



# Preterm children: what happens to them when they grow up

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the women's  
the royal women's hospital  
victoria australia



# What will happen to my baby when he/she grows up?





# Growing interest in adult outcomes

## SURVIVAL OF THE LITTLEST

Babies born before 28 weeks of gestation are surviving into adulthood at higher rates than ever. What are the consequences, in later life, of being born so early? **By Amber Dance**

**THIS IS AN EXCITING TIME FOR US TO REALLY MAKE A DIFFERENCE TO THEIR HEALTH.”**

**20| Nature | Vol 582 | 4 June 2020**



### Study highlights heart-health issues for adults who were preemies

By Michael Merschel, American Heart Association News



(AndyL/E+, Getty Images)

Erin Wegener was a tiny baby facing enormous challenges.

Born at 29 weeks' gestation, she weighed only 1 pound, 14 ounces. Her first three months were lived in the neonatal intensive care unit. Family photos show her covered in gauze, sustained by too many tubes to count. Her entire hand just about fit inside her father's wedding ring.

## THE AGE

National Victoria

This was published 3 years ago

### Hospital researchers put life-long focus on Victoria's tiniest premature babies

By Rachel Kleinman

November 24, 2016 – 11:37am

Save Share A A A

When you walk through the doors into a neonatal intensive care unit you enter a world where the babies are often dressed in dolls' clothes. One where precious oxygen is fed through tiny tubes into feeble lungs and where the jangling of parents' nerves can almost be heard against the humming of machines.

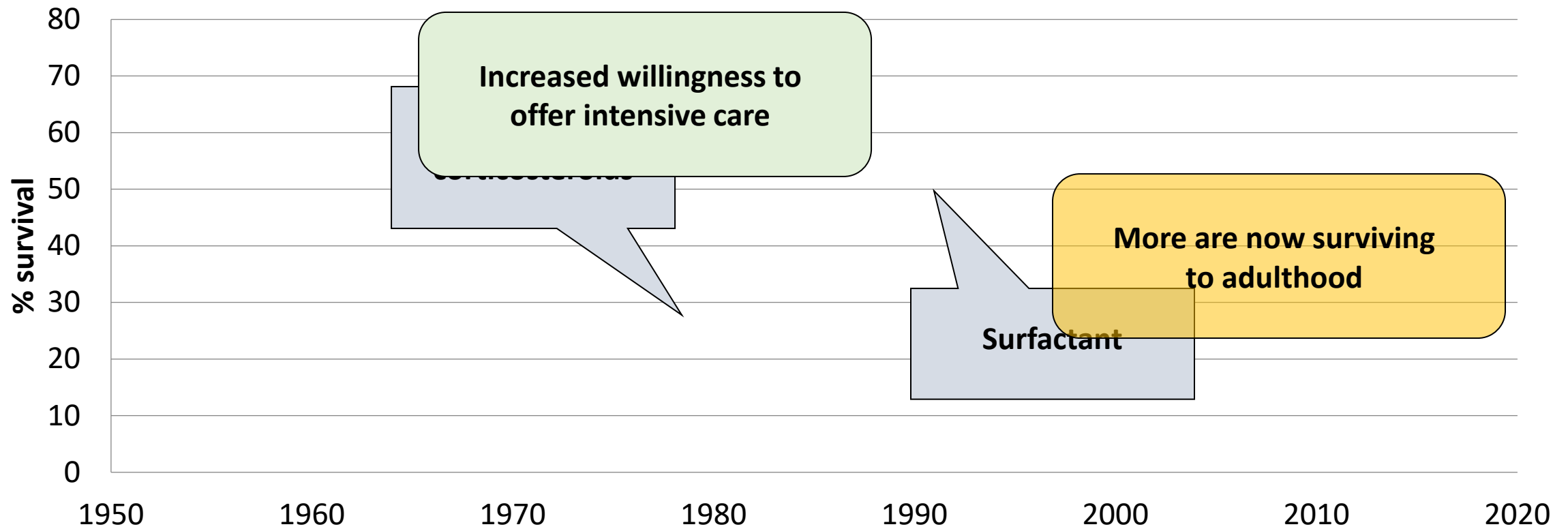
Each evening, parents tear themselves away from this strange, surreal place, leaving these tiny, fragile beings behind in their plastic incubators.



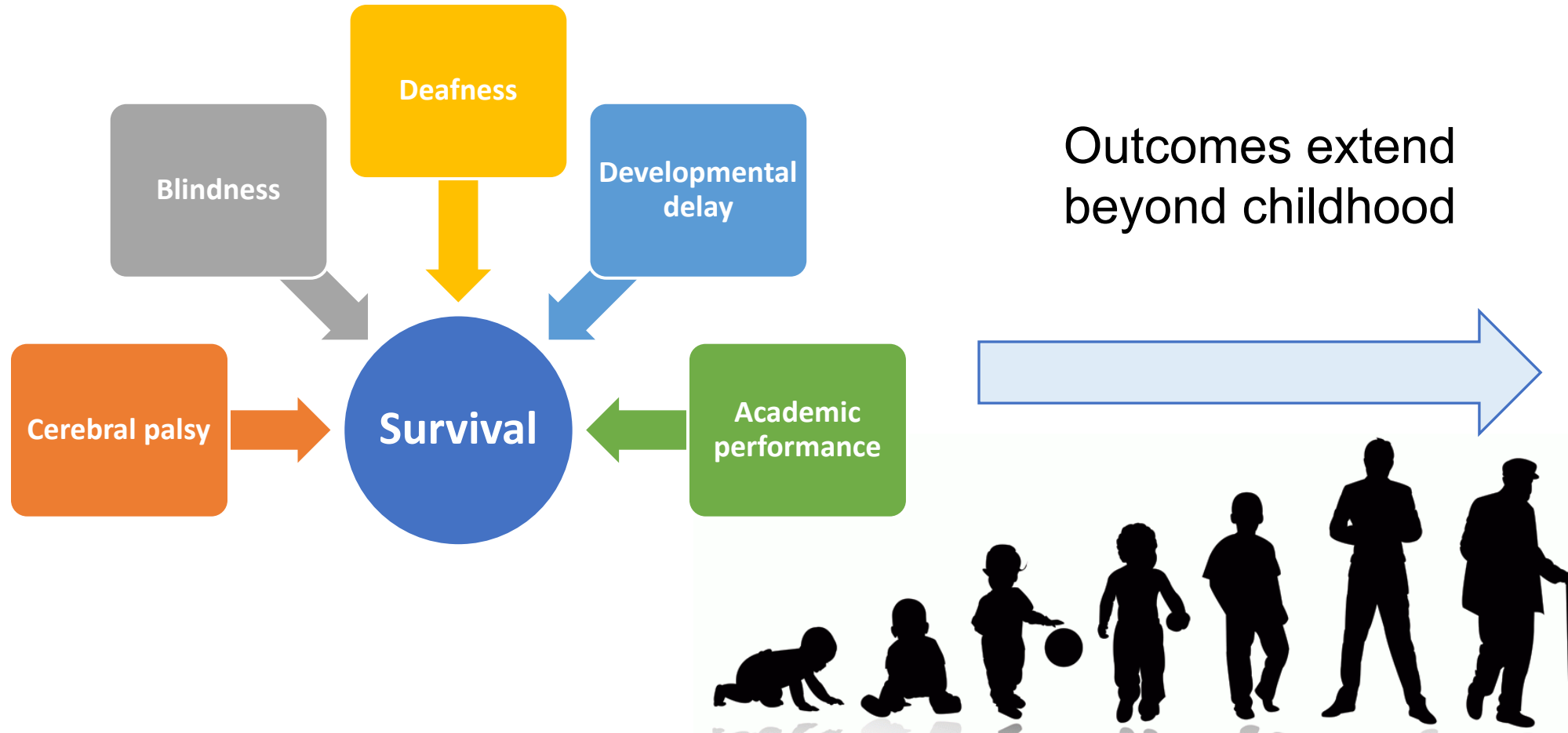
(left to right) Louise Pallot with her mother Therese Scalzo. Louise was a prem baby born at 26 weeks. JOE ARMAO

