



# Health of ART Offspring:

What is known about the health of children and young adults born after IVF or ICSI?



# VARTA

Victorian Assisted Reproductive  
Treatment Authority



## Anna MacLeod

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VARTA is an independent statutory  
authority funded by the Victorian  
Department of Health



[www.varta.org.au](http://www.varta.org.au)

# What is known about the health of children and young adults born after IVF or ICSI?

*Four decades in the making - the latest evidence*

**Prof Robert McLachlan AM, FRACP, PhD**

Director, Healthy Male [Andrology Australia]

Hudson Institute of Medical Research, Monash University

Consultant Andrologist, Monash IVF Group

# **What we want to understand about our infertility**

**Can we have a child naturally?**

**Can we have a child with ART?**

**What type of ART and its particular success rates and risks?**

**Will our child be healthy?**

**Will they have fertility problems?**

**What can we do to help ourselves... lifestyle, age and others?**

# **What we want to understand about our infertility**

**Can we have a child naturally?**

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**What type of ART and its particular success rates and risks?**

**Will our child be healthy?**

**Birth, childhood, adults**

**Will they have fertility problems?**

**Post puberty**

**What can we do to help ourselves... lifestyle, age and others?**

# Health of ART offspring

**Victorian story:** - Murdoch Children's Research Institute, Monash IVF & Melbourne IVF

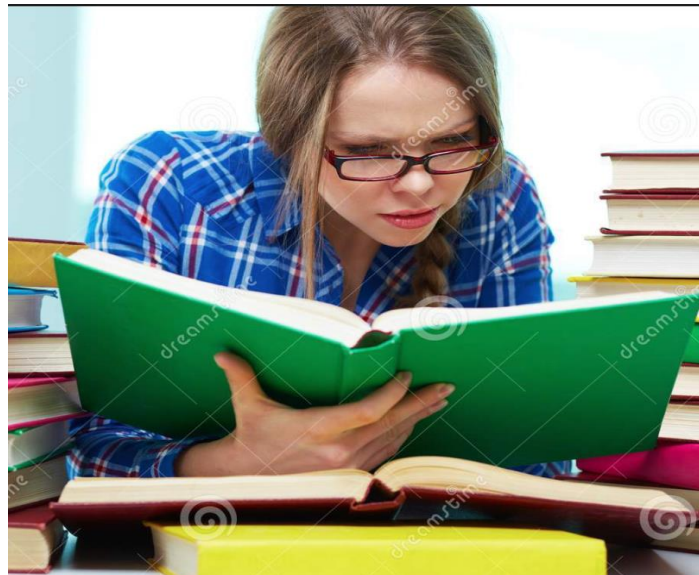
Collaborative effort from leading academic programmes

Ultimate 'post marketing' survey - decades of follow up and complexities

long memories



diligence, sensitivity



great patience

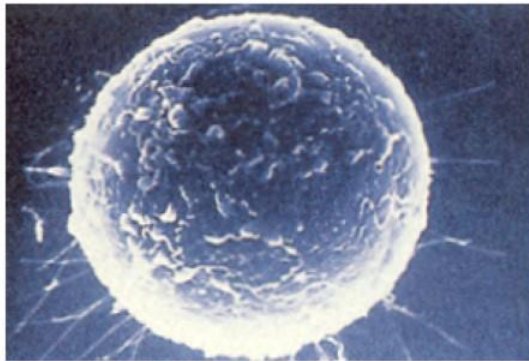




# Insemination

## Standard Insemination

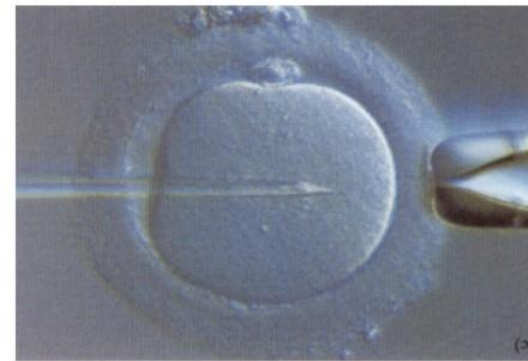
30,000 motile sperm compete



'IVF'

## Intracytoplasmic sperm injection

Single sperm selected based on shape & motility



'ICSI'

