What Can Happen After A Stroke?

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http://www.med.unsw.edu.au/adfoap

Stroke in Australia

- Age adjusted annual incidence rates:
  - Males 132 /100,000
  - Females 77 /100,000
- Crude annual event rate for all strokes 258 /100,000
- Fatality rate 24% @ 4 wks & 38% @ 1 yr
- Steady reduction in mortality from stroke over past 25 years
- Increased longevity → more dementia

Stroke in Australia (2003)

- Third most common cause of death
- 9006 deaths; 7% of all deaths
- 346,700 survivors of stroke
- 282,600 Australians had a disability of whom ½ had disability from stroke
- Most stroke survivors live at home
- Only 12% in shared accommodation
- ½ of stroke survivors with disability living at home need assistance

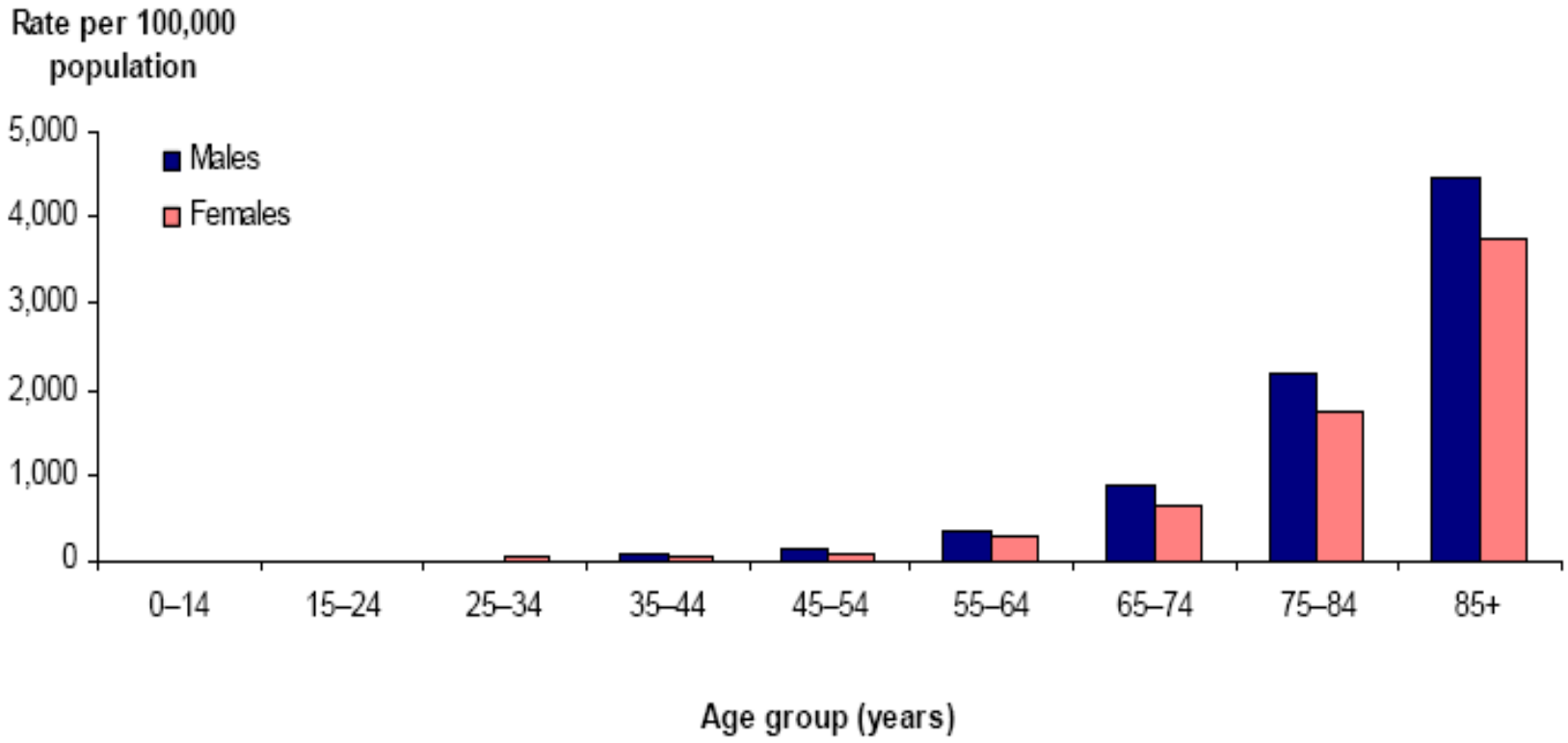
Senes S, AIHW, 2006

Sequelae of stroke

- 1 in 5 die with 1 month of first ever stroke[1]
- One in three die within 12 months[1]
- Secular trend is for >> survival, < hospital[n,] > dementia [2]
- Increased risk of VaD and of AD
- Of 30-day survivors, half survive 5 years[2]
- By end of first year, half survivors are dependent on others of ADL [4]
- HR QoL 2 years after stroke is reduced for most survivors; very poor for many [5]

[1]Thrift et al, 2000; [2] Bennett DA, Stroke 2006; [3]Hankey et al, 2002;
[4] Hankey et al, 1998; [5] Sturm et al, 2004

Stroke attack rates in Melb 1996/7

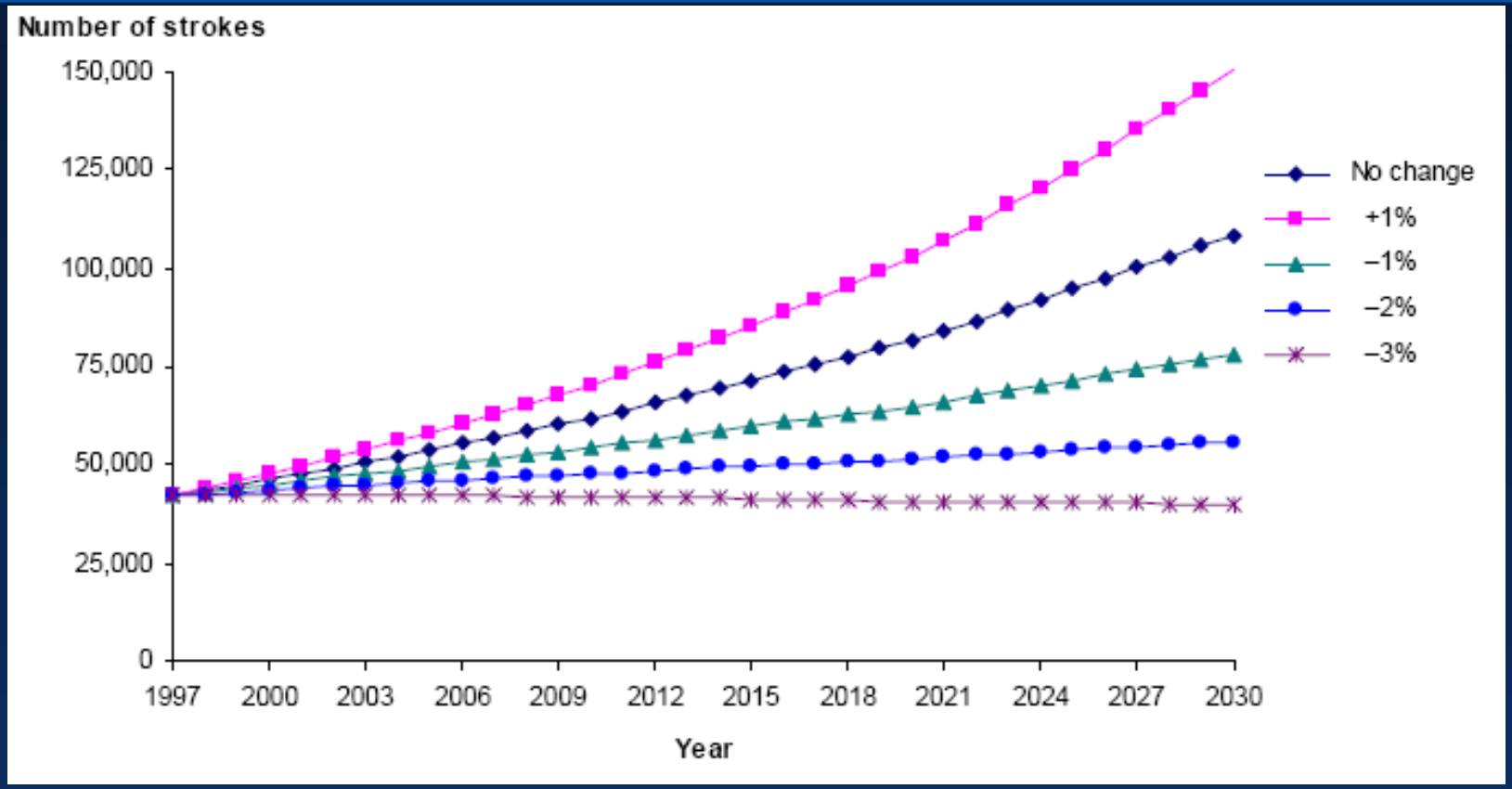


Source: NEMESIS (Thrift et al. 2000).