# Why are adult outcomes important?

## Survival of Extreme Preterms in Victoria



# Outcomes following preterm birth



# Outcomes in adulthood

Neurodevelopment  
and disability

**Cardiometabolic health – growth, BP,  
glucose tolerance, lipids**

**Lung health**

**Mental health**

**Quality of life**

**Transition to adult life**

# Why interest in cardiometabolic health?

## Barker Hypothesis:

“.....that intrauterine growth retardation, low birth weight, and premature birth have a causal relationship to the origins of hypertension, coronary heart disease, and non-insulin-dependent diabetes, in middle age.”

*Fetal and Infant Origins of Adult Disease (1992)*

# (I) Cardiometabolic health: growth & body composition



- Extremely preterm born shorter and lighter than term-born
- With increasing age:
  - Remain shorter
  - “Catch up” weight & BMI
- Lower lean body mass
- Increased central adiposity



*Weiler 02, Saigal 06, Hovi 07, Bracewell 08, Euser 08, Evensen 09, Darlow 13, Roberts 13*



# VICS program of research

- Prospective longitudinal studies
- All infants <28 weeks or <1000g birthweight in the state of Victoria, & controls
- Six cohorts and follow-up:

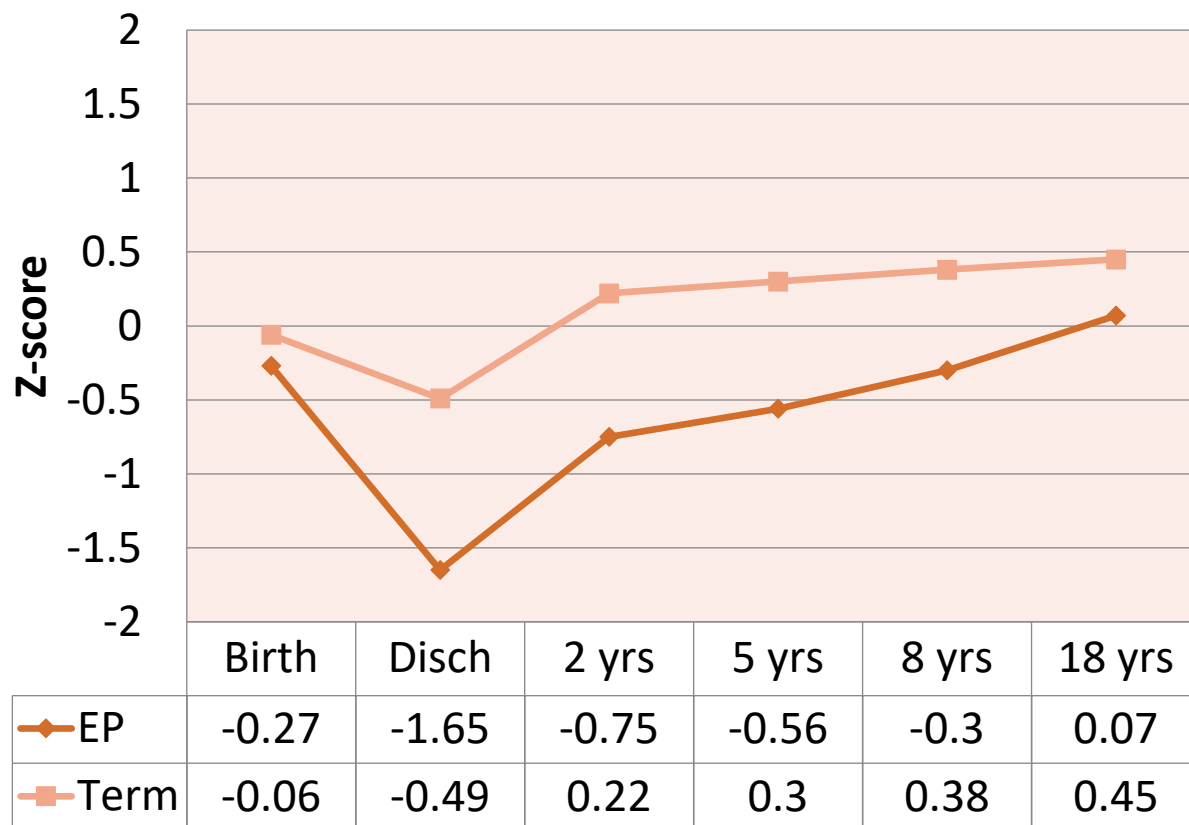


Year of birth	2 years	5 years	8 years	14 years	18 years	25 years
1979-80	*	*	*	*		
1985-87	*	*	*			
1991-92	*	*	*		*	*
1997	*		*			
2005	*		*			
2016-17	*					



