

**Mortality and long-term sequelae from childhood to adulthood for extremely preterm or tiny survivors**

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**WH (Bill) Kitchen**

- First (and only) trial of “intensive care”  
ability to measure pO<sub>2</sub>, infuse glucose and HCO<sub>3</sub>  
1000-1500 g birthweight  
1966-1970 Royal Women's Hospital
- increased survival
- increased “handicap” in survivors
- limited viewpoint

**WH (Bill) Kitchen**

- Victorian Infant Collaborative Study (VICS) Group
- Extremely low birthweight (birthweight 500-999 g)  
1979-80, 1985-87, 1991-92, 1997, 2005
- Extremely preterm infants (<28 weeks)  
1991-92, 1997, 2005

**Outcome into Adulthood of Very Tiny or Preterm Infants**

- Mortality
- Long-term sequelae  
neurological  
blood pressure  
growth  
respiratory  
functional

**Survival rates**

- Denominator
- Numerator

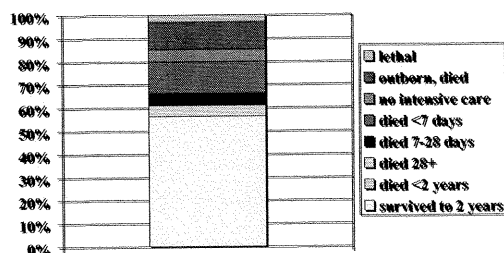
**Denominator**

- Who don't you like?  
Lethal anomalies  
Not born in your hospital  
Not admitted to nursery  
Not offered intensive care
- Sample size - uncertainty

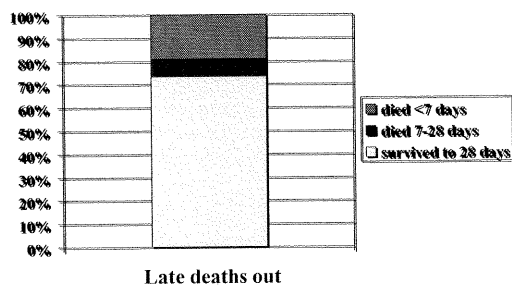
## Numerator

- What age?  
 First 7 days  
 Neonatal (28 days)  
 40 weeks PM age  
 Primary hospitalisation  
 Later in life?

## An Example - Victoria 1991-92 survival 23-27 weeks



## An Example - Victoria 1991-92 survival 23-27 weeks

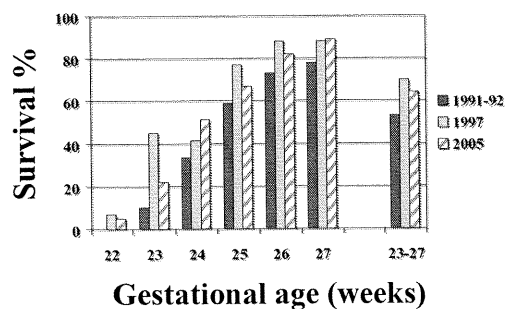


## Victoria – 22-27 week livebirths free of lethal anomalies

1991-92	n=428 (3.28/1000 livebirths)
1997	n=217 (3.51/1000 livebirths)
2005	n=270 (4.10/1000 livebirths)

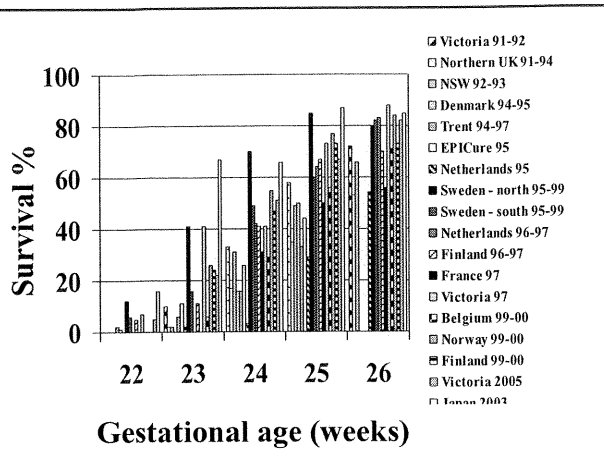
- Compare the survival and neurological morbidity of 22-27 week infants born in Victoria in 2005 with  
 – 22-27 week infants born in 1991-92 and 1997