Figure 1: Stroke attack rates in Melbourne, 1996–97

Senes S, AIHW, 2006

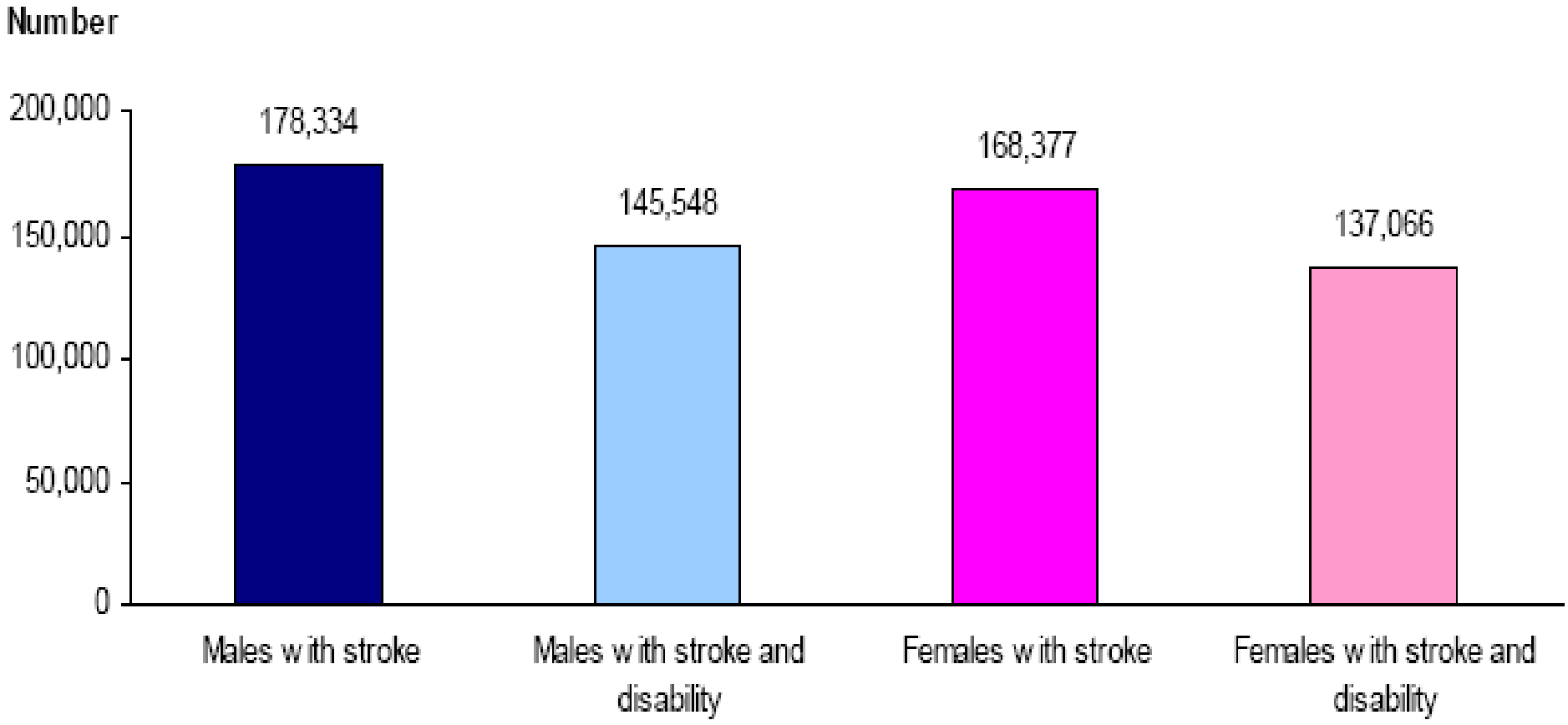
Projected number of strokes



Senes S, AIHW, 2006. Varying rates of stroke attack

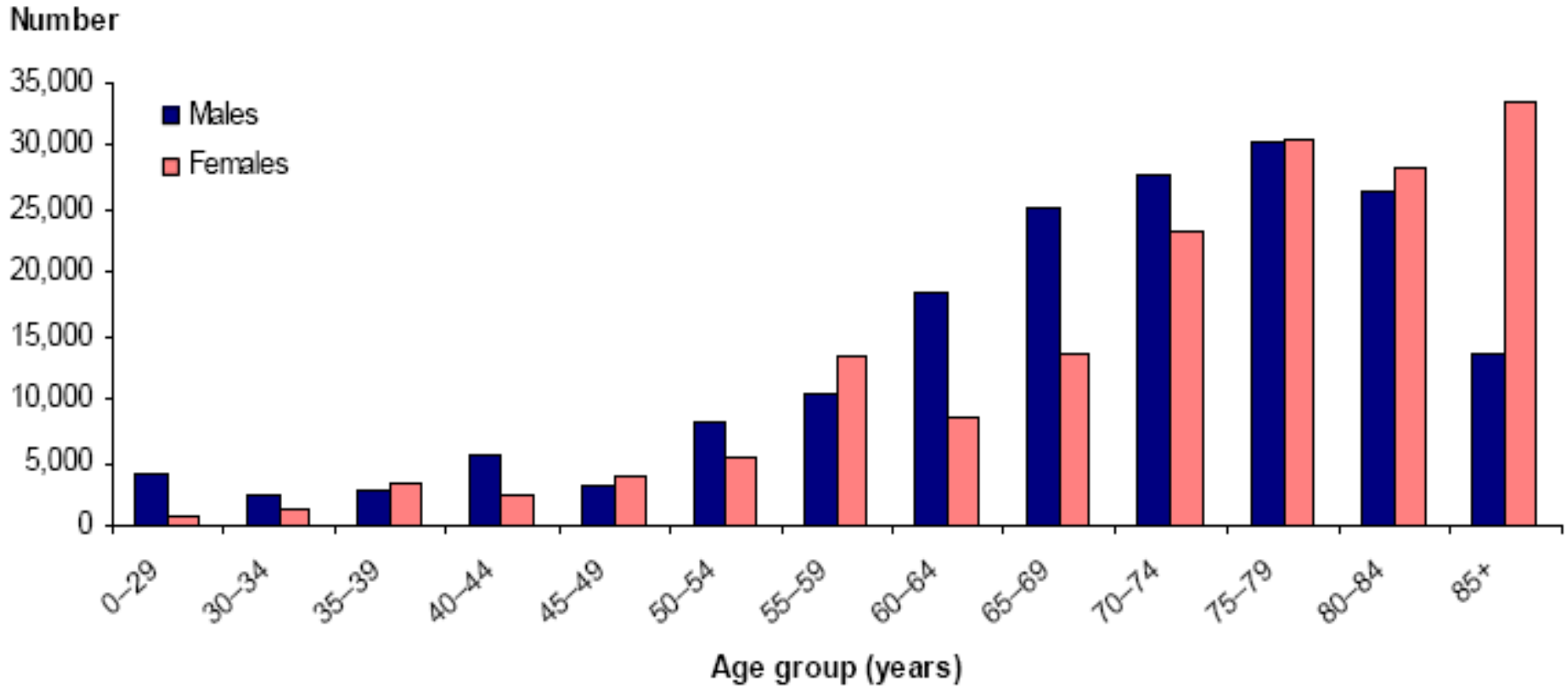
AIHW: Senes S 2006. How we manage stroke in Australia. AIHW cat. no. CVD 31. Canberra: Australian Institute of Health and Welfare.

Numbers of people with stroke and disability in Australia (2003)



AIHW analysis of ABS 2003 Survey of Disability, Ageing and Carers Confidentialised Unit Record File.

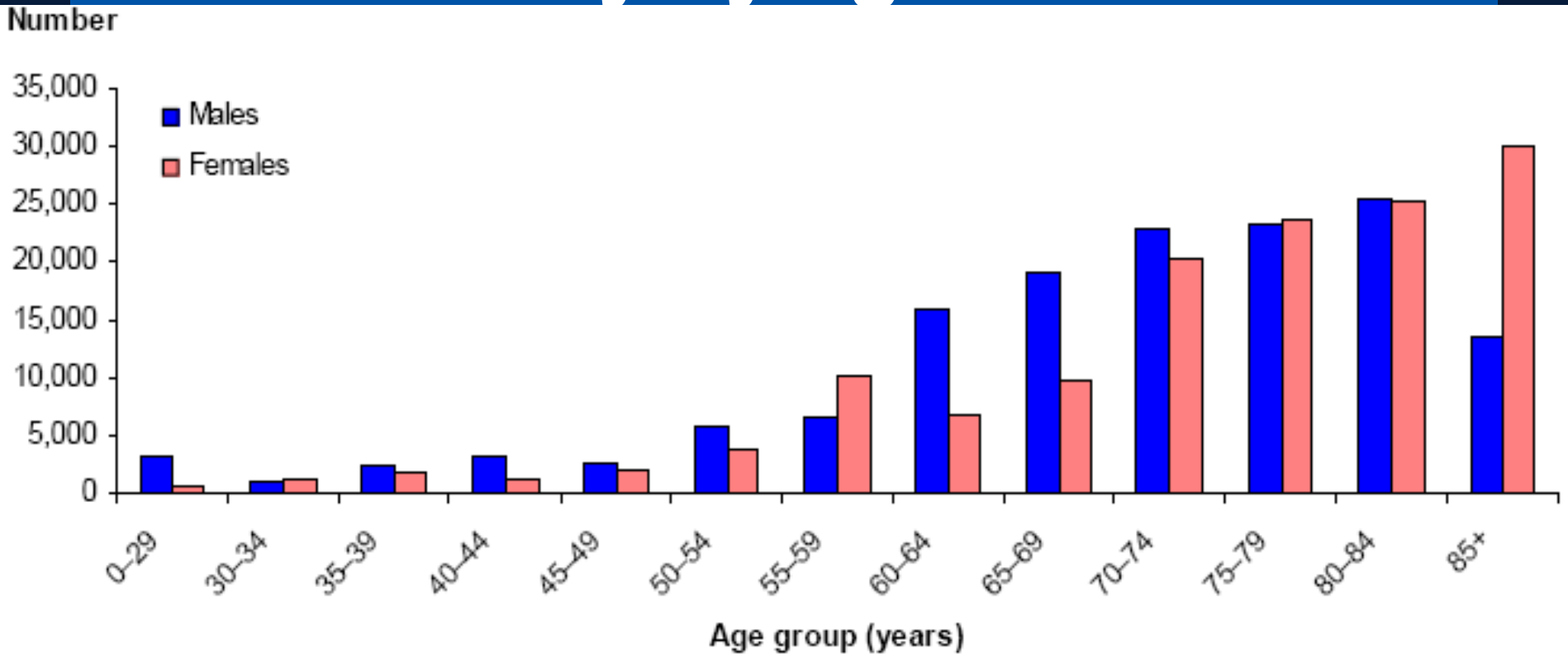
People with stroke by age and sex



Source: AIHW analysis of ABS 2003 Survey of Disability, Ageing and Carers Confidentialised Unit Record File.