ICSI announcement by Belgian Group

Adelaide Glenelg Stamford Hotel December 1992

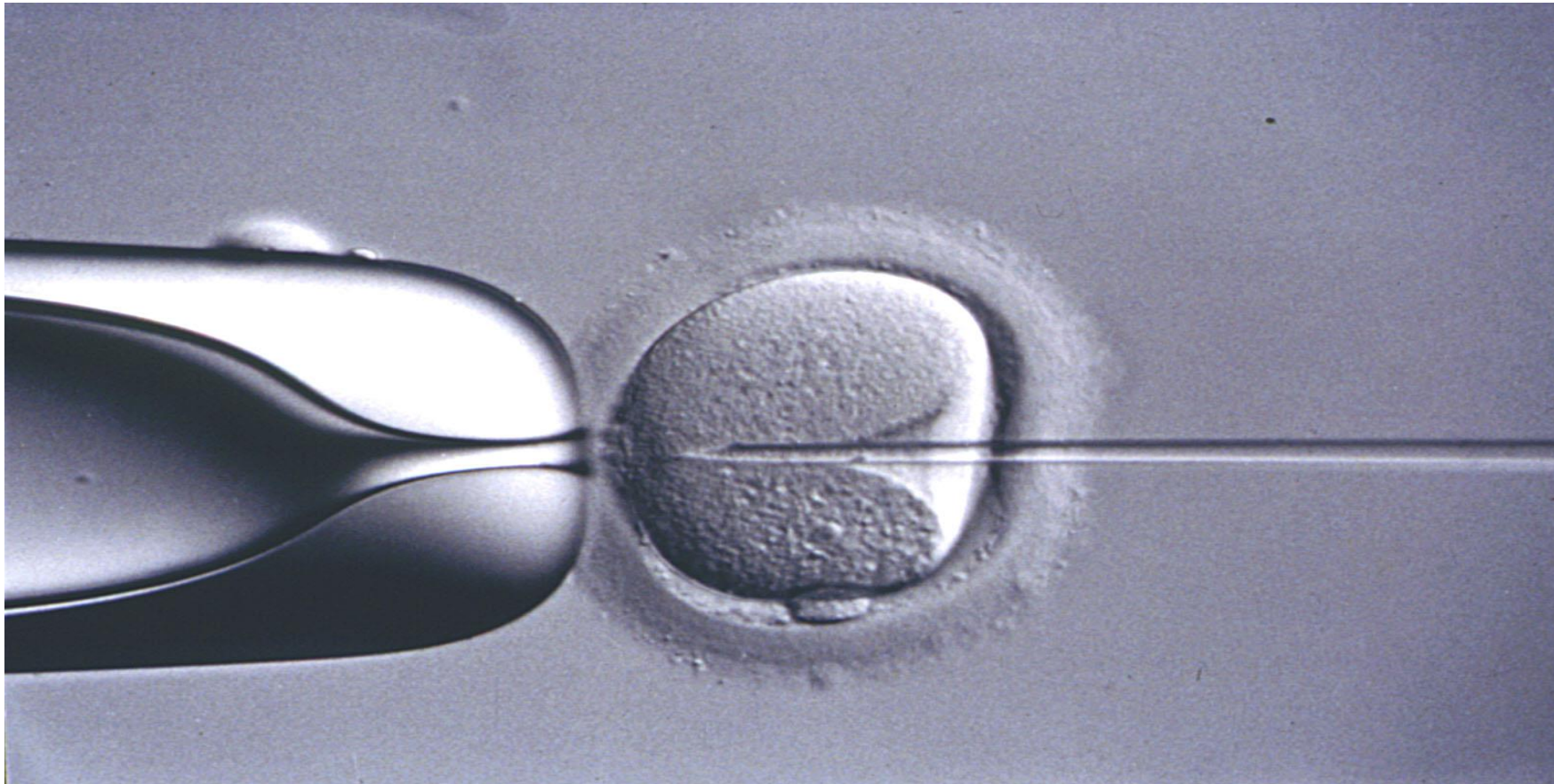




**Intracytoplasmic sperm injection (ICSI)** allows successful pregnancy in previously sterile couples

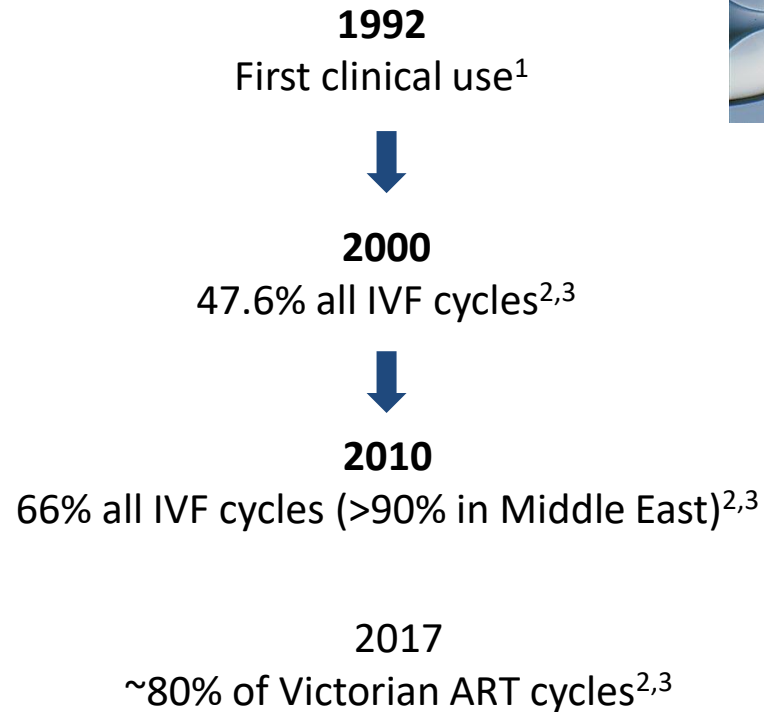
Only one sperm per egg needed ICSI –

Bypass (not treatment) for male infertility