## Survival Rate



## Why Improved Survival?

- Surfactant since 1991
- Better surfactant in 1997
- More offered intensive care in 1997; fewer <24 weeks in 2005



## Assessment at 2 years

- Survivors assessed at age 2 years, corrected for gestation
- Blinded paediatricians and psychologists
- Cognitive outcome – Bayley Scales

## Why have term controls?

- Cognitive outcome – Bayley Scales
- Bayley I and II – Mental Developmental Index (MDI)
- Bayley III – Cognitive and Language Composite Scores

## Why have term controls?

- Cognitive outcome – term controls
- Bayley I MDI – 1991-92      114.9 (19.5)
- Bayley II MDI – 1997            99.2 (15.4)
- Bayley III - 2005
- Cognitive CS                      108.9 (14.3)
- Language CS                      108.2 (14.8)

## Impairments

- Developmental delay if either MDI or Cognitive or Language Composite Scores <-1 SD relative to mean and SD of controls
  - Severe (<-3 SD)
  - Moderate (-3 SD to <-2 SD)
  - Mild (-2 SD to <-1 SD)
- Cerebral Palsy
- Deafness (requiring hearing aids or worse)
- Blindness (acuity <6/60 in the better eye)

### Disabilities

- **Severe**
  - severe CP, blindness, severe developmental delay
- **Moderate**
  - moderate CP, deafness, moderate developmental delay
- **Mild**
  - mild CP, or mild developmental delay
- **Nil**
  - the remainder

### Utilities

- 1.0 no disability**
  - 0.8 mild disability**
  - 0.6 moderate disability**
  - 0.4 severe disability**
  - 0.0 dead**
- Multiply for multiple impairments**

### Quality-adjusted survival rate

$$\frac{\Sigma \text{ utilities}}{N \text{ livebirths}}$$
  

$$\frac{\Sigma \text{ survivors}}{N \text{ livebirths}}$$

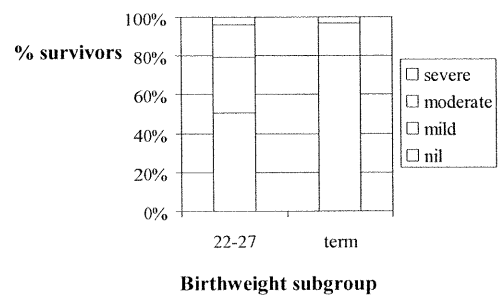
### Follow-up rates at 2 years

1991-92	98%
1997	99%
2005	95%

### Impairments - 2005

	22-27	Term
<b>Cerebral palsy</b>	10%	0%
<b>Blind</b>	0%	0%
<b>Deaf</b>	2%	0.5%
<b>Developmental delay</b>		
Severe	4%	0%
Moderate	12%	2%
Mild	32%	18%
Nil	52%	80%

### Disabilities



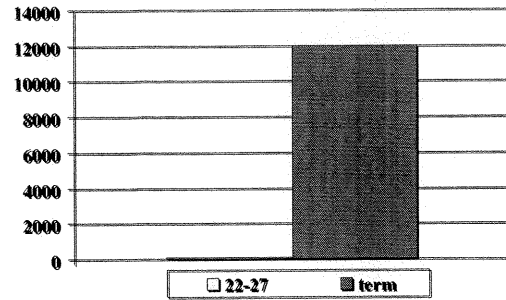
## Disabilities

Burden of illness – 2005 births

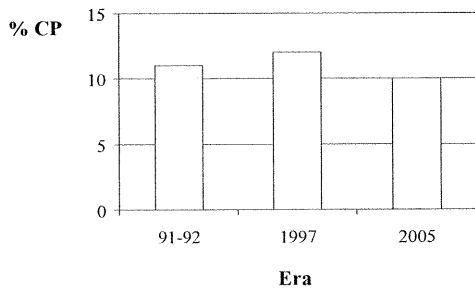
22-27 weeks 172/year @49% disabled = 84/year