Senes S, AIHW, 2006

People with stroke and disability by age and sex



Source: AIHW analysis of ABS 2003 Survey of Disability, Ageing and Carers Confidentialised Unit Record File.

Senes S, AIHW, 2006

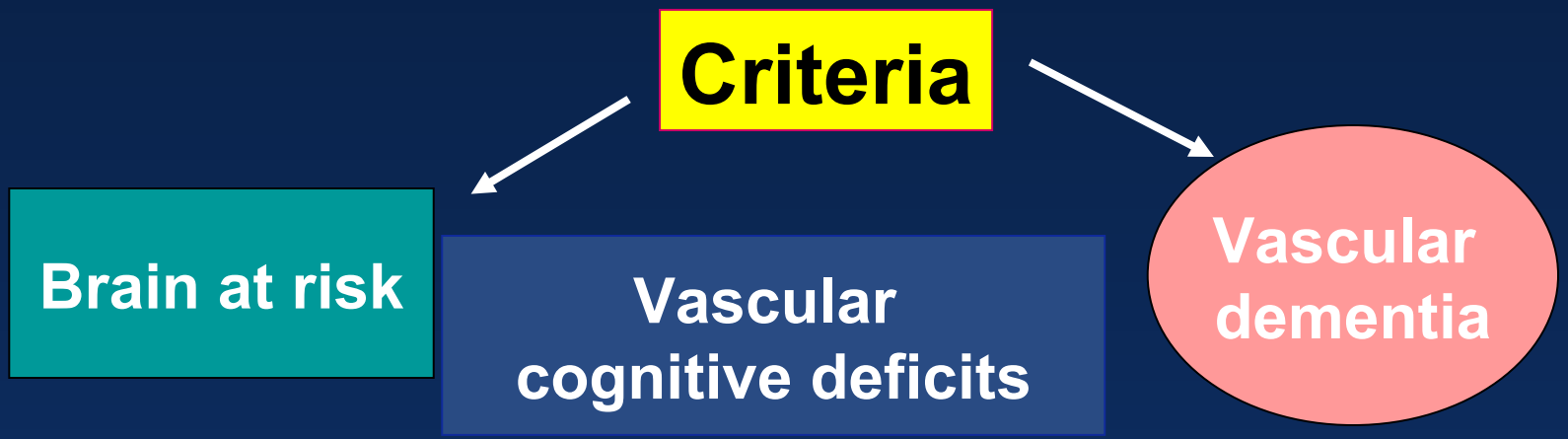
Cost of stroke

- Allocated funds for cerebrovascular disease $896m in 2000/01, ie 1.8% of total health expenditure
- 50% of costs from aged care homes; 40% from hospitals

Senes S, AIHW, 2006

Vascular Cognitive Impairment

- VCI as an overarching category



- VCI as the vascular equivalent of MCI

Disability types following stroke

- Restrict^{n} in physical activity or work 51.4%
- Speech difficulties 28.9%
- Learning or understanding 28.2%
- Nervous or emotional condition 14.7%
- Mental illness * 5.0%

Senes S, AIHW, 2006

AIHW analysis of ABS 2003 Survey of Disability, Ageing and Carers Confidentialised Unit Record File.

Outline

- Depression
- Apathy
- Dementia
- Doing Well
  - Sydney Stroke Study

Post-stroke Depression (PSD)

- Prevalence
- Duration
- Predictors
- Pathogenesis

Rates of PSD vary 21- 71%

- pt selection

(*in-pt/out-pt/community*)

- depression definition

(*major/minor/dysthymia*)

- follow-up

(immediate/1, 3, 6 m/yrs)

- scales and raters *(clinician/self-rated/informant)*

Mean Rates:

- Major 20%
- Minor 21%
- Combined 34%

PSD: Duration

- Major depression 9/9 better at 2 year follow-up[1]
- Minor depression 3/12 better at 2 year review[1]
- Mean duration of major depression = 34 weeks[2]
- Mean duration of minor depression = 13 weeks[2]
- Majority of MDE remit by 1 yr f-up, but…[3]
- 30% of in hospital MDE still depressed at 1 yr; 25% at 2 yrs and 20% at 3 year follow-up[3]

[1]Chemerinski E, Robertson RG *Psychosomatics* 2000;41:5-14
[2]Morris PLP et al, *Int J Psychiatric Medicine* 1990;20: 327-342
[3]Astrom M et al *Stroke* 1993;24:52-57

Pathogenesis of PSD

- Traditional Robinson finding: PSD associated with left frontal lesions has been challenged
- Robinson revised original assertion to include time from stroke and differentiated depressive diagnoses from depressive symptoms
- Correlation strongest in 1st m & disappear in longitudinal follow-ups, ie after 6 m
- Could discrepancy result from time of assessment after stroke?

Carson AJ Lancet 2000
Steffens DC et al *Stroke* 2002;33:1636-1644
Morris PLP et al *J Neuropsychiatry Clin Neurosci* 1996; 8:153-159
Narushima K et al *J Neuropsychiat Clin Neurosci* 2003;15:422-430

PSD - site of lesion

- Dispute about whether severity of depression is correlated with proximity of anterior border of lesion to frontal pole in left hemisphere but not right hemisphere[1]
- PSD also linked to small lesions in basal ganglia[1] and areas of limbic structures[2]

[1]Shimoda K, Robinson RG *Biol Psych* 1999; 45:187-192
[2]Desmond DW et al, J Int Neuropsychol Society 2003; 9:429-439

PSD before 6 m - site of lesion[1]

- Interval: most studies < 1 m post stroke and none > 6 m
- Controlled for FH and PPH
- Depression > common with left lesions
- Left hemisphere: 6 of 8 studies → inverse relationship of depressive Sx and distance from frontal pole (r = - 0.53)
- Right hemisphere: 1 of 5 studies → sig. 'r'

[1]Shimoda K, Robinson RG *Biol Psych* 1999; 45:187-192

Site of lesion not correlated with PSD

- Carson et al examined depressive diagnoses not symptoms and did not find association[1]
- Compared PSD in first month and later depression
- Heterogeneity greatest with acuity - in first month and in hospital patients

[1]Carson AJ et al *Lancet* 2000;356:122-126

Methodology of PSD research

- Depressive Sx vs Dx
- Interval from stroke
- Depressive Sx may be stroke Sx
- Lack of insight (48% overtly sad denied pts depression)[1]
- Communication and comprehension difficulties
- Emotionalism vs depression
- Pathological crying vs PSD: dissociation[1]
- Hospital vs community subjects
- Effects of anti-depressant treatment
- Differential attrition → depressed Ss opt out

[1]Carota A et al, *Neurology* 2005;64:428-433

PSD - mechanisms?

- Depletion of monoamines after lesions in the frontal lobe or basal ganglia?
- Decrease in serotonin-receptors?
- Disruption of dopaminergic pathways?
- Psychological?

Associations of PSD

- Age – inconsistent; ?younger more at risk[1]
- Baseline severity of disability – robust[1]
- >severe stroke[2]
- dementia[2]
- females[2]
- Non-somatic symptoms more indicative than somatic symptoms[2]

[1]Carota A et al, *Neurology* 2005;64:428-433
[2]Desmond DW et al, J Int Neuropsychol Society 2003; 9:429-439

Review of psychosocial risk factors for PSD[1]

- Female
- PH depression
- Barthel Index↓
- Lower MMSE
- Dysphasia

(Replicated findings)

- Living alone
- Age - younger
- Age - older
- Social distress 6m *prior* to stroke
- Lower SES - risk
- Lower SES - protective

[1] Ouimet MA *Can J Psychiatry* 2001;46:819-828

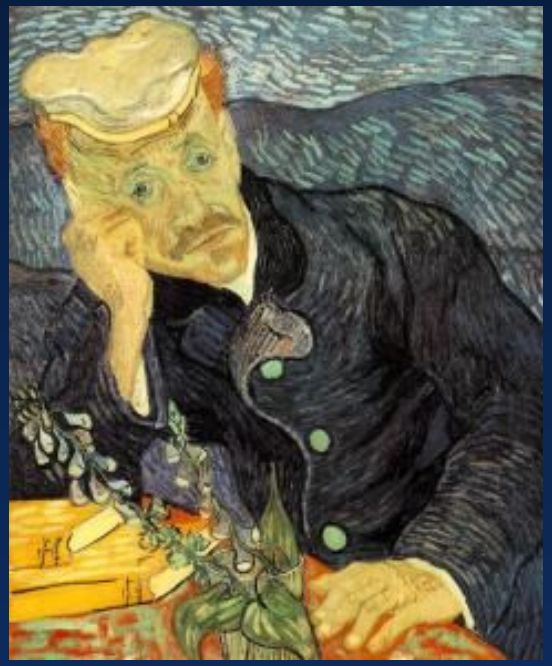
Apathy

- Prevalence
- Pathogenesis

Apathy Defined

Is:

- A loss of motivation or drive
- A symptom of depression
- A distinct syndrome



Important issues:

- prevalence
- risk factors
- differentiation from depression

Apathy by another name

- Synonyms
  - Abulia (very severe apathy)
  - Amotivational state
  - Negative symptoms (usually re Sz)
- Symptom vs syndrome

Pathogenesis[1]

- Anterior cingulate - R, L, both
- Frontal regions - various, small studies
- Subcortical regions - bilateral basal ganglia, post limb of internal capsule