## (1) Growth: weight

### Weight z-scores: EP vs term controls

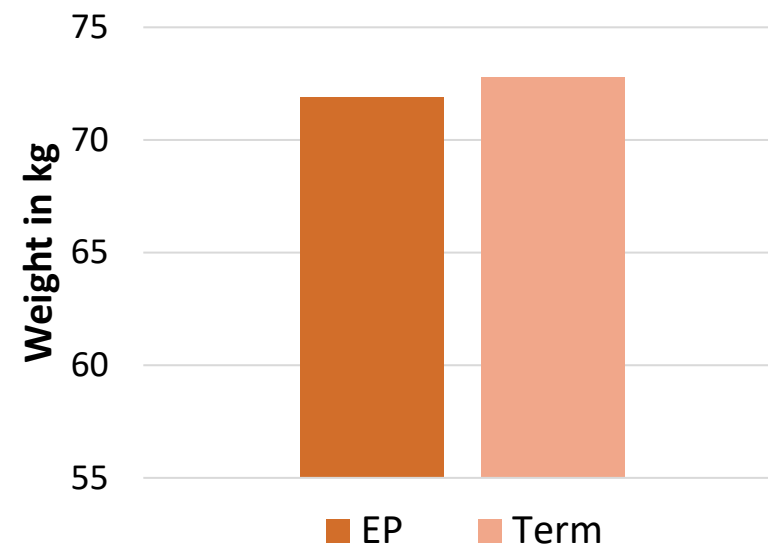


### Growth of Extremely Preterm Survivors From Birth to 18 Years of Age Compared With Term Controls

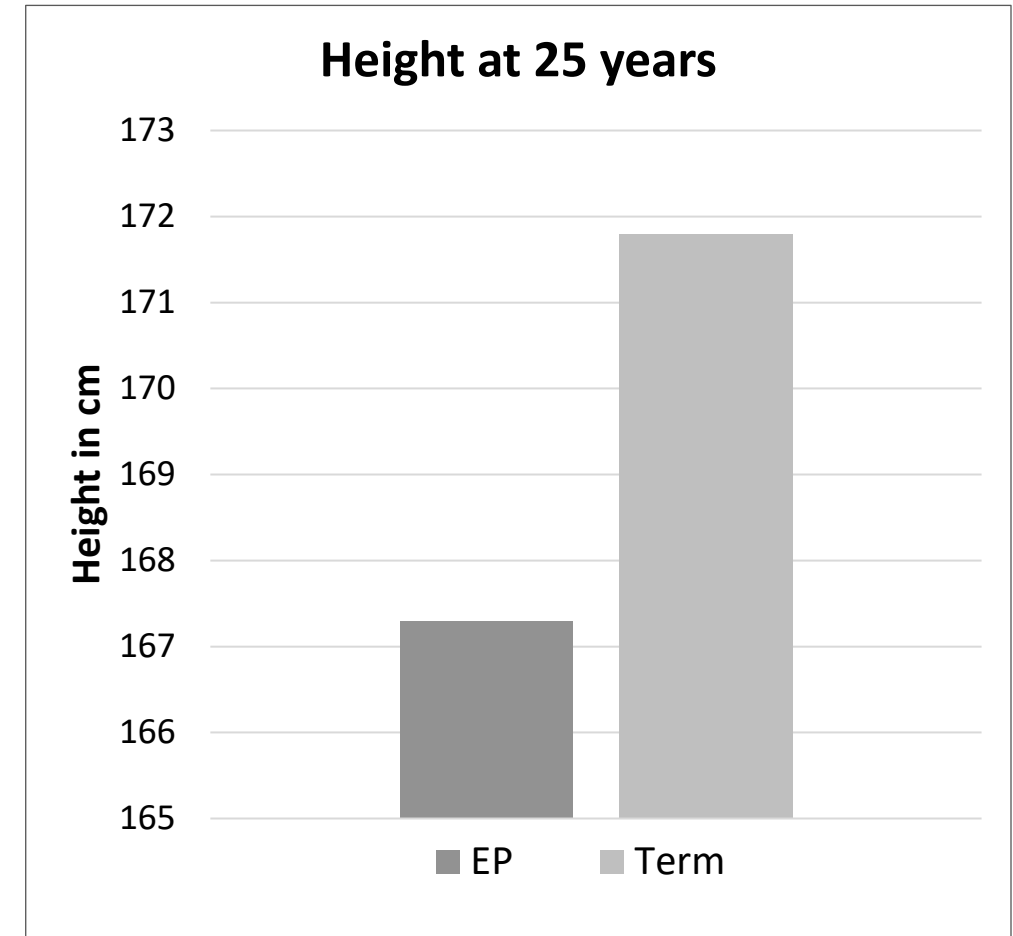
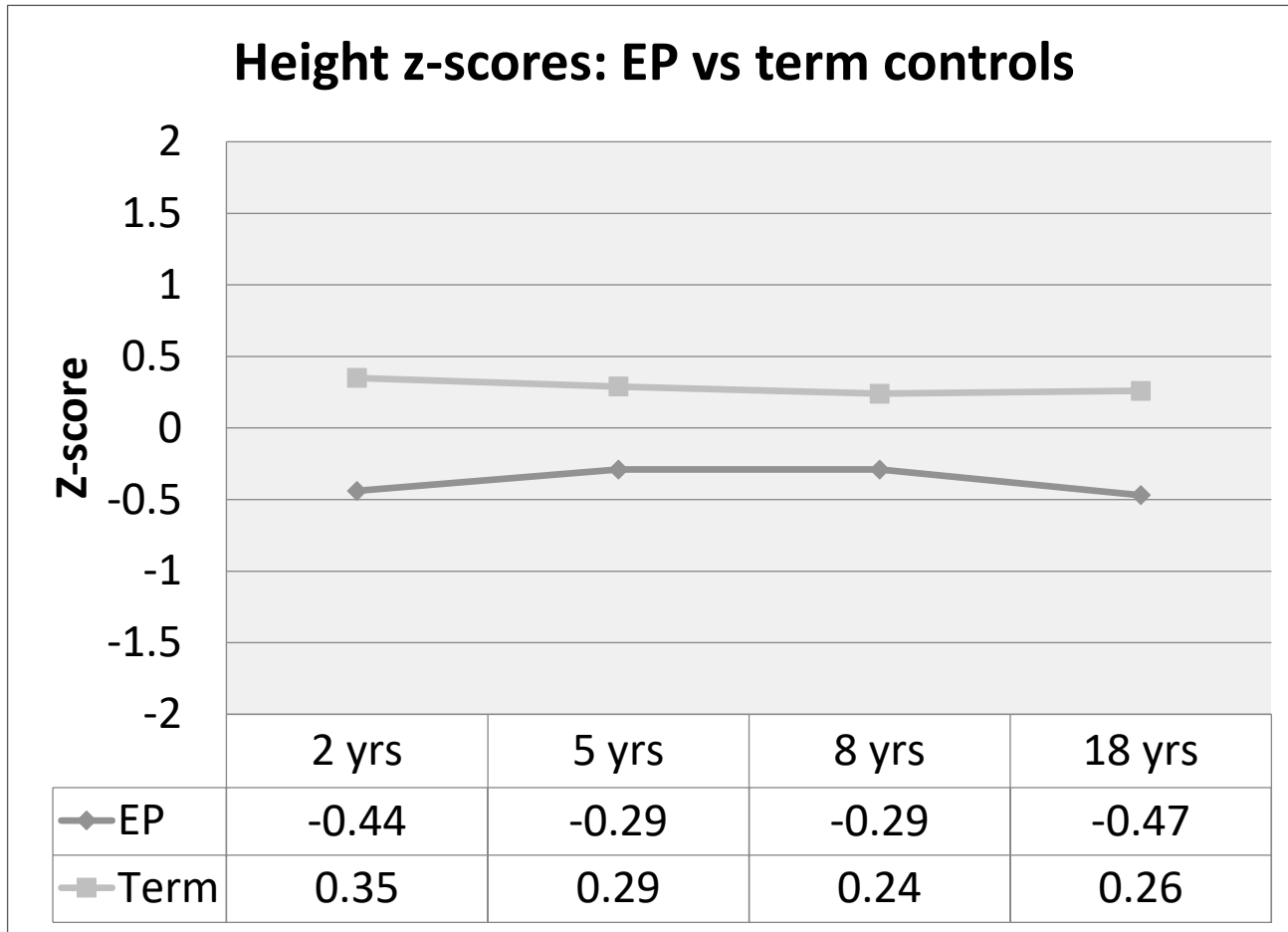
Gehan Roberts, Jeanie Cheong, Gillian Opie, Elizabeth Carse, Noni Davis, Julianne Duff, Katherine J. Lee, Lex Doyle and on behalf of the Victorian Infant Collaborative Study Group

*Pediatrics* 2013;131:e439; originally published online January 6, 2013; DOI: 10.1542/peds.2012-1135