Controls 60,000/year @20% disabled = 12,000/year

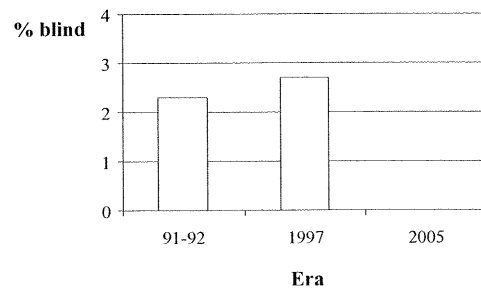
## Numbers with Disability



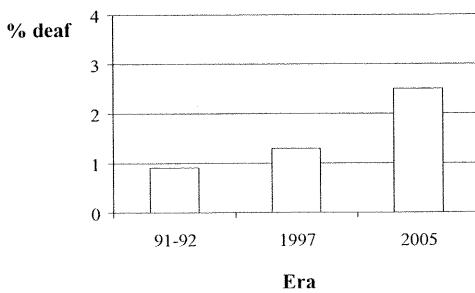
## Cerebral Palsy



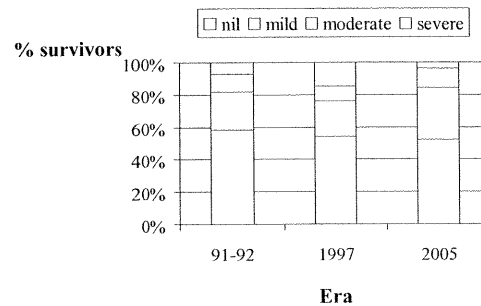
## Blindness

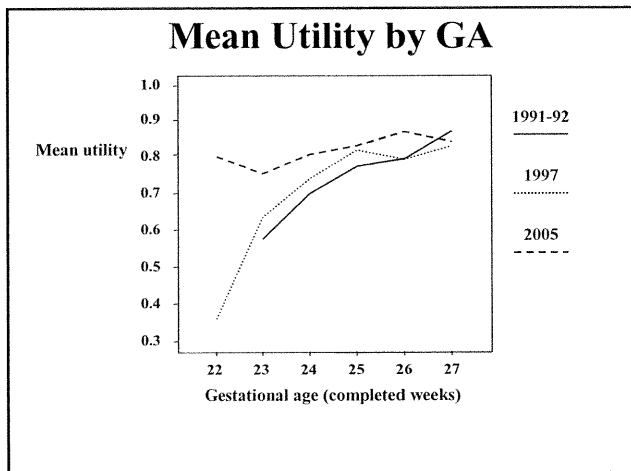
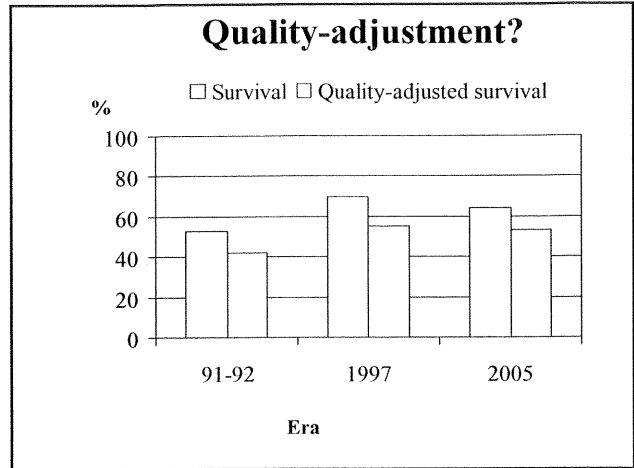
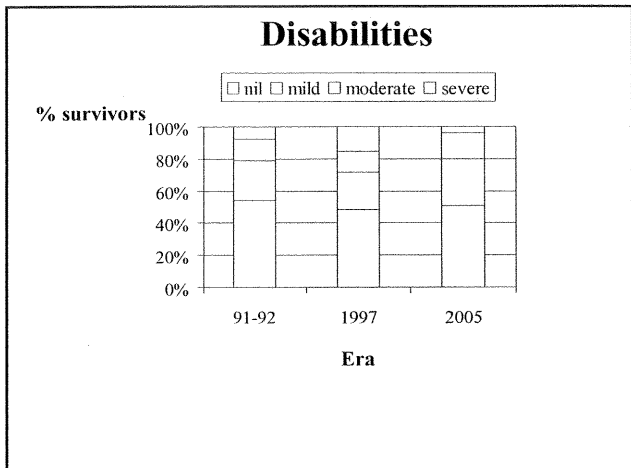