Summary: neuroimaging and autopsy implicate subcortical-frontal circuits

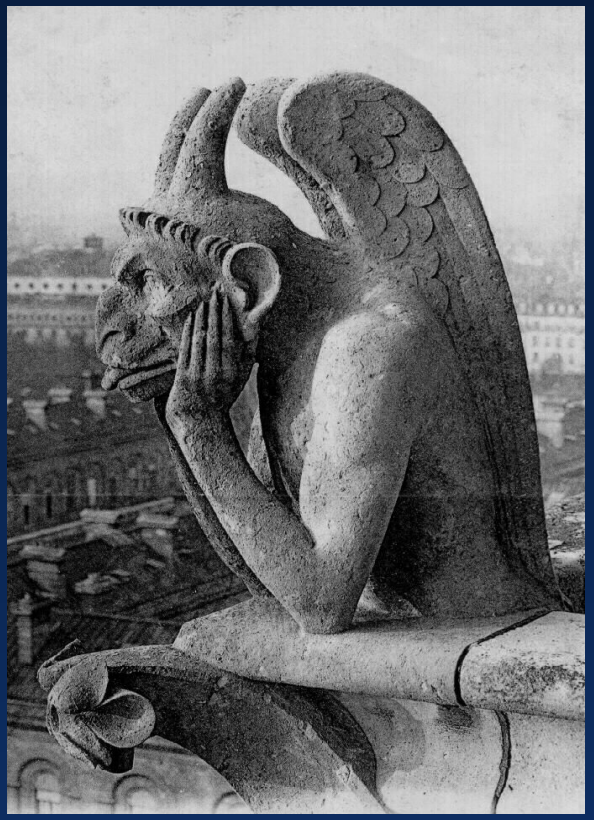
- esp. anterior cingulate and dorsolateral prefrontal cortex …
- … & thalamus, basal ganglia and white matter tracts connecting these regions

[1]Van Reekum R *J Neuropsychiatry and Clin Neurosciences* 2005;17:7-19

Apathy - Risk Factors

Few studies; mixed factors:

- Advancing age[1]
- Increased functional loss[1]
- Lower MMSE and verbal fluency[1,2]
- Correlate with general cognitive tests such as IQ



[1]Starkstein et al 1993; [2]Okada et al, 1997;

Associations

- Depression (weak correlation)
- Not with illness severity
- Association with slowing

Clinical Relevance

- Closely associated with length of stay
- Pts less likely to seek rehab

✂⇧ caregiver burden

- CG may misinterpret loss of drive as laziness or defiance
- Different treatments for post-stroke depression and apathy

Sydney Stroke Study Team

Sydney Stroke Study

Longitudinal study:

- **Clinical and psychiatric assessments**
  - **SCID interview: DSM-IV**
  - **Hamilton Depress^{n} Rating Scale (HDRS-17) (cut 10/11)**
  - **Geriatric Depression Scale (GDS-15) (cut 5/6)**
  - **Apathy Evaluation Scale (AES,Marin,1991) (cut 36/37)**
  - **Neuropsychiatric Inventory (NPI)**
- **Neuropsychological testing**
- **Neuroimaging (MRI)**

Study Design

Stroke Group

205 pts admitted to Stroke Units & met criteria

→

27 withdrew
3 died
6 uncontact.
1 dementia

→

168 3m Ax
First-ep 69.7%

Control Group

130 controls recruited from community groups

→

108 eligible & given baseline assessment

Clinical Scales

	Patients n=167	Controls n=108
Age	72.4 (8.7)	71.2 (6.0)
Gender (m)	56.9%	48.1%
Nart-R IQ	104.2 (10.3)	114.1 (7.7)***
IQCODE	3.1 (0.3)	3.1 (0.1)
ADL+IADL	11.7 (3.3)	13.9 (0.3)***
MMSE	27.7 (2.6)	28.8 (1.4)***
ESS	93.8 (9.5)	

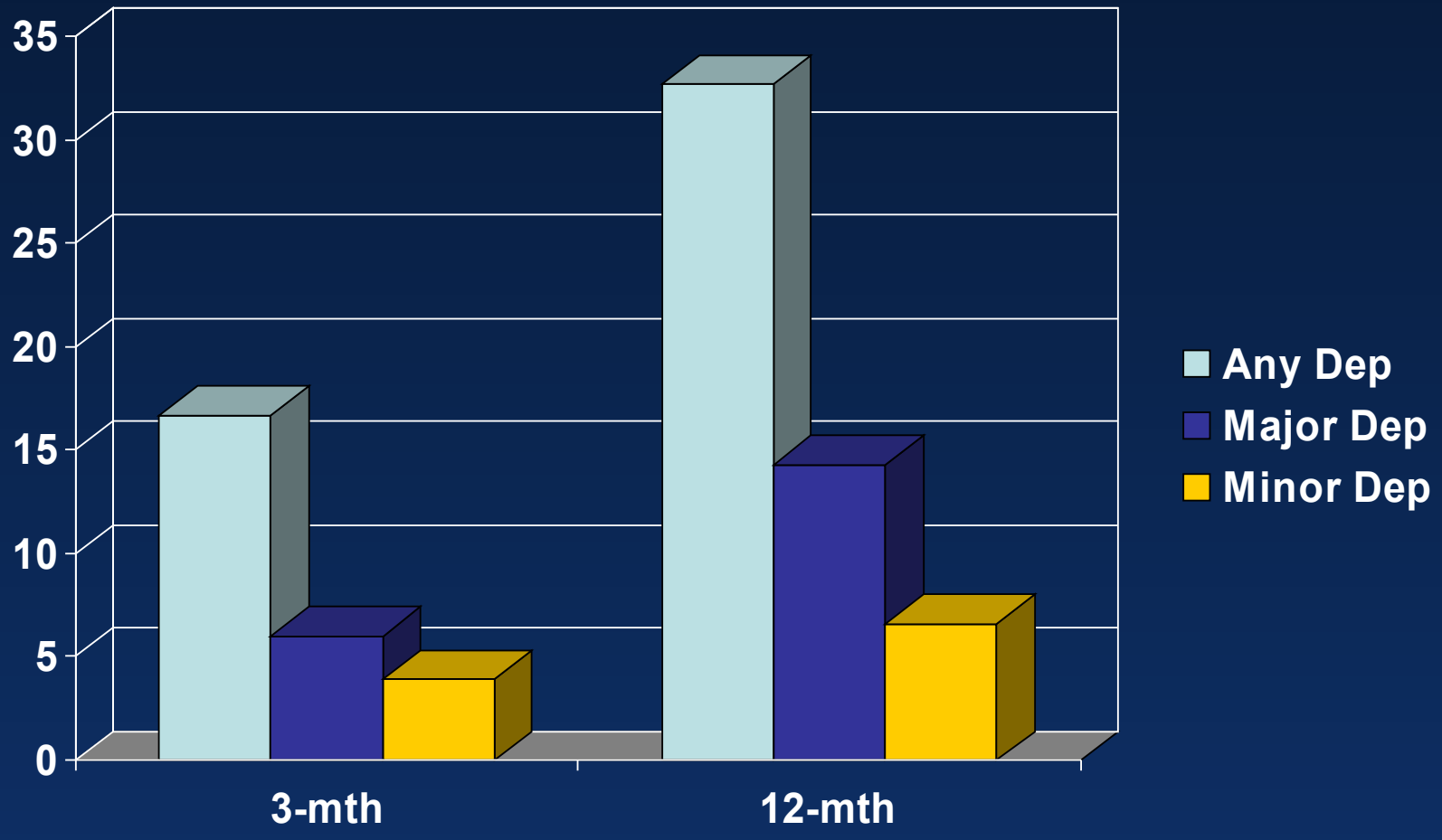
*p≤0.05; **p≤0.01; ***p≤0.001

Depression Criteria

Any depression:

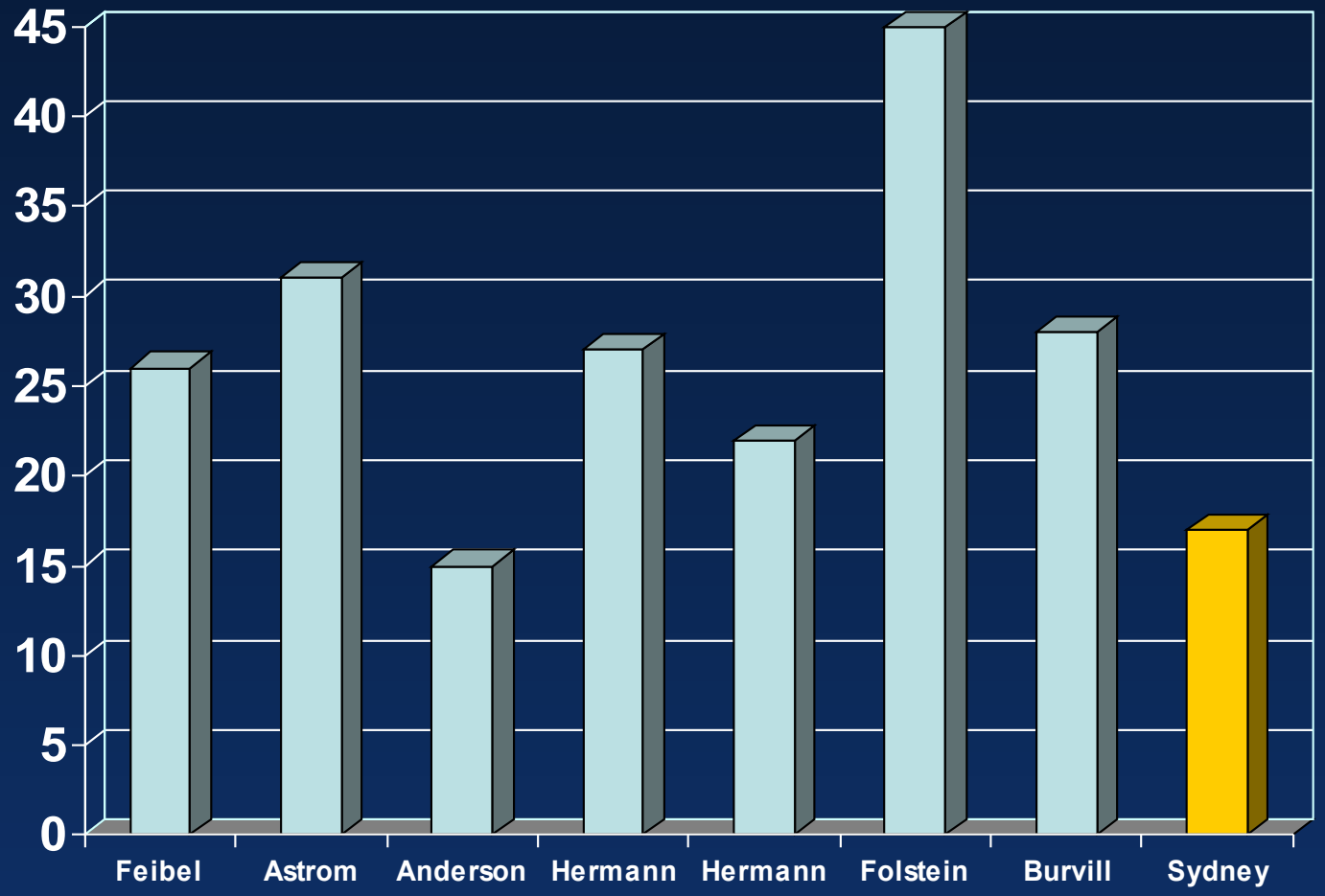
- **DSM-IV: Major or minor depression**
- **HDRS-17 total > 10**
- **GDS total > 5**
- **Treatment with antidepressants since stroke**