# Increasing use (misuse) of ICSI

- Worldwide



<sup>1</sup>Palermo *et al.* Lancet 1992

<sup>2</sup>Mansour *et al.* Human Reproduction 2014

<sup>3</sup>Dyer *et al.* Human Reproduction 2016

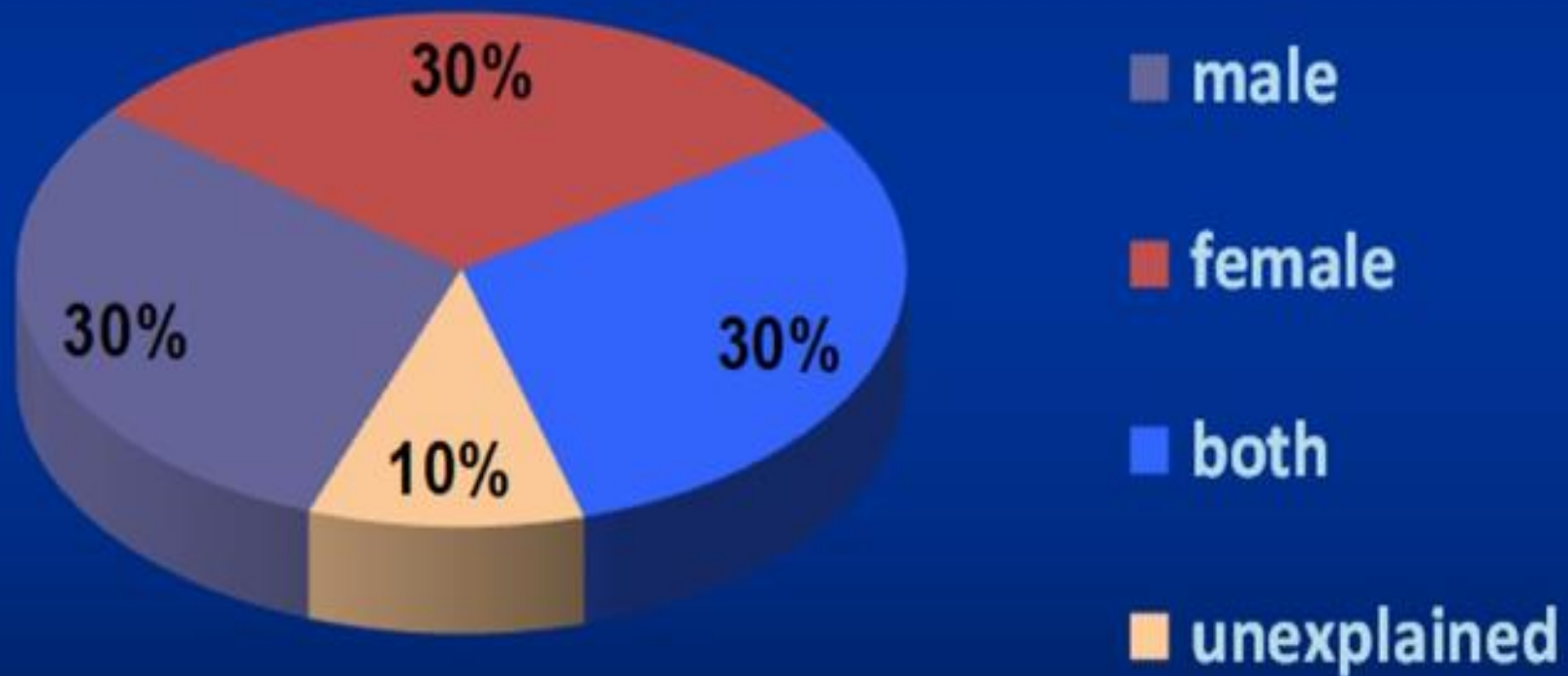
**Decreasing use of ICSI - ANZARD data**  
**62.9% of embryo transfer cycles in 2015 → 58.2% in 2019**