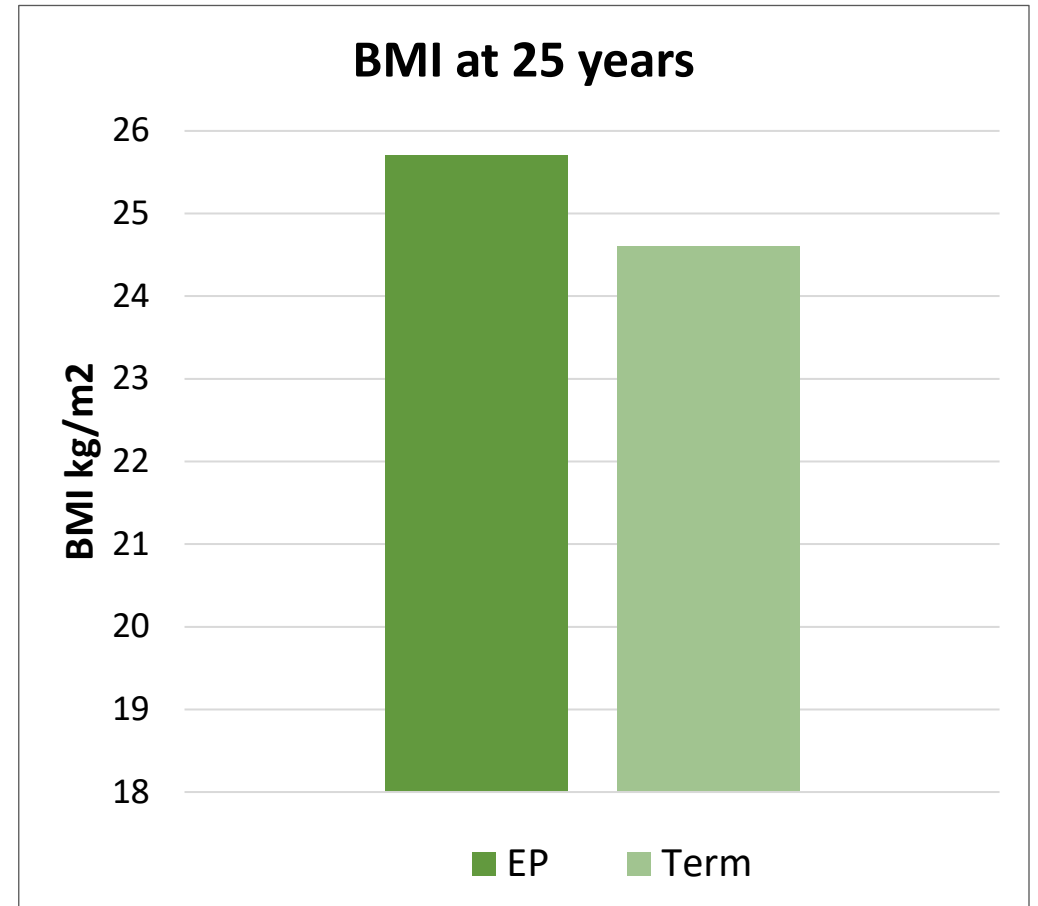
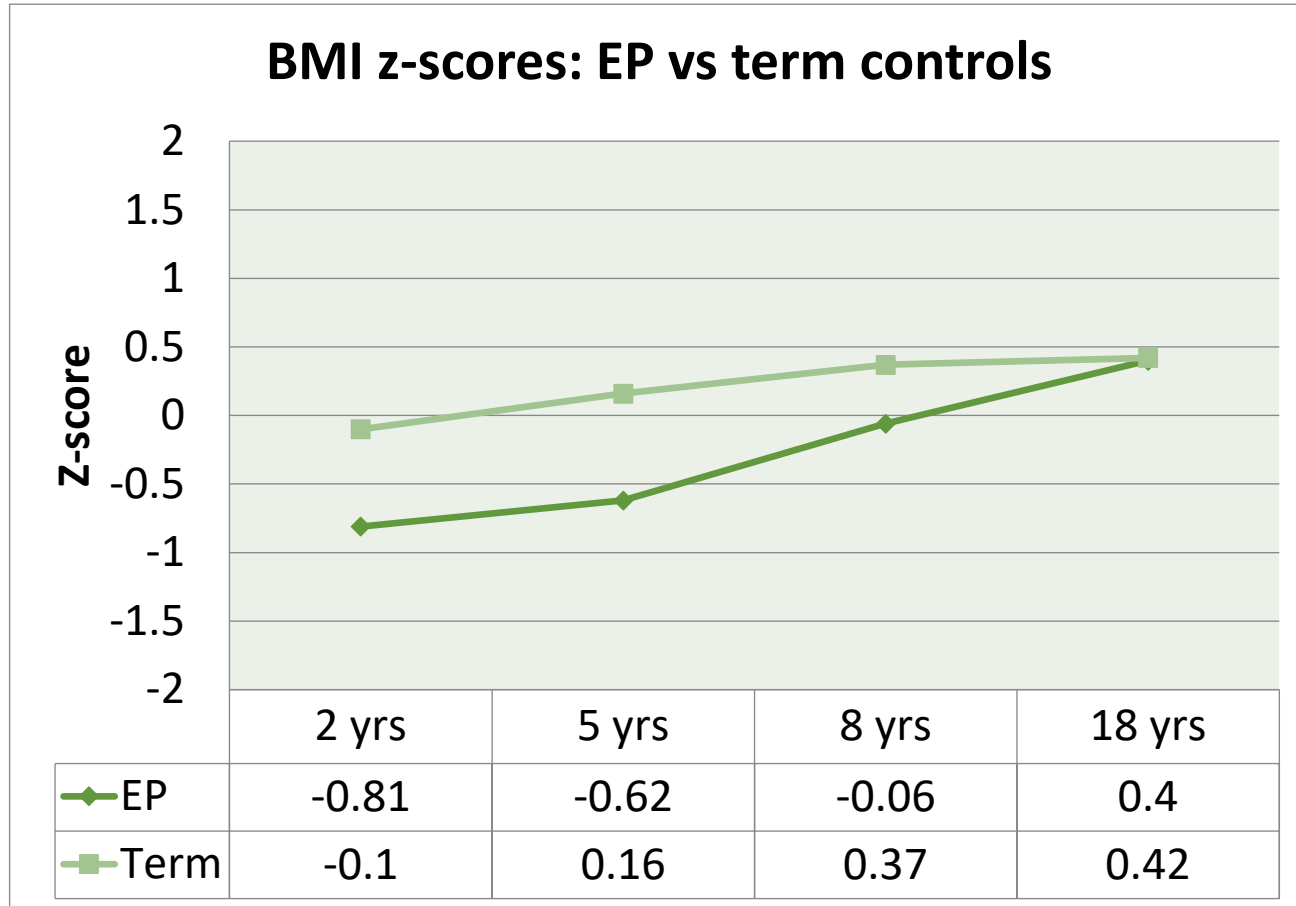
### Weight at 25 years



# (1) Growth: height



# (1) Growth: BMI





# (I) Cardiometabolic health: blood pressure



## Cardiovascular disease:

- main cause (30%) of mortality in developed world
- High BP is important risk factor

## Morbidity: for every 2mm Hg ↑ in diastolic BP

- 17% ↑ in prevalence of hypertension
- 6% ↑ in coronary artery disease
- 15% ↑ in stroke or transient ischaemic attacks