SSS: Post-stroke Depression (%)



N=164

Comparison of Rates @ 3m (%)



Why relatively low rates in SSS?

- Chemerinski & Robinson (2000) review of 24 studies - mean 34% overall "depression" @ 3-mth

Apathy?

- SSS pts with "apathy", "depression" or "apathy + depression" = 36%

Interval medications?

- On antidepressants at 3-month: 8.5%

SSS: PSD Correlates @ 3m

- Age
- Gender
- Premorbid IQ
- Years of education
- MMSE
- ADL+IADL
- IQCODE
- ESS
- Apathy

- Hypertension
- Diabetes
- Coronary artery Δ
- Peripheral vascular Δ
- Atrial fibrillation
- Smoking
- Hypercholesterolaemia

All not significant

SSS: PSD Correlates @ 12m

- Depressed persons significantly worse according to:
  - MMSE (t=2.73; p=0.007)
  - ADL+IADL (t=3.27; p≤0.001)
  - CDR (t=-4.01; p≤0.001)
  - AES (t=-3.17; p=0.004)

SSS: Correlates of PSD @ 3 or 12m

SIGNIFICANT

- History of depression
- Total brain atrophy

NOT-SIGNIFICANT

- Stroke Volume
- Number of strokes
- Total WMD
- Side of stroke (clinical signs)

Relationship Between Depression and Dementia?

Does depression cause dementia?

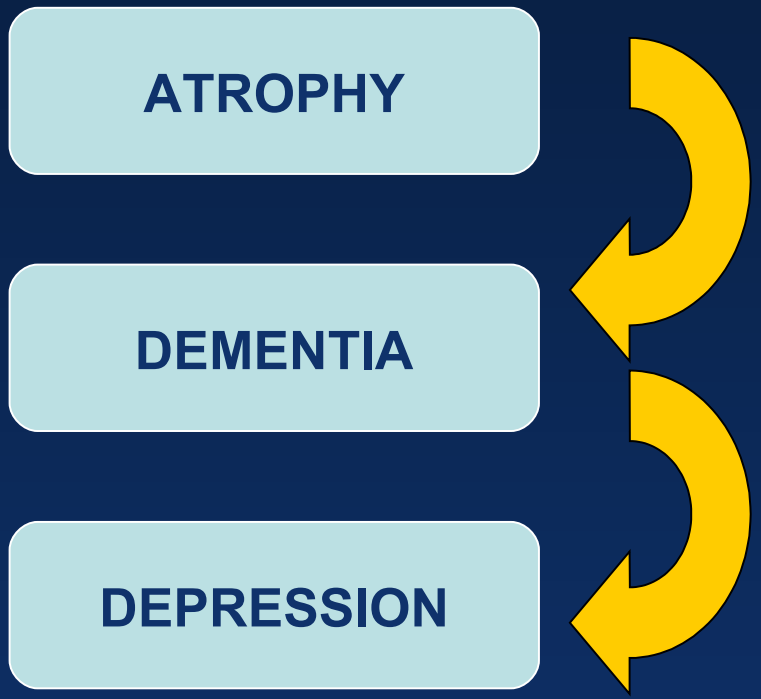
- Dep^{n} @ 3m does not predict dementia @ 12m (dementia @ 3m as covariate)

Does dementia cause depression?

- Dementia @ 3m does predict dep^{n} @ 12m (dep^{n} at 3m as covariate)
- At 12m, 42.4% of patients w dementia @ 3m are depressed vs 14.0% without dementia