# Trends in ART procedures – the ground always moves – ANZARD 2019

- Major changes in laboratory culture procedures
- Shift from cleavage stage [day 3] to blastocyst transfers
- Increase in embryo cryopreservation and thaw cycles

# Causes of infertility:

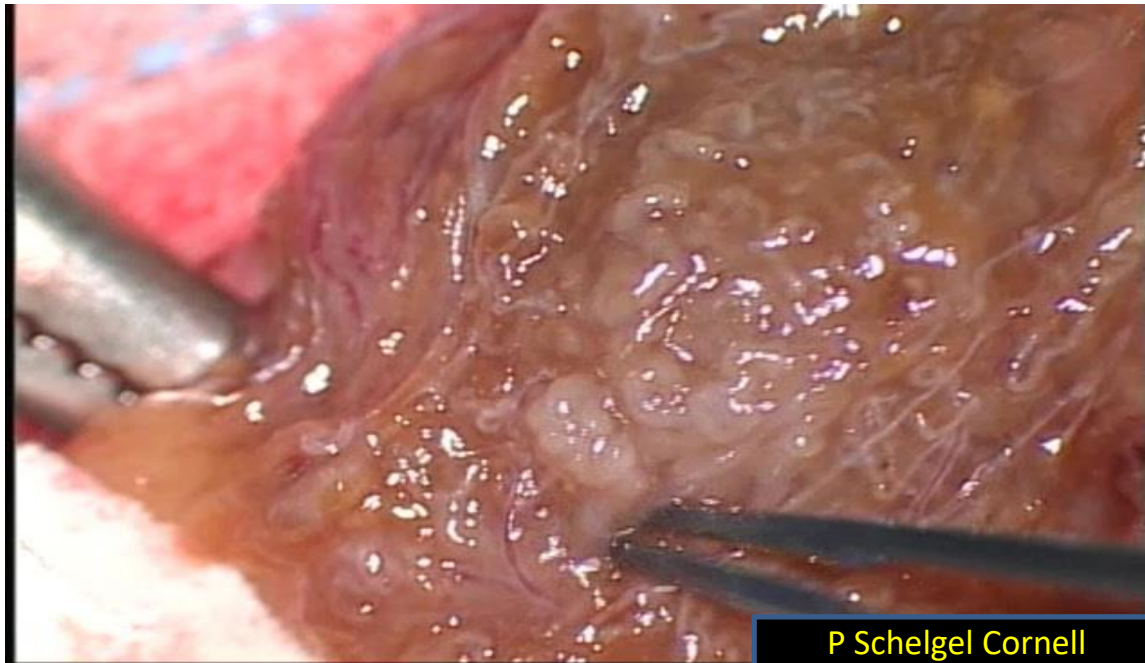
**gender equity!**



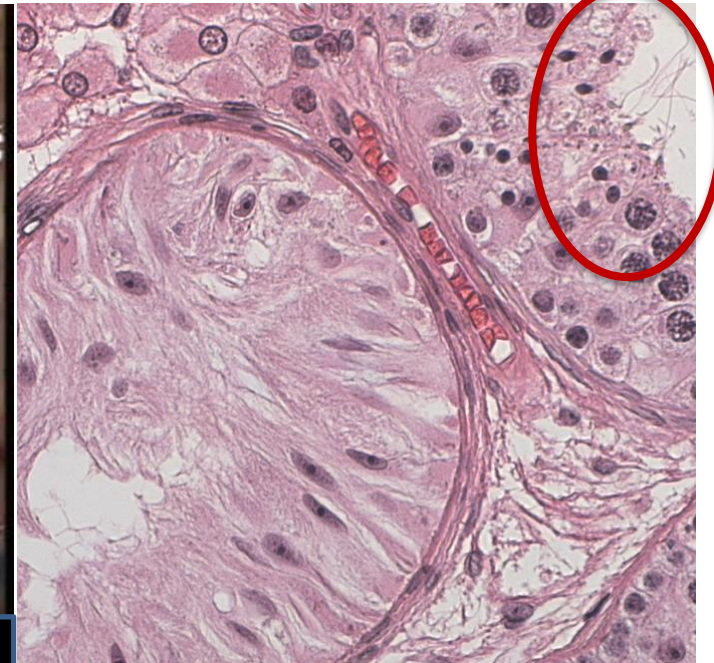


# Microdissection testicular sperm extraction

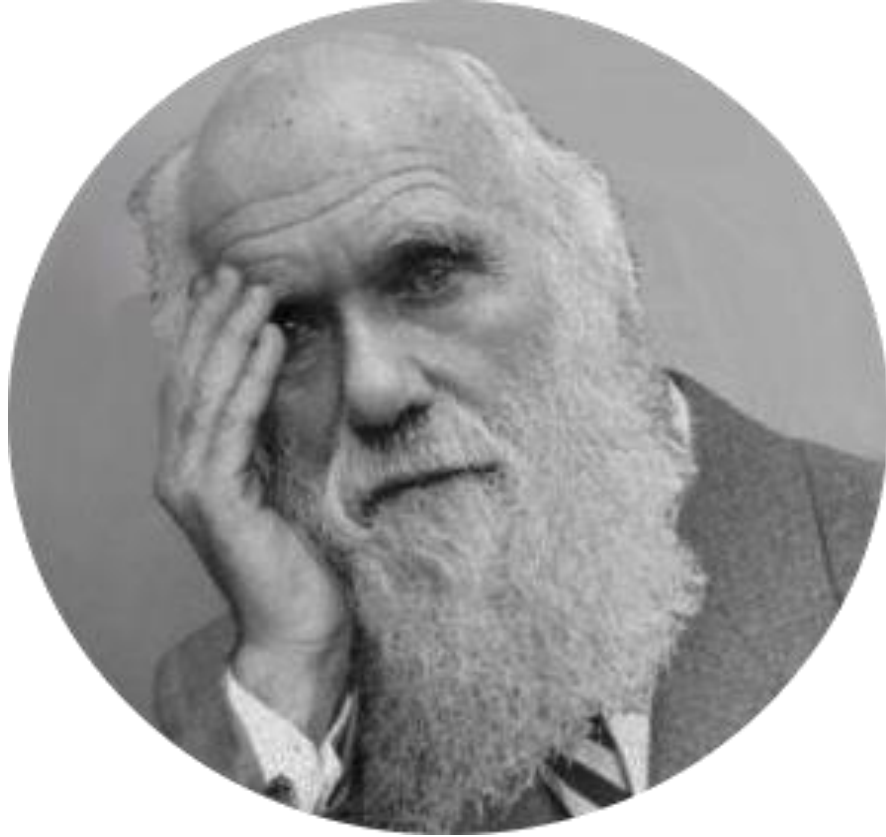
‘MicroTESE’



P Schelgel Cornell







*Oh Dear,  
you did  
WHAT  
exactly?*

*First IVF, now  
this!!*

# **What we want to understand about our infertility**

**Can we have a child naturally?**

**Can we have a child with ART?**

**What type of ART and its particular success rates and risks?**

**Will our child be healthy?                      Birth, childhood, adults**

**Will they have fertility problems?              Post puberty**

**What can we do to help ourselves... lifestyle, age and others?**

**What of the children of ART offspring..**

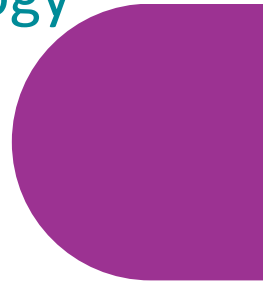
**Ongoing commitment to understand impact of future generations**

# What is known about the health of children and young adults born after IVF or ICSI?

Is ART safe for the offspring?

Prof Jane Halliday

Reproductive Epidemiology



# History - early collaborations with the IVF centres in Victoria on birth outcomes

## 1999 Donor insemination: Are birth outcomes OK? YES

Hoy J, Venn A, Halliday J, Kovacs G, Waalwyk K.

