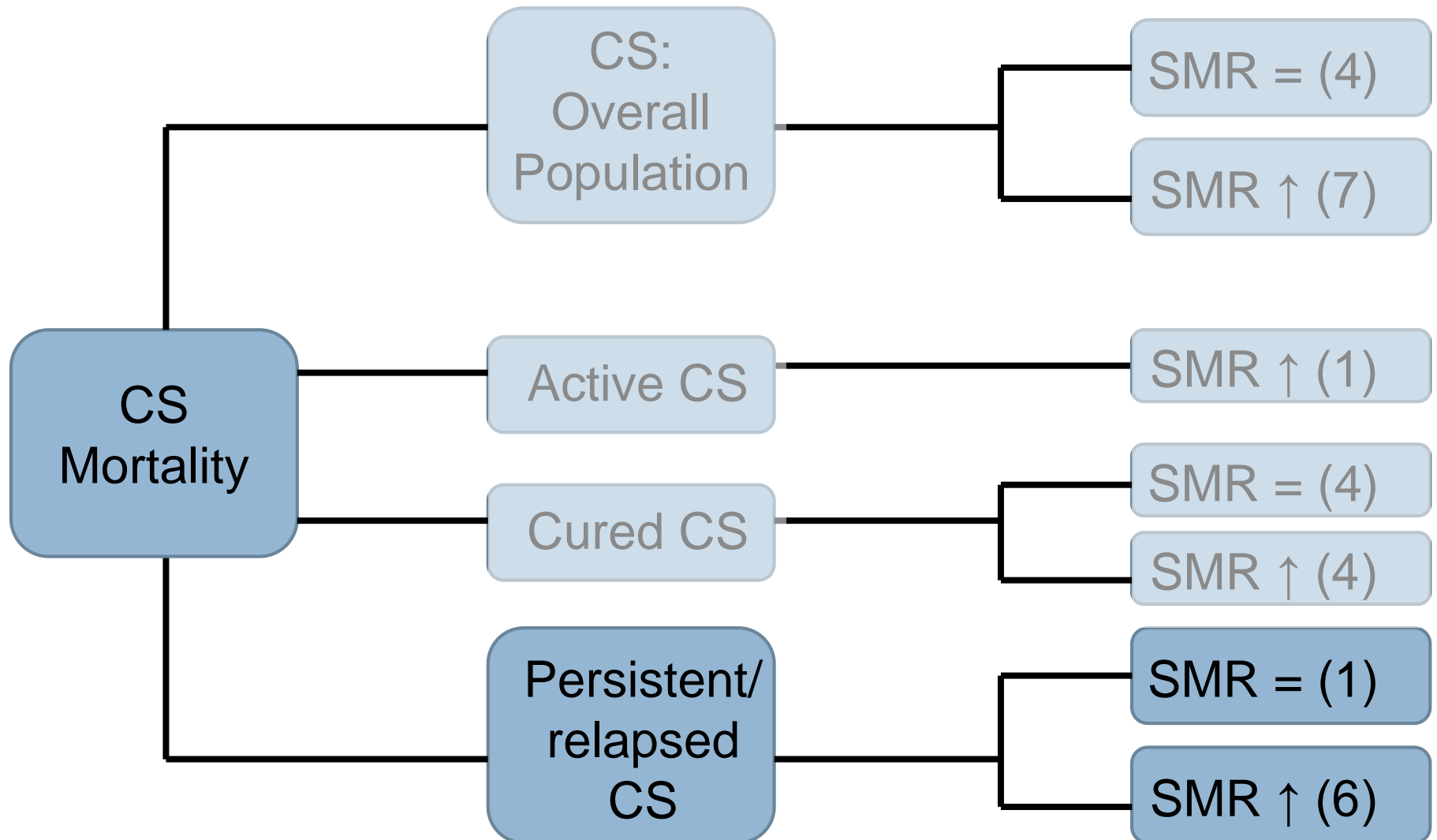
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# Literature overview