*Arch Intern Med 95;155:701-9*



## Extreme prematurity

- Higher BP in multiple studies

## Epidemiology/Population

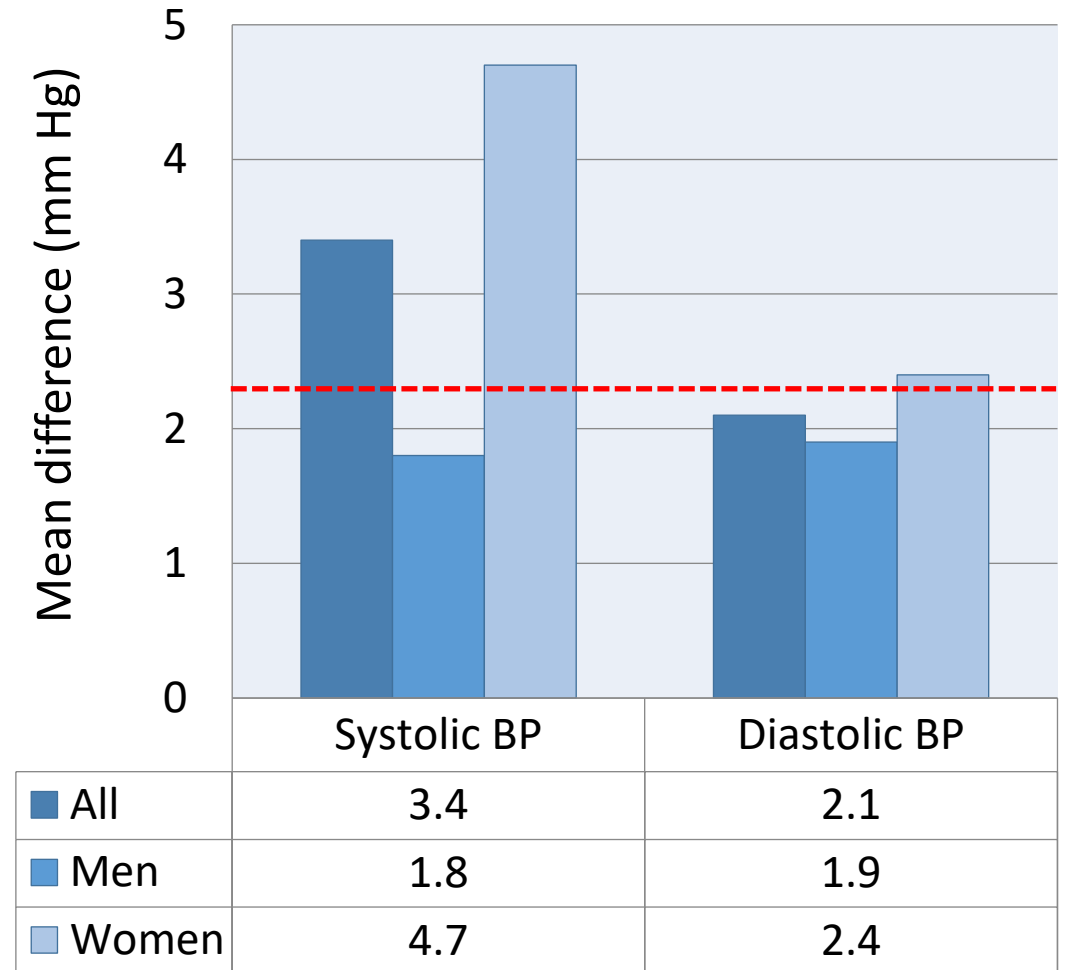
### Blood Pressure in Young Adults Born at Very Low Birth Weight

#### Adults Born Preterm International Collaboration

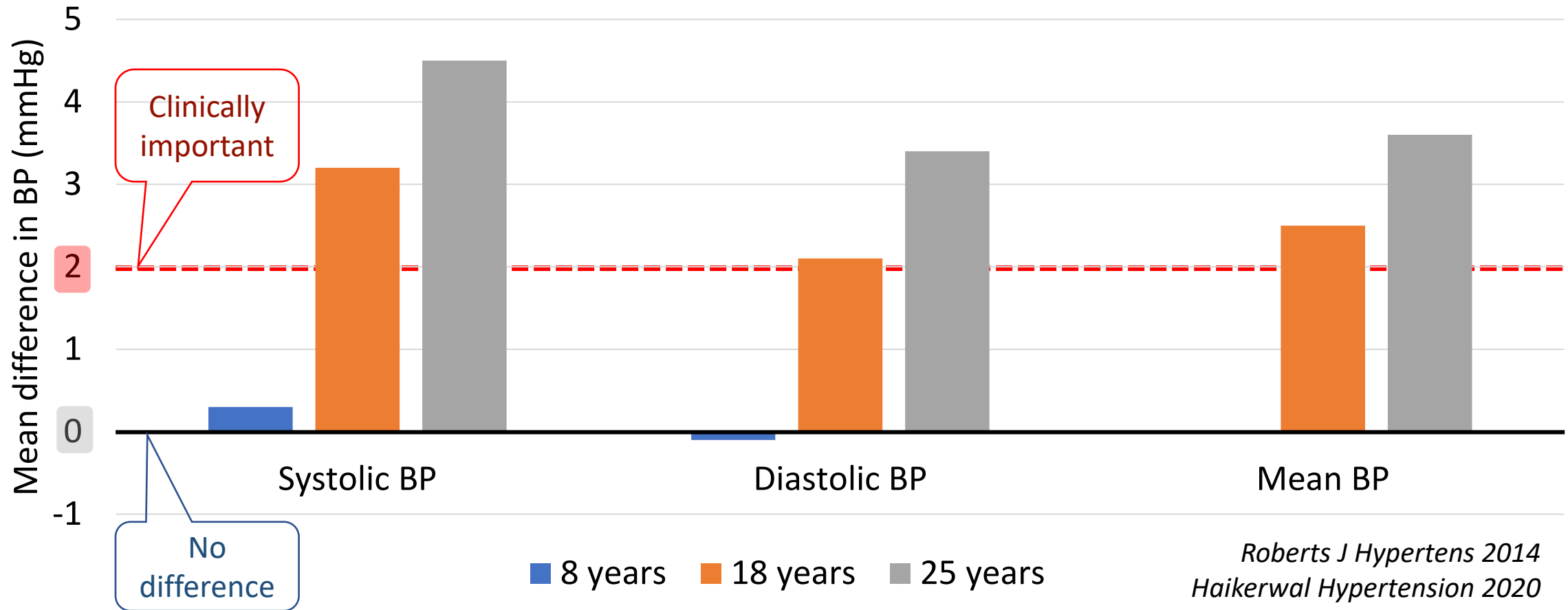
Petteri Hovi, Betty Vohr, Laura R. Ment, Lex W. Doyle, Lorcan McGarvey, Katherine M. Morrison, Kari Anne I. Evensen, Sylvia van der Pal, Ruth E. Grunau, APIC Adults Born Preterm International Collaboration,\* Ann-Mari Brubakk, Sture Andersson, Saroj Saigal, Eero Kajantie

- Individual participant data meta-analysis
- 9 cohorts
- VLBW (n=1571) & controls (n=777)
- Mean gestational age 29.3 weeks
- Age range 16-24 years

## Higher blood pressure in preterms



# Increasing Blood Pressure differences from 8 to 25 years



*Roberts J Hypertens 2014  
Haikerwal Hypertension 2020*

# (I) Cardiometabolic health: glucose tolerance, lipid profiles

- Abnormal glucose tolerance
- Similar fasting glucose & insulin
- Conflicting data on lipid profiles

*Hovi 2007, Parkinson 2013, Flahault 2020, Cheong 2020*

## SUMMARY

- Weight and BMI catch up with age
- Higher BP, and ?increasing difference with age
- Abnormal glucose tolerance
- No definite differences in lipid profiles
- ? At risk of cardiovascular complications at an earlier age