## Deafness



## Developmental Delay





### 22-27 week infants Victoria 1990s-2000s

- Survival rates peaked in the late 1990s
- Neurological impairments and disabilities
  - remain higher than in NBW infants
  - some improvements in 2005
- More innovations are required to improve long-term outcomes for EPT infants

### Summary of Early Childhood Outcomes

- Increased survival rates
- Impairment/disability rates might be improving in survivors
- Impairment/disability rates remain too high relative to controls

### Outcome into Adulthood of Very Tiny or Preterm Infants

- Mortality
- Long-term sequelae
  - neurological
  - blood pressure
  - growth
  - respiratory
  - functional

## Royal Women's Hospital Cohort

- 156 VLBW survivors born 1977-82
- 38 NBW controls
- 18-22 years of age

## Blood Pressure

1. Standard mercury sphygmomanometer BP
  - Sitting position
  - Systolic and diastolic BP recorded
2. Ambulatory blood pressure (ABP)
  - Monitor worn for 24 hours
  - Readings averaged for entire 24 hour, awake and asleep periods

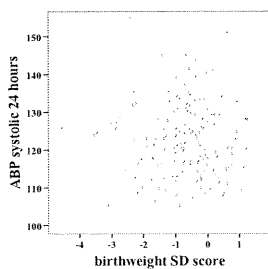
## Systolic Blood Pressure (mm Hg)

	Prem	Controls
Sphygmomanometer	125	116
Mean diff	8 (95% CI 3, 14)*	
Ambulatory	122	117
Mean diff	5 (95% CI 1, 8)*	
Awake	127	122
Mean diff	5 (95% CI 2, 8)*	
Asleep	110	106
Mean diff	4 (95% CI 0.1, 7)*	

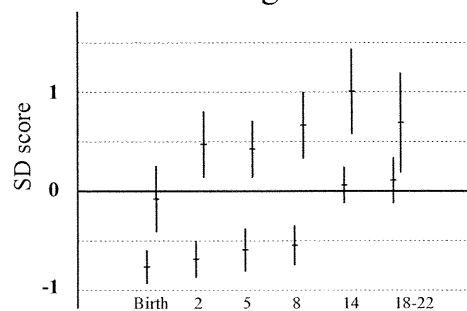
## Diastolic Blood Pressure (mm Hg)

	Prem	Controls
Sphygmomanometer	72	68
Mean diff	4 (95% CI 1, 8)*	
Ambulatory	69	68
Mean diff	1 (95% CI -1, 4)	
Awake	74	72
Mean diff	2 (95% CI -1, 4)	
Asleep	58	57
Mean diff	1 (95% CI -2, 4)	