# Studies showing similar SMR in persistent/relapsed CS

First Author	Patient type (n)	Study design	SMR persistent/recurrent disease	Main death causes
Hassan-Smith, 2012	CD (80)	Retrospective single center study	4.12 (1.12-10.54)	Cardiovascular disease, malignancy, infectious disease

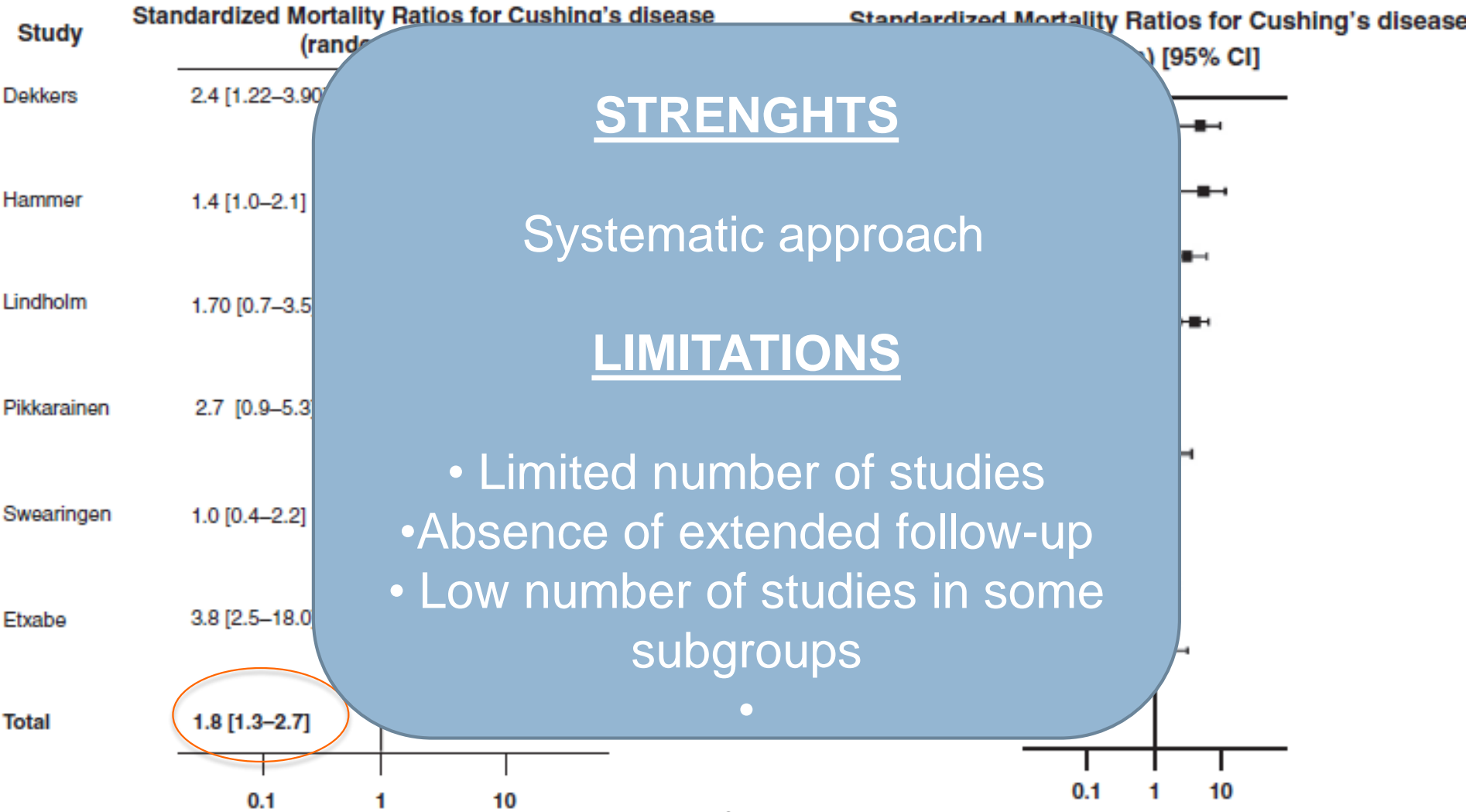
# Studies showing increased SMR in persistent/relapsed CS patients