## (II) Lung health

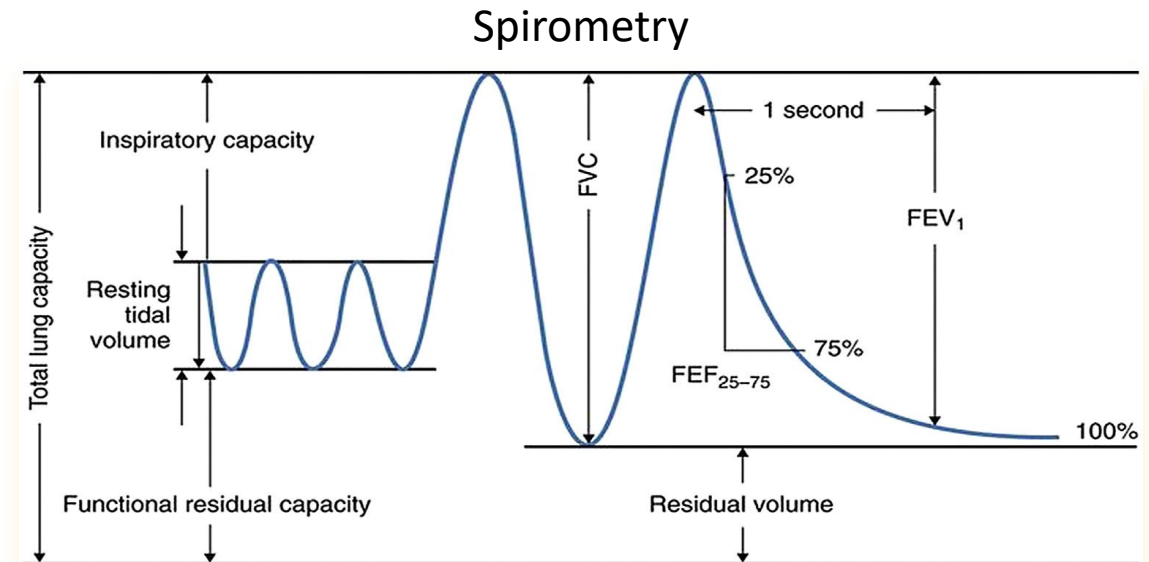
### Preterm at risk of later lung compromise

- Exposure to higher FiO<sub>2</sub> than in utero
- Ventilation
- Infection/inflammation
- “Bronchopulmonary dysplasia”

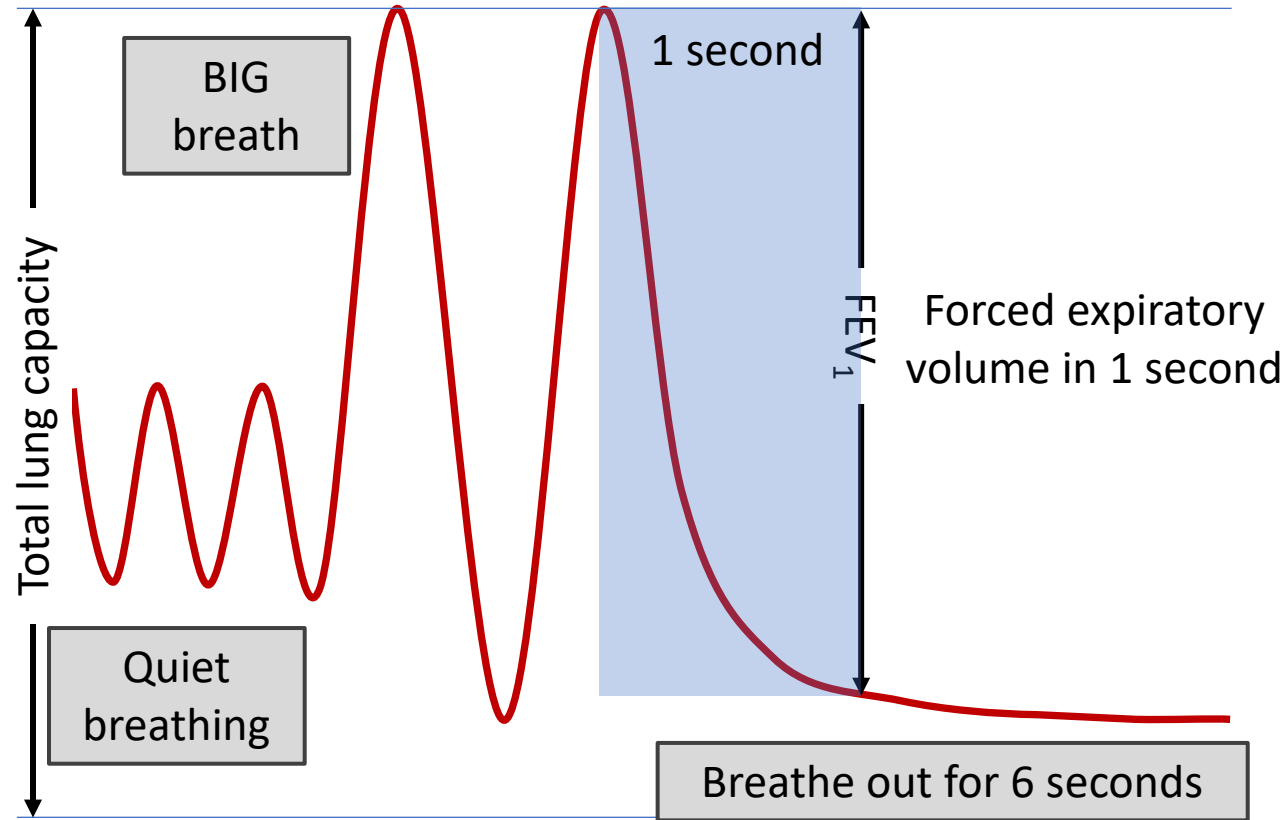


### Obstructive pattern

- ↓ FEV<sub>1</sub>
- ↓ FEV<sub>1</sub>/FVC
- ↓ FEF<sub>25-75</sub>



# Spirometry: Expiratory flows (FEV<sub>1</sub>)



## PATIENT INFORMATION

### Spirometry

#### What is spirometry?

Spirometry tests how much, how fast and how long you can breathe in and out. It involves doing different types of breathing into a tube that is connected to a computer or small machine. This helps determine how well your lungs are working and if there is anything affecting your breathing. The three main measurements are:

- how much air your lungs can hold or lung volume (called 'forced vital capacity')
- how much air you can breathe out in 1 second (called 'forced expiratory volume in 1 second')
- the comparison between these two measurements (called 'forced expiratory ratio').

#### Why has my GP recommend have spirometry?

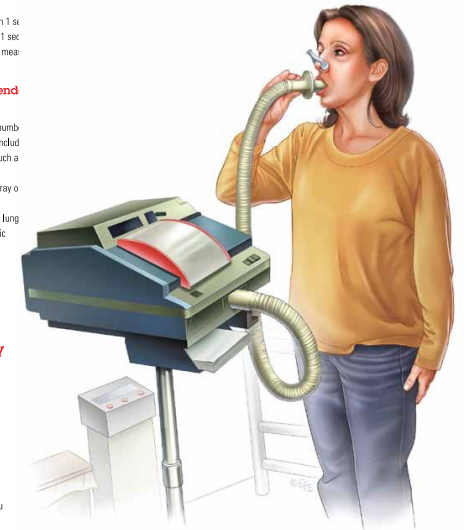
Spirometry is common and useful in a number of different situations. Common reasons include:

- looking for the cause of problems such as shortness of breath or wheeze
- following up a finding on a chest X-ray or lung test
- diagnosing and monitoring common lung diseases such as asthma and chronic obstructive pulmonary disease
- detecting early problems in people who have been exposed to things that may damage the lungs such as cigarette smoke, certain dusts and some medications.