Conclusions

- **PSD is associated with advancing brain disease**



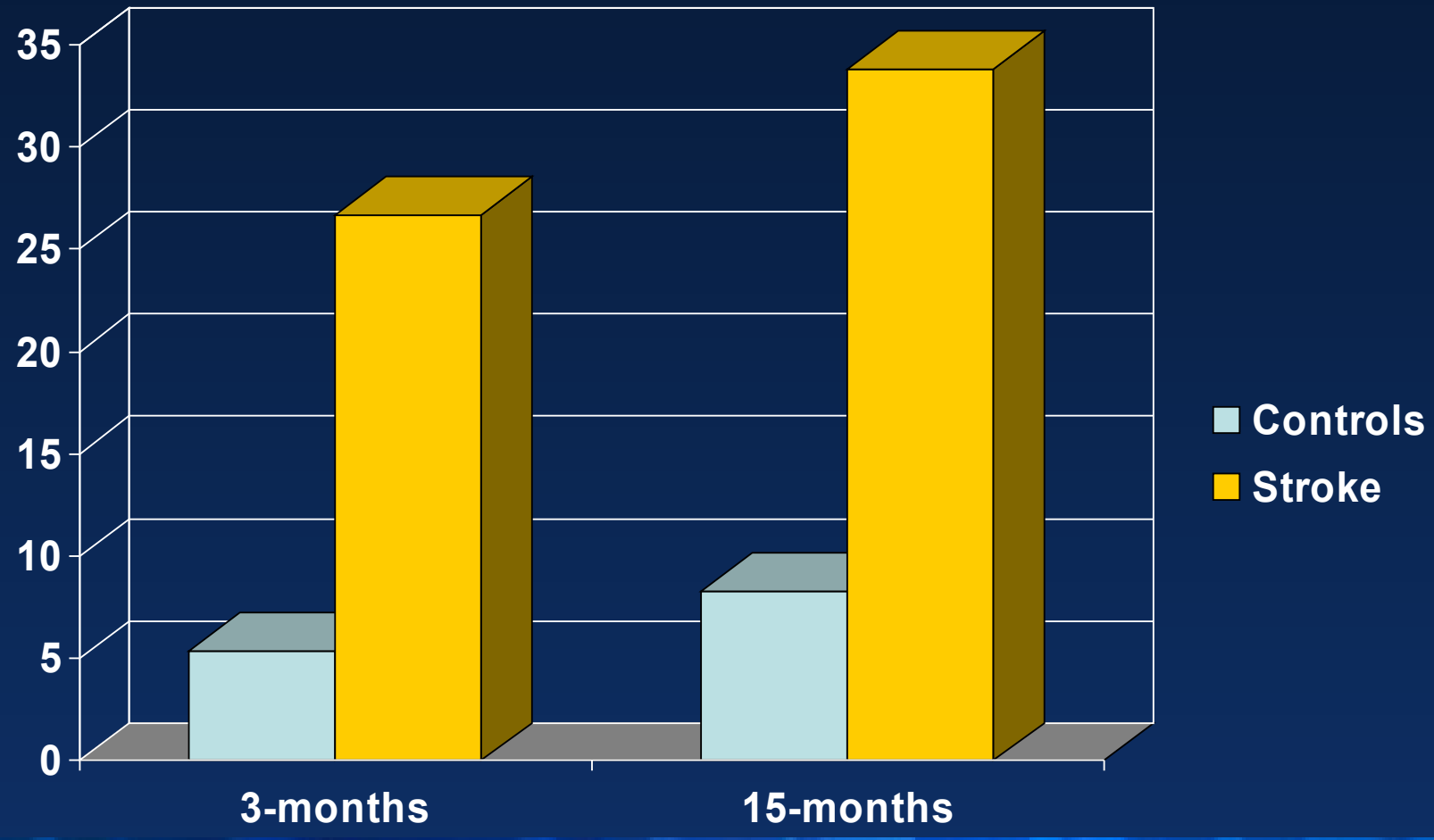
Post-stroke Apathy

Modified HDRS

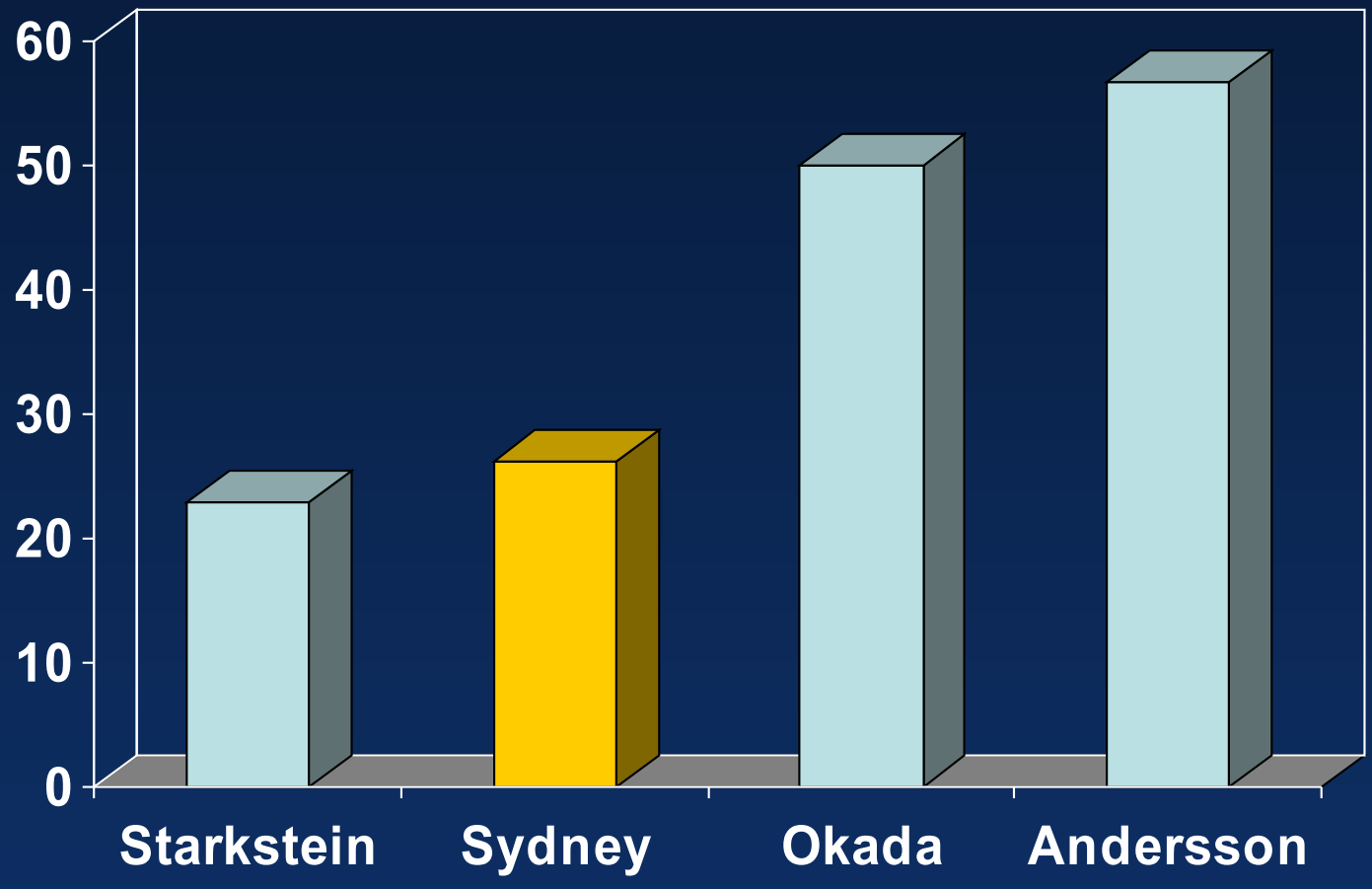
HDRS-14 = HDRS-17 *minus* apathy items

- **Diminished work/interest**
- **Psychomotor retardation**
- **Lack of energy**

SSS: Apathy Prevalence (%)



Comparison of Apathy Rates



SSS: Demographics

	Apathetic n=36	Non-Apathetic n=99
Age	75.2 (7.0)	71.1 (9.2)**
Gender (m)	61.4%	61.5%
NART-R IQ	101.8 (9.4)	105.1 (10.4)
IQCODE	3.2 (0.5)	3.0 (0.5)
ADL	4.3 (1.7)	5.3 (1.3)**
IADL	5.1 (2.3)	7.0 (1.7)**
MMSE	26.8 (3.3)	28.3 (1.9)**
HDRS-17	3.6 (4.9)	2.4 (3.0)

*$p \leq 0.05$; **$p \leq 0.01$

Cardiovascular Risk Factors

- Hypertension
- Diabetes
- Coronary artery disease
- Peripheral vascular disease
- Atrial fibrillation
- Smoking
- Hypercholesterolemia

All not significant

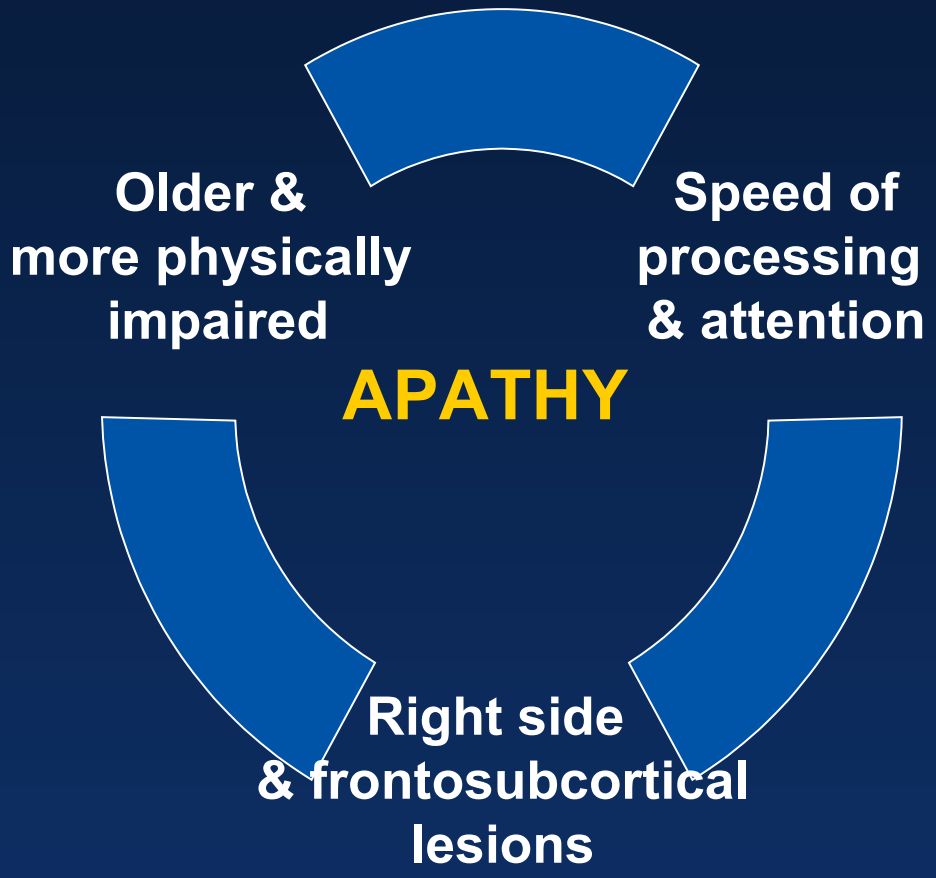
Neuropsychological Tests

- Apathetic patients performed worse on tests of attention/ concentration and processing speed only

Neuroimaging Results

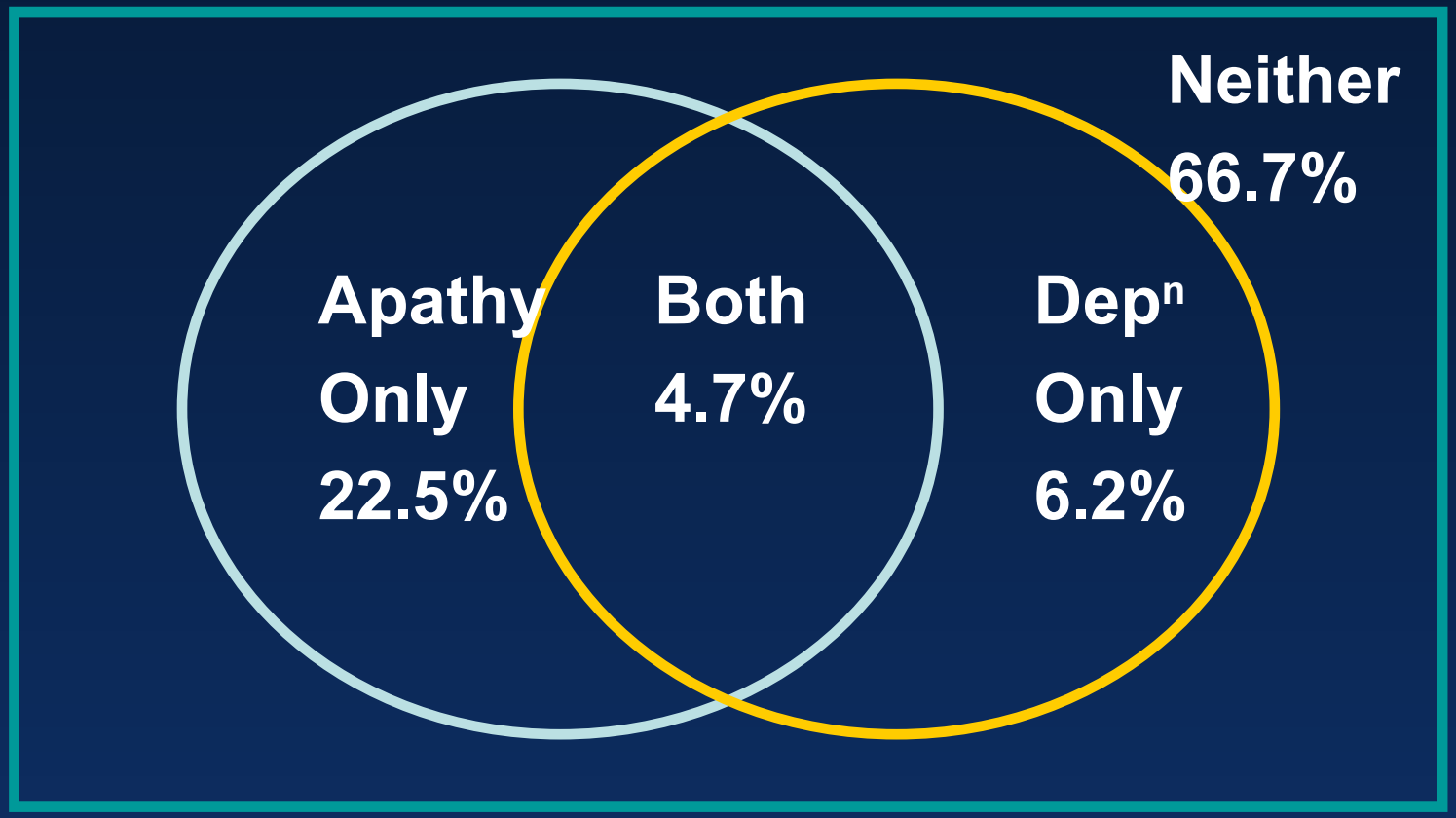
- No link with size of stroke or number of previous strokes
- Associated with regions affected by the stroke i.e. right frontal and subcortical areas