First Author	Patient type (n)	Study design	SMR persistent/recurrent disease	Main death causes
Lindholm, 2001	CS (166), CD (73)	National registry study	5.06 (1.86-11)	Stroke, sepsis, aortic aneurysm rupture
Hammer, 2004	CD (289)	Retrospective single center study	2.8 (1.35-5.9)	Cardiovascular disease
Dekkers, 2007	CD (74)	Retrospective single center study	4.38 (1.38-9.07)	Cardiovascular disease, malignancy, infectious disease
Clayton, 2011	CD (60)	Retrospective single center study	16 (6.7-38.4)	Cardio-cerebrovascular disease, malignancy, aortic aneurysm rupture
<b>Yaneva, 2013</b>	<b>CS(386),CD (240)</b>	<b>Retrospective single center study</b>	<b>2.4 (0.87-8.19)</b>	<b>Cardio- &amp; cerebrovascular disease, infectious disease &amp; sepsis</b>
Ntali, 2013	CS(209),CD(182)	Retrospective multi center study	9.9 (3.6-21.9)	Cardiovascular diseases, infectious disease & sepsis, malignancy



# **Literature overview: Meta-analyses & Systematic Reviews**

# Meta-analysis: SMR in CD population





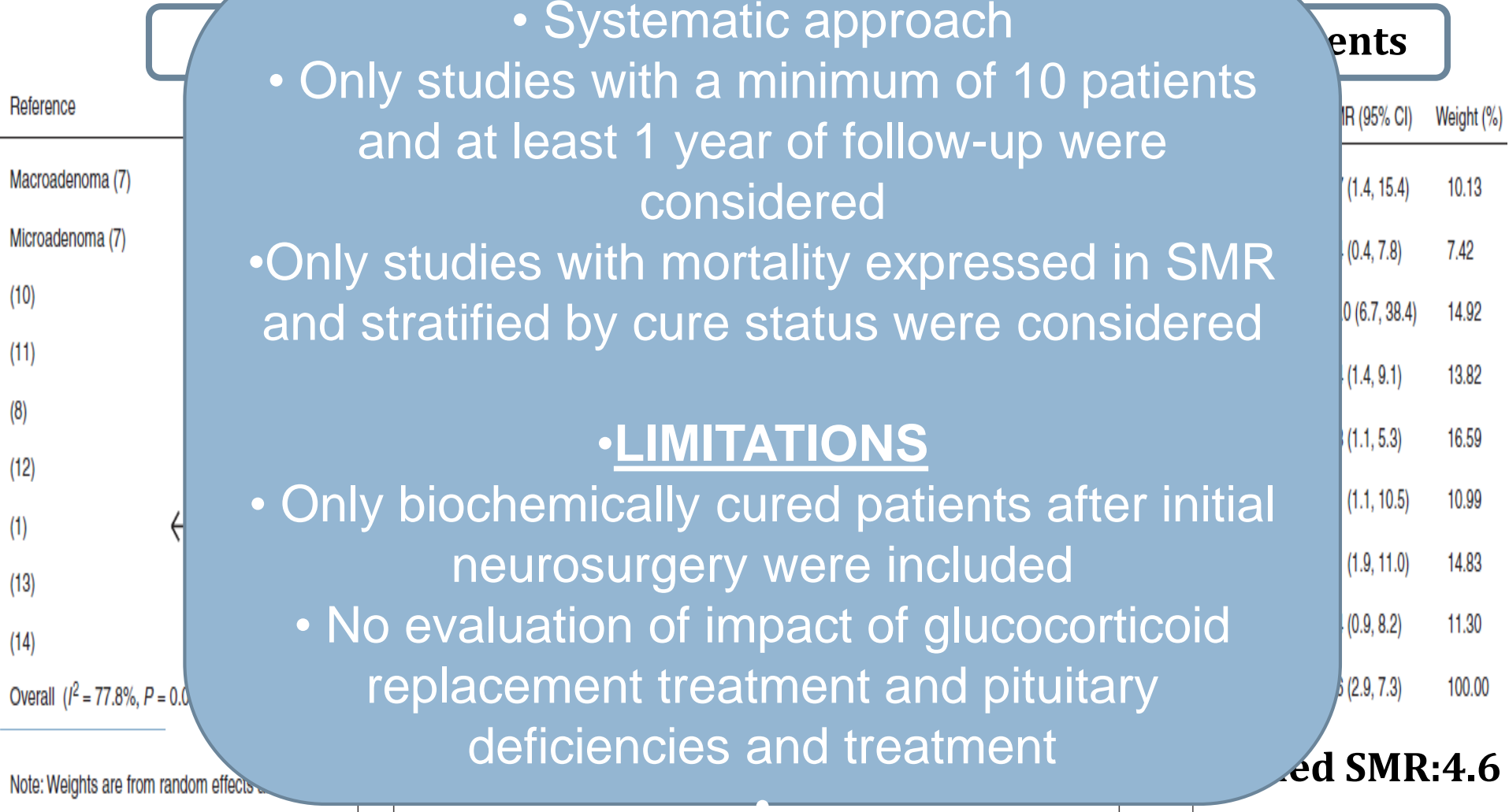
# SMR in cured and uncured CD patients was significantly increased compared to general population