#### What does spirometry involve?

Spirometry may be performed at a general practice clinic or at a hospital or laboratory. It does not hurt, but some people get quite puffed or occasionally dizzy. The test, including an explanation of the test by the operator, usually takes 10–20 minutes. To help guess the size of your lungs you will be weighed and measured. You will then stand or sit up straight for the test. You may be asked to wear a peg on your nose to make sure all the air comes

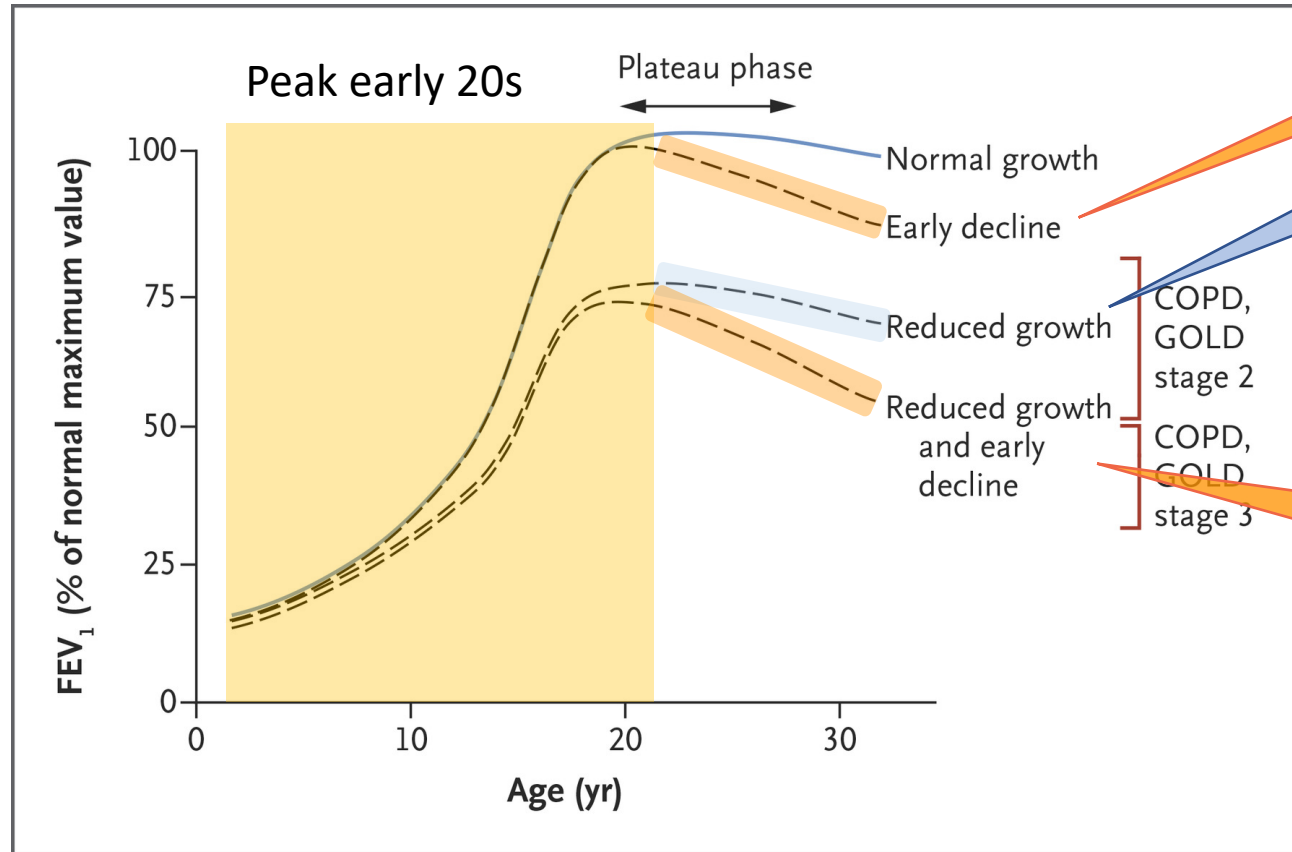
out your mouth. You will take a really big breath in and then wrap your lips tightly around a special mouthpiece. You then breathe out as forcefully and fully as you can. With the mouthpiece still in your mouth you finally take another big breath in before having a rest and breathing normally. You will need to repeat this cycle at least three times to make sure the measurements are accurate and consistent. The person running the test will explain



Reprinted from: AUSTRALIAN FAMILY PHYSICIAN VOL. 45, NO. 4, APRIL 2011 221

Lee Australian Family Physician 2011

## (II) Lung function: normal growth trajectory



Smoking

Preterm

Preterm + smoking

McGeachie NEJM 2016

# Expiratory airflow in late adolescence and early adulthood in individuals born very preterm or with very low birthweight compared with controls born at term or with normal birthweight: a meta-analysis of individual participant data

*Lex W Doyle, Sture Andersson, Andy Bush, Jeanie L Y Cheong, Hege Clemm, Kari Anne I Evensen, Aisling Gough, Thomas Halvorsen, Petteri Hovi, Eero Kajantie, Katherine J Lee, Lorcan McGarvey, Indra Narang, Pieta Näsänen-Gilmore, Sigurd Steinshamn, Maria Vollsaeter, Elianne J L E Vrijlandt, for the Adults born Preterm International Collaboration*

- 11 studies
- VP/VLBW (n=935) & controls (n=722)
- Reduced expiratory airflow

*Lancet Respir Med 2019;  
7: 677-86*

## Participants with values <5<sup>th</sup> percentile

	VP/VLBW	Controls	Odds Ratio
FEV <sub>1</sub>	24%	7%	4.16
FVC	11%	6%	2.12
FEF <sub>25-75</sub>	29%	8%	4.50

## SUMMARY

- Worse expiratory airflows, not reaching peak lung function
- ? Destined to have COPD at an earlier age