The Overall Picture



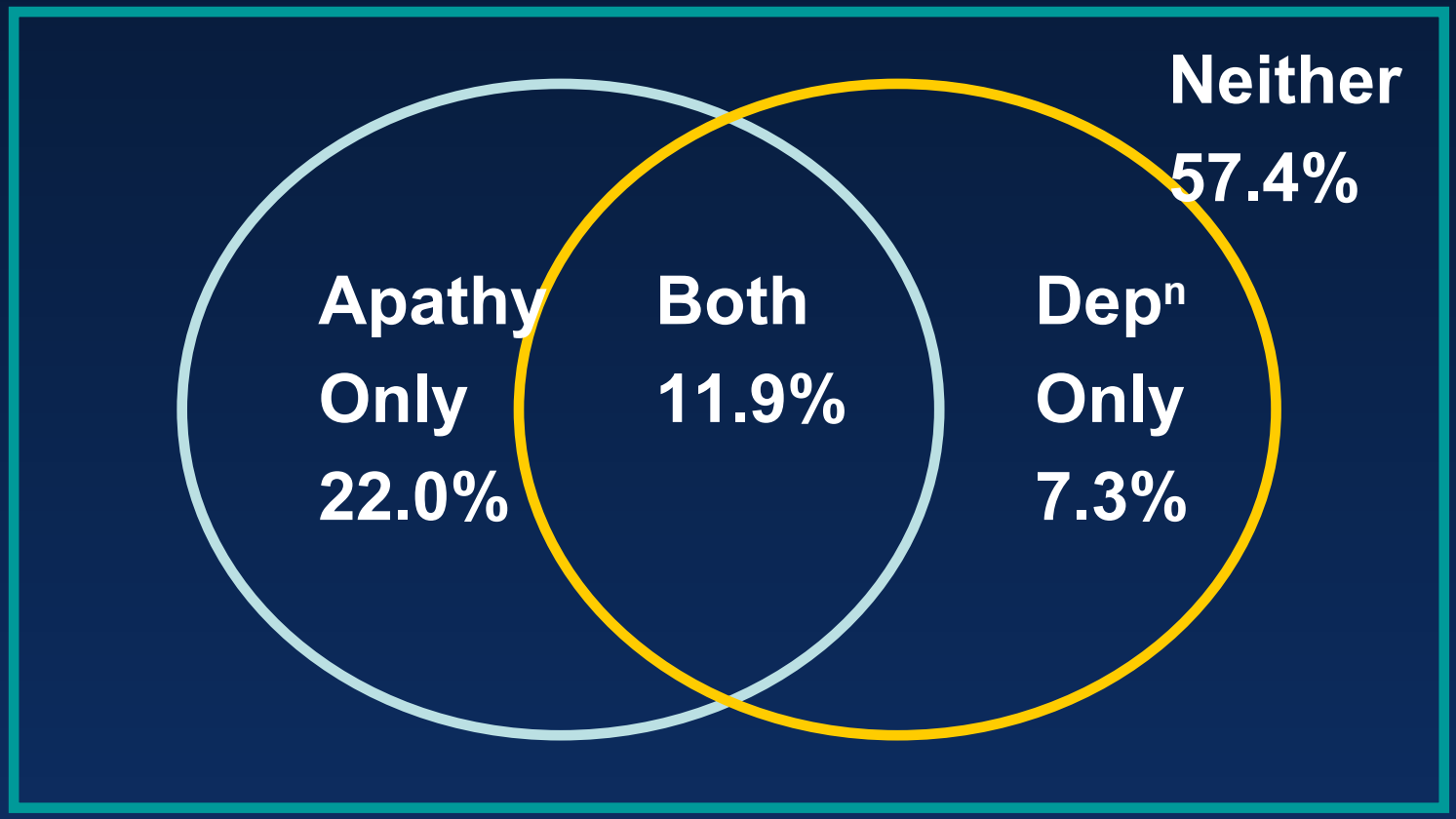
The Independence of Apathy & Depression Following Stroke

Prevalence at 3-months



Odds ratio = 2.20. 95% CI 0.71, 6.95; n.s.

Prevalence at 12-months



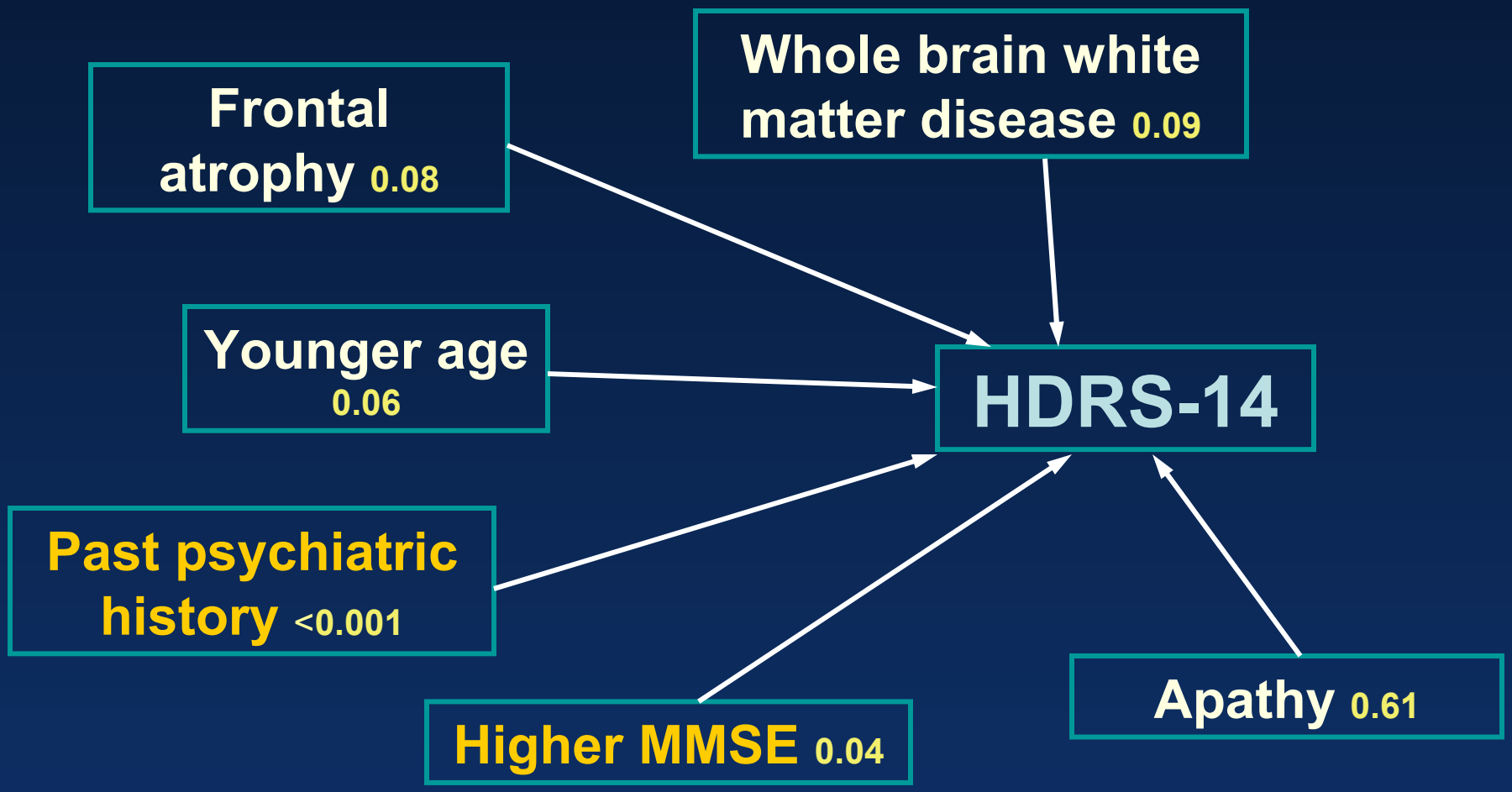
Odds ratio = 4.30. 95% CI 1.60, 11.75; sig

Is Dementia A Common Causal Factor?