## STRENGTHS

- Systematic approach
- Only studies with a minimum of 10 patients and at least 1 year of follow-up were considered
- Only studies with mortality expressed in SMR and stratified by cure status were considered

## LIMITATIONS

- Only biochemically cured patients after initial neurosurgery were included
- No evaluation of impact of glucocorticoid replacement treatment and pituitary deficiencies and treatment



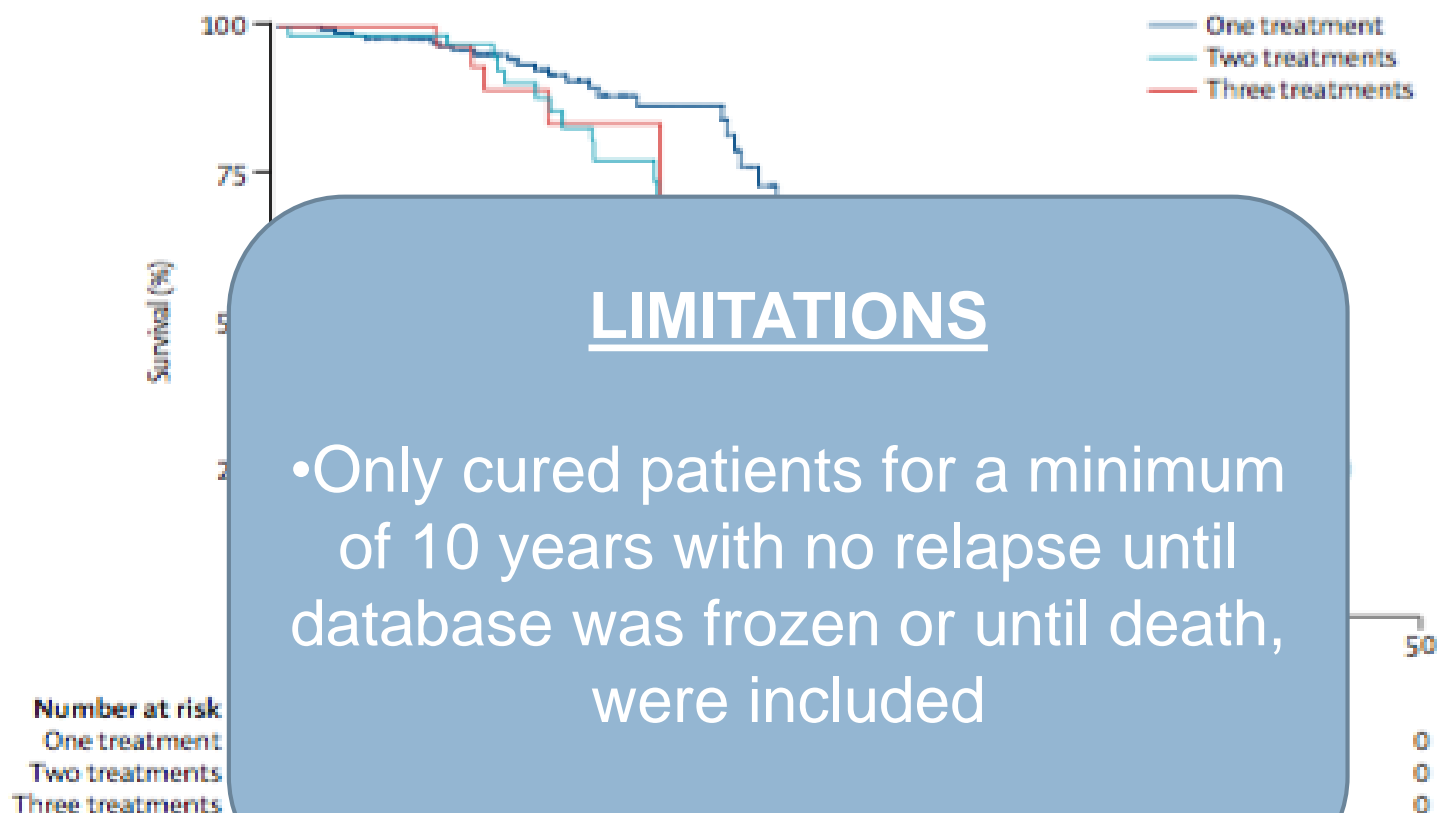
# Mortality of Long-term cured CD patients