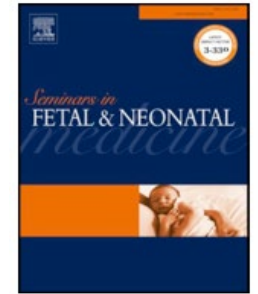
# (III) Mental health

## Mental health outcomes of adults born very preterm or with very low birth weight: A systematic review



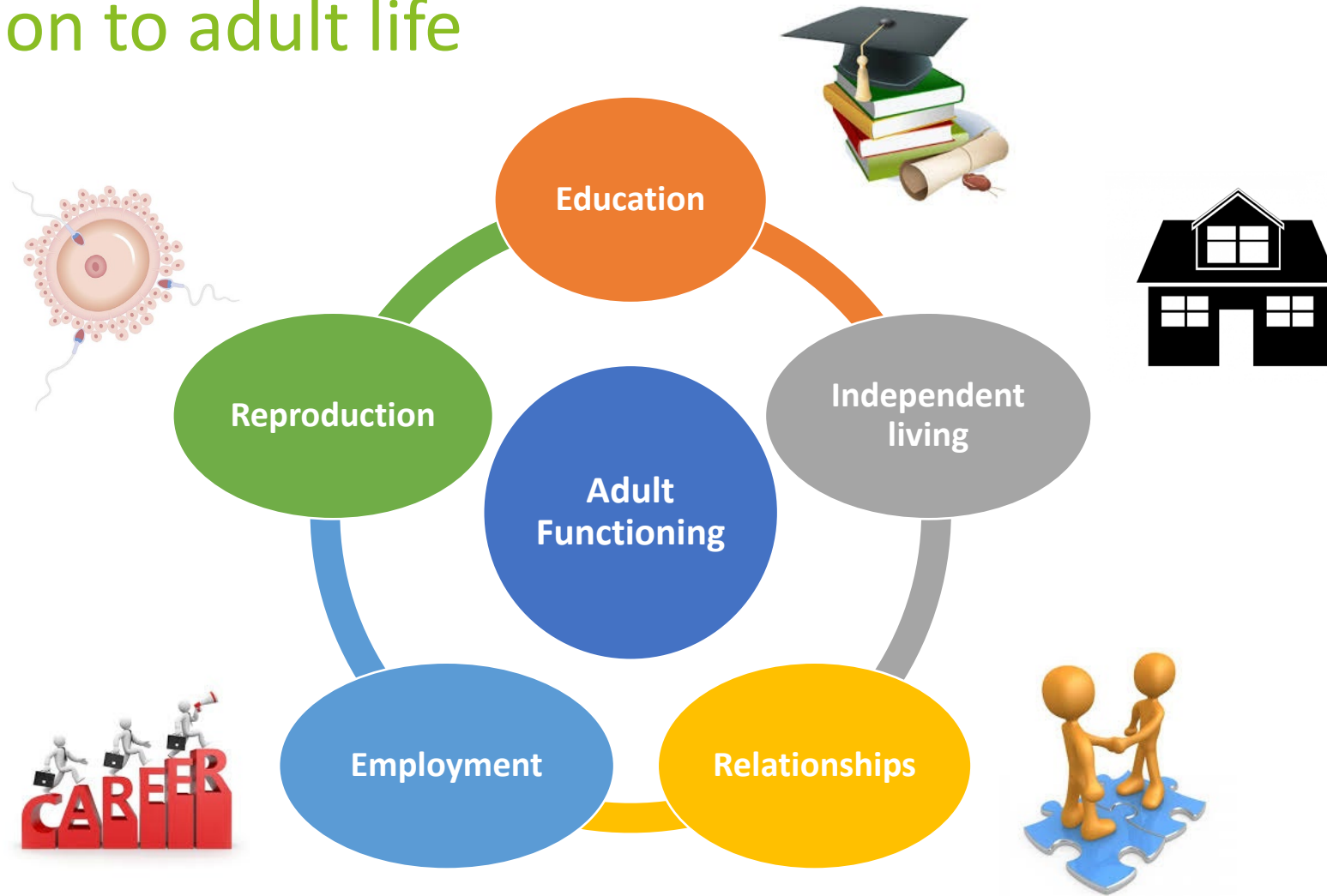
Rachel Robinson<sup>a,\*</sup>, Marius Lahti-Pulkkinen<sup>a,b,c</sup>, Daniel Schnitzlein<sup>d,e,f</sup>, Falk Voit<sup>d</sup>, Polina Girchenko<sup>a</sup>, Dieter Wolke<sup>g,h,d</sup>, Sakari Lemola<sup>h,i</sup>, Eero Kajantie<sup>b,j,k,l</sup>, Kati Heinonen<sup>a</sup>, Katri Räikkönen<sup>a</sup>

Seminars in Fetal and Neonatal Medicine 25 (2020) 101113



- 13 studies (UK, USA, Germany, Canada, Australia, Scandinavia)
- 29-35 years; VP/VLBW & controls
- Results are mixed: any mental health diagnosis, individual diagnoses (mood disorders, depression, bipolar, anxiety, internalizing problems)
- Increased psychotropic medication (OR 1.3-4.0)

# (IV) Transition to adult life



# Education & employment

## School completion

- Mixed reports: some disadvantage, others report similar rates
- Female advantage
- Related to socio-economic class

## Employment

- Higher unemployment, lower net income, more on social benefits
- Partly explained by disability



*Moster 08, Lindstrom 07, Saigal 06, Lefebvre 05, Hack 02*

# Independent living & relationships

## Living with parents

- Mixed reports
- More likely for EP adults in 20s (1.7 fold)
- Other cohorts report similar rates (55% vs 47%)



## Marriage / cohabitation

- Lower proportion in EP adults between 23-29 yrs (RR 0.7)



*Moster 08, Lindstrom 07, Kajantie 08*



# Reproduction

## Biological parenthood

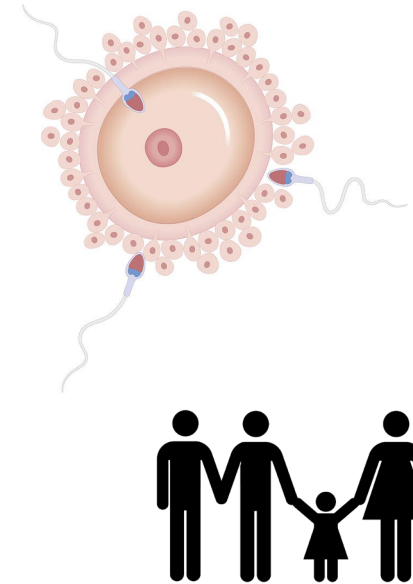
- Lower in EP (29%) vs controls (43%)

## Risk of preterm offspring

- Seen in preterm women only
- Higher in EP women (14%) vs controls (6.4%)

## Why is this so?

- Biological, physiological, psychosocial, nutritional, economic



*Swamy 08, deKeyser 12*

# Risk-taking behaviour

## Lower rates in EP compared with controls

- Drugs and alcohol
- Smoking – cigarettes or marijuana
- Delinquent behaviours
- Incarceration or contact with police

## Why is this so?

- ↑ parental monitoring, shy personality, ↓ social opportunities



*Lindstrom 07, Hack 02, Hille 08, Cooke 04*

## (V) Quality of life

### “Health related quality of life” (HRQoL)



- Allows individual to weigh aspects of their health & provide personal evaluation
- Various questionnaires e.g. HUI3, SF-36
- Complements “biomedical model” of reporting functional limitations
- Self report vs proxy report

# Health Related Quality of Life: adults born preterm

Study	Age studied Measure	Results
Husby 2016 Norway	20-23 yrs SF-36	VLBW < controls
Baumann 2016 Bavaria	26 yrs HUI3	Very preterm < full term (parents & self) Change from adolescence to adulthood: similar (self), worse (parents)
Darlow 2013 New Zealand	22 yrs SF-36 Rosenberg self esteem	VLBW = controls
Saigal 2006 Canada	12-16 yrs HUI3 (direct)	ELBW = controls No difference within ELBW despite disability
Saigal 2016 Canada	12-16 yrs, 22-26 yrs, 29-36 yrs HUI3 (indirect)	ELBW < controls No differential decline with age

# Health Related Quality of Life: perspectives are important

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## SUMMARY

- In general, Health Related Quality of Life is rated well
- No differential decline with age
- “Disability paradox” – discordance between functional limitations and high valuation
- Perspectives are critical
  - Patient – clinical decision-making
  - Population – allocation of resources



# Young adult outcomes following preterm birth

## Increased “physical health” challenges

- Blood pressure & Cardiovascular health
- Lung function

## Function and quality of life

- Doing “pretty well”
- ? Increased risk of mental health

## Awareness of health risks

- Education of primary and adult physicians
- Adoption of healthy lifestyle choices

**LONG TERM  
SURVEILLANCE  
IS KEY**

# Victorian Infant Collaborative Study Group

Jeanie Cheong

Peter Anderson

Silvia Arvanitakis

Merilyn Bear

Rosemarie Boland

Alice Burnett

Elizabeth Carse

Margaret Charlton

Marissa Clarke

Janet Courtot

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Lex Doyle

Julianne Duff

Rachel Ellis

Anjali Haikerwal

Marie Hayes

Leah Hickey

Elisha Josev

Elaine Kelly

Marion McDonald

Bronwyn Novella

Gillian Opie

Gehan Roberts

Alicia Spittle

Penelope Stevens

Anne-Marie Turner

## Participating centres:

Royal Women's Hospital

Mercy Hospital for Women

Monash Medical Centre

Royal Children's Hospital

Paediatric Infant Perinatal Emergency Retrieval

Victorian Perinatal Data Collection Unit

Murdoch Children's Research Institute

University of Melbourne

**Funding:** National Health & Medical Research Council of Australia