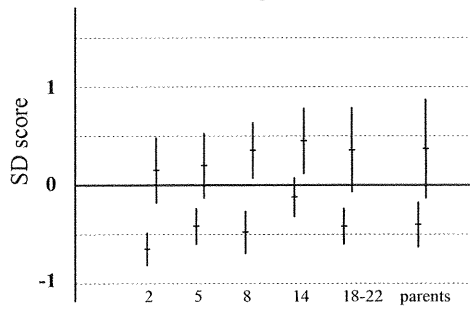
## Intrauterine growth restriction



## Growth Weight



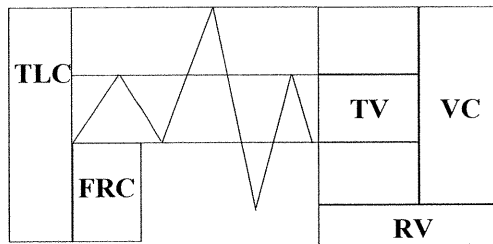
## Growth Height



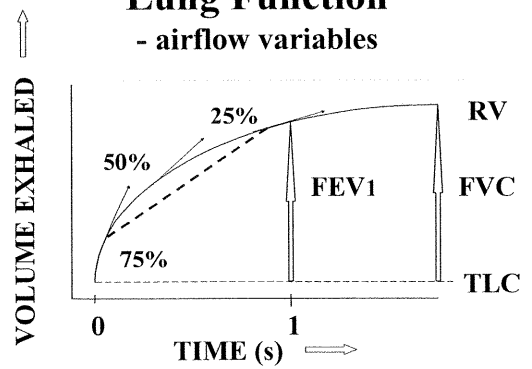
## Outcome into Adulthood of Very Tiny or Preterm Infants

- **Mortality**
- **Long-term sequelae**
  - neurological
  - blood pressure
  - growth
  - respiratory
  - functional

## Lung Function - static volumes



## Lung Function - airflow variables



## Respiratory variables

	VLBW	Control	Mean difference (95% CI)
FEV <sub>1</sub>	91.9	99.4	-7.4 (-12.4, -2.3)*
FVC	97.9	96.5	1.5 (-2.9, 5.8)
FEV <sub>1</sub> /FVC - %	81.1	88.7	-7.6 (-11.3, -3.8)*
MMEF <sub>25-75%</sub>	72.4	91.1	-18.7 (-27.3, -10.2)*
V <sup>*</sup> <sub>EMAN75%</sub>	82.1	92.5	-10.5 (-17.4, -3.5)*
V <sup>*</sup> <sub>EMAN50%</sub>	77.0	92.0	-15.0 (-24.2, -5.8)*
V <sup>*</sup> <sub>EMAN25%</sub>	75.6	94.0	-18.4 (-29.3, -7.5)*
TLC	100.2	98.9	1.3 (-3.0, 5.6)
RV	115.1	104.0	11.1 (-0.2, 22.4)
RV / TLC - %	29.2	26.5	2.7 (0.3, 5.1)*

## Functional

- Long-term cohort studies
  - Saigal, Hack
- National register data
  - Europe (Sweden, Norway, Denmark)



## Functional

### Saigal et al - Canada

- More restrictions on daily activities and self care
- High self-assessment of quality of life
  - Teenage years, through to adulthood
- Educational achievement and employment similar
- Living independently and parenting similar
- More shyness, behavioural inhibition, lower sociability and emotional well-being

## Functional

### Hack et al - USA

- Less resilience
- Better achievement in work performance
- Less risk-taking
- Similar health and well-being

## Functional

Sweden (Lindstrom et al; Pediatrics 2007)

N=570,768 livebirths 1973-1979

Fewer married; more live at home; employment similar

Lower education – post secondary

24-28 weeks	26.2%
29-32 weeks	33.7%
33-36 weeks	35.5%
37-38 weeks	38.2%
39-41 weeks	39.8%

## Functional

Sweden (Lindstrom et al; Pediatrics 2007)

N=570,768 livebirths 1973-1979

Receiving economic assistance

24-28 weeks	13.2%
29-32 weeks	5.6%
33-36 weeks	2.7%
37-38 weeks	1.9%
39-41 weeks	1.5%

## Functional

Norway (Moster et al; NEJM 2008)

N=903,402 livebirths 1967-1983

Disability pension

23-27 weeks	10.6%
28-30 weeks	8.2%
31-33 weeks	4.2%
34-36 weeks	2.4%
37+ weeks	1.7%

## Functional

Norway (Swamy et al JAMA 2008)

N=1,167,506 singletons 1967-1988

1967-1976 for reproductive data

RR for reproduction c/w term

	male	female
22-27 weeks	0.59	0.78
28-32 weeks	0.81	0.89

Preterm women – more likely to have preterm offspring

## **Summary Early Adulthood Outcomes**

- **Higher blood pressure**
- **Poorer growth?**
- **Airway obstruction**
- **Functional outcomes better than expected, but other morbidities appearing**