	SMR (95% CI)	P value
<b>Cause of death</b>		
Overall	1.61 (1.23-2.12)	<b>0.0001</b>
Cancer	0.79 (0.41-1.51)	0.41
Circulatory	2.72 (1.88-3.95)	<b>&lt;0.0001</b>
<b>Sex</b>		
Male	1.11 (0.6-2.06)	0.75
Female	1.81 (1.33-2.46)	<b>&lt;0.0001</b>
<b>GC replacement therapy</b>		
No	1.01 (0.54-1.89)	0.96
Yes	1.99 (1.45-2.72)	<b>&lt;0.0001</b>

- Mortality was significantly higher in patients with cured CD than general population.
- Sex-related difference was not significant.
- Pts taking glucocorticoids had a significantly higher SMR.

**FACTORS WITH IMPACT ON MORTALITY:**  
Presence of diabetes had a mortality hazard ratio of 2.82 (p<0.0096), for hypertension hazard ratio was 1.59 (p=0.008).

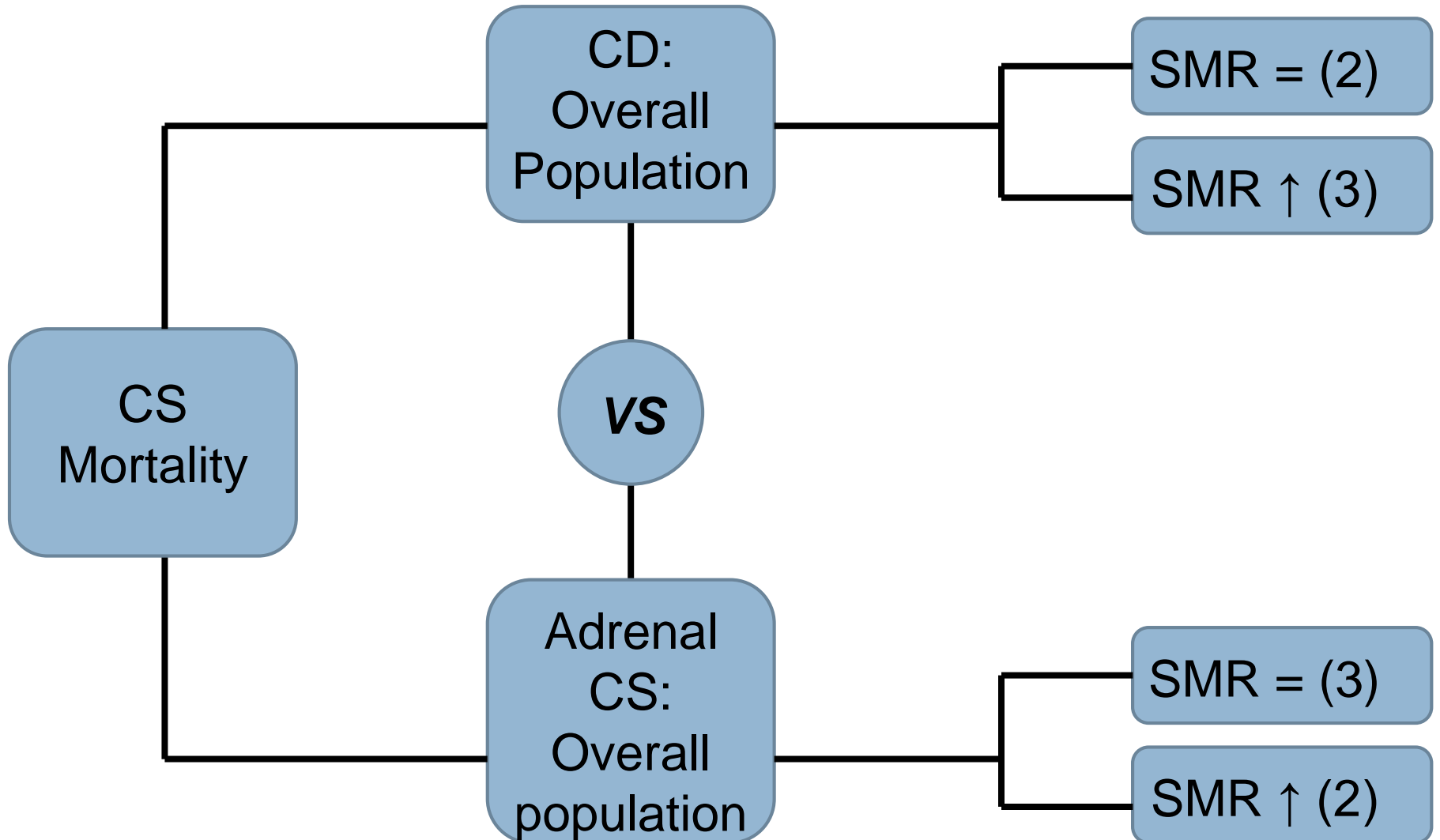
# Association between mortality and number of treatments



**An higher risk noted with a higher number of treatments**

HRs : 1.77 (95% CI 0.93–3.38) for two versus one treatments ( $p=0.08$ ),  
2.6 (1.15–5.87) for three versus one treatments ( $p=0.02$ ).

# Literature overview



# Cushing's disease vs adrenal CS

First Author	Patient type (n)	SMR CD population	SMR adrenal CS population
Pikkarainen, 1999	CS (74), CD (43)	SMR = (2.67)	SMR = (1.35)
Lindholm, 2001	CS (166), CD (73)	SMR = (1.7)	SMR ↑ (3.4)
Bolland, 2011	CS (253),CD(188)	SMR ↑ (macro:3.5 , micro: 3.2)	SMR ↑ (7.5; 14*)
Yaneva, 2013	CS(386),CD (240)	SMR = (1.88)	SMR = (1.67; 1.14*)
Ntali, 2013	CS(209),CD(182)	SMR ↑ (9.9)	SMR = (5.3)

# THANK YOU

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