- Dementia at index* predicts ..
  - .. depression at 12-15 m (correcting for index depress^{n}; OR=5.6, 95%CI 1.95, 15.77; n=132)
  - .. apathy at 12-15 m (correcting for index apathy; OR=11.89, 95% CI 2.76, 51.22,; n=95)
- Neither index apathy (OR=1.65, 95% CI 0.25, 10.82; n=106) nor depression (OR=1.79, 95% CI 0.27, 11.86; n=119) predicts dementia at 12-15 m (correcting for baseline dementia)

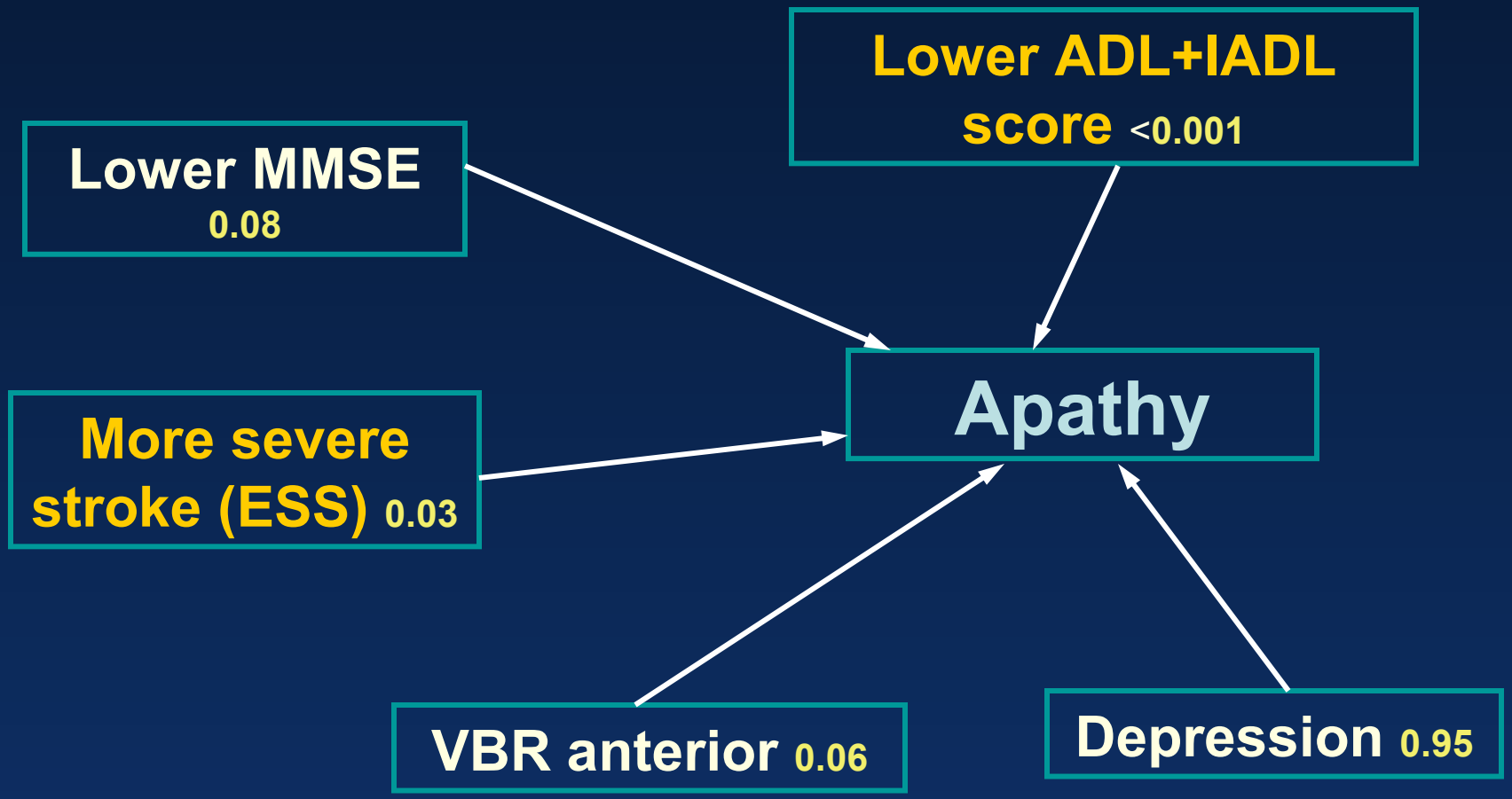
*Index = 3-6 month assessment

Depression Model



(chi square=80.40; df=24; p≤0.001); n.b. numbers indicate path coefficients and p-values.

Apathy Model



(chi square=80.40; df=24; p≤0.001); n.b. numbers indicate path coefficients and p-values.

And so?

- Post-stroke apathy and depression are independent syndromes:
  - prevalence
  - different risk factors and correlates
- The small overlap between these constructs cannot be explained by common items within the HDRS (ie diminished work/interest, psychomotor retardation, lack of energy)

Treatment Issues

Depression:

- Antidepressants esp SSRIs
- Sertraline prophylaxis (DB RCT PSD: PBO 30%; Rx 10%)

Apathy:

- Acetylcholinesterase inhibitors
- Psychostimulants - dopaminergic drugs
- Modafinil (Provigil)
- Mainly small/post hoc studies

Issues & Future Directions

Delineation of apathy & depression

- Educate GPs to recognise and treat these illnesses
- Different Rxx
  - (eg SSRI vs ChEI)

Who are we missing?

- 20% depressed but not on antidepressant medication

Epidemiology of Vascular Dementia

- 2nd most common dementia (after AD)
- Prevalence:
  - 65-69 years: 1.4%
  - May reach >25% at 85+years
  - Lifetime risk: M 34.5% , F 19.4%
  - Incidence: 0.17 - 0.71/100 person yrs
  - Stroke: 25-30% at 3 months
- More common in Western countries, with age and possibly in men
- Is preventable

Dementia after stroke

- 6 - 32% in *clinical* samples; 9-fold ↑ [1,2]
- 10 year risk in *population* sample 19.3% vs 11% in non-stroke controls; 2-fold↑ [3]
- SSS: Inclusion criterion: no dementia before stroke; but 3-6m after stroke …
  - 21% VaD
  - 37% VaMCI [4]

Tatemichi TK+ 1993; [2]Pohjasvaara T+ 1998; [3] Ivan CS 2004; [4] Sachdev, Brodaty et al 2006

Variability in rates of dementia after stroke

- Population studied
- Criteria used for diagnosis of dementia
- Exclusion of pre-stroke dementia
- Age of population
- First or repeat strokes
- Length of follow-up
- Death rate

Who develops dementia after stroke?

- Older age[1]
- Less education, lower premorbid IQ
- Prior pathology
- Prior cognitive decline [1]
- Cerebrovascular disease risk factors
- [1] Sachdev et al, 2006; [2] Ivan et al, 2004

- Interval stroke [1]
- ApoE3[2]
- Number of cerebro-vascular risk factors[1]
- Excess WMLs [1]
- Stroke volume [1]

Who Does Well After Stroke?

Desmond et al (1996)

- 151 stroke patients
- Interview 3-mths & 12 to 36-mths post-stroke
- Improvement = more than 2SDs above change in control group scores (n=19)
- Improvers
  - more likely to have a left hemispheric infarct vs brain stem/cerebellar infarct
  - lower incidence of diabetes
  - more impaired cognitive summary score at baseline

Ballard et al (2003)

- 115 stroke patients (80.4 ± 3.8 yrs)
- Tested at 3-mths & at 15-mths post-stroke
- Improvement = greater than 2 point increase in MMSE score (n=18)
- Decliners = diagnosis of dementia (n=10)
- Improvers versus stable group
  - significant lower attention, orientation and total cognition scores on CAMCOG
  - diabetes = sig less likely to be an improver

Aims

- Previous studies have only examined those in highest echelon of improvement and improvement has been defined cognitively [1,2]
- People who are performing ‘at ceiling’ have not been examined
- SSS = study of *‘doing well’* following stroke

[1] Desmond et al 1996; [2] Ballard et al, 2002

Definition of “Doing Well”

- Cognitively & functionally
- ‘Doing well’ = MMSE score of ≥ 28/30 and a combined ADL/IADL score = 14 at one-year follow-up
- Study sample = 96 patients (& 75 controls) with complete MMSE, ADL and IADL scale scores at both time points

3-group combined analysis

- MMSE>27 *and* ADL+IADL=14
- *Rule of thirds*
  - Doing well n=31
  - Not doing well n=27
  - Mixed n=38

MMSE > 27

- Those with an MMSE score ≥ 28 were
  - Younger
  - More years of education
  - Higher premorbid IQ
  - Less apathy at 3-6 mths
  - Less likely to have dementia at 3-6 mths
- No sig diffs wrt marital status, depression, total atrophy, more than one stroke, interim stroke or social support

ADL + IADL = 14

- Those with an ADL+IADL score = 14/14 were
  - Younger
  - Higher premorbid IQ
  - Lesser stroke severity
  - Less apathy at 3-6 mths
  - Less likely to have dementia at 3-6 mths
- No sig diffs wrt marital status, depression, total atrophy, more than one stroke, interim stroke or social support

3-group combined analysis

- Significantly worse if:
  - Older age
  - Lower premorbid IQ
  - More Apathy
  - Higher ESS score
  - More total atrophy on MRI
  - Diagnosis of dementia
  - Atrial fibrillation

3-group combined analysis

- No significant differences for:
  - Marital status
  - Years of education
  - Social support
  - Having have more than one stroke
  - Interim cerebrovascular event
  - Diagnosis of major or minor depression

Detrimental Factors

Apathy is linked to poorer outcomes

- has a biological origin i.e. is not laziness
- people with motivational problems are less likely to seek rehabilitation services
- moderating variable or proxy for atrophy?

Protective Factors

Does more brain reserve help?

- higher premorbid IQ = better outcome
- BUT no rel'ship with yrs of education
- consistent with lack of direct relationship between brain pathology and clinical outcomes

Methodological Issues

- Relatively large sample and broad range of Ax
- Those performing at ceiling also included
- Outcomes considered functionally & cognitively
- First & repeat stroke patients included but no sig differences on stroke variables
- Limited subjects in MRI sub-study
- More patients doing poorly may have dropped out of the study however their 3-month parameters were similar to those who continued

In Conclusion

- Apathy, depression and dementia are common sequelae of stroke
- Furthermore, apathy and depression are independent constructs which merge over time due to increasing brain pathology
- Dementia is an important causal factor for both apathy and depression

In Conclusion

- Apathy has previously been under-recognised and under-treated
- Depression after stroke is also not adequately treated and most patients not taking antidepressants at follow-up
- More education for health professionals

In Conclusion

- However the news is not all gloomy
- A sizeable proportion of patients have good outcomes after stroke
- Predictors of good outcomes include younger age, less apathy and better premorbid IQ

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http://www.med.unsw.edu.au/adfoap

The End

Yeah, I used to get depressed watching the news, too. Then I discovered the miracle of apathy.