Perinatal and obstetric outcomes of donor insemination

using cryopreserved semen in Victoria, Australia. *Human Reproduction* 7: 1760-1764 (1999)



## 2003 Mixed sex twins: Are IVF twin birth outcomes the same as for non-IVF twins? NO

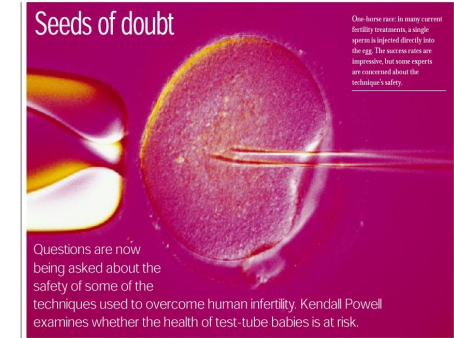
*IVF more pre-term and more obstetric problems*

Smithers P, Halliday J, Hale L, Talbot M, Breheny S, Healy D.

Mixed sex twins: IVF compared with non-IVF. *Fertility and Sterility*, 80(3): 666-668 (2003)

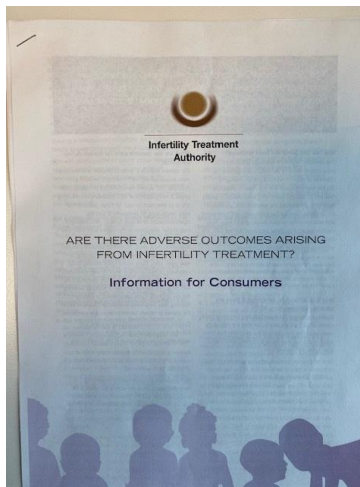


news feature



## 2004 Imprinting syndromes after IVF – are they more frequent? YES, but still very rare (1 in 3700)

## 2005



**Infertility Treatment  
Authority:  
Consumer information**

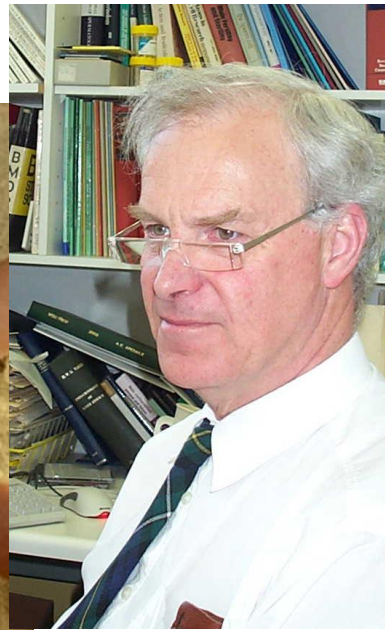
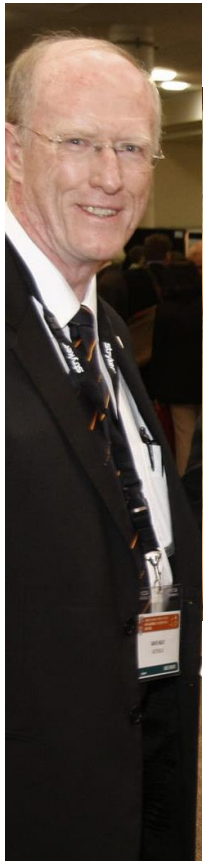


Halliday J, Oke K, Breheny S, Algar E, Amor D.

Beckwith Wiedemann syndrome and IVF:

a case control study. *Am J Hum Genetics*, 75: 526-528 (2004)

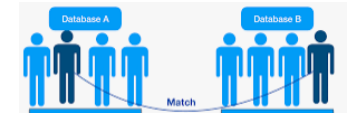
2005 onwards



### Chief Investigators:

- Monash IVF: David Healy
- Melbourne IVF: Gordon Baker
- Melbourne Assisted Conception Centre (MACC)
- Murdoch Childrens Research Institute (MCRI): Jane Halliday
- Perinatal Data Collection Unit, Dept Human Services: James King

- Willingness of IVF clinics to share data
- Ability to do record linkage to birth outcome data



Funded by The BUPA Foundation 2005-2007





## Aims:

To determine **outcomes at birth** for  
≈ **8000** babies (born 1991 –2004),  
after **IVF and ICSI** procedures,  
using

**non-frozen and frozen-thawed embryo  
transfers,**

compared with:

**Gamete  
intrafallopian  
transfer (GIFT)**

*N* ≈ 850

**Sub-fertile  
couples**

*N* ≈ 2100

**A control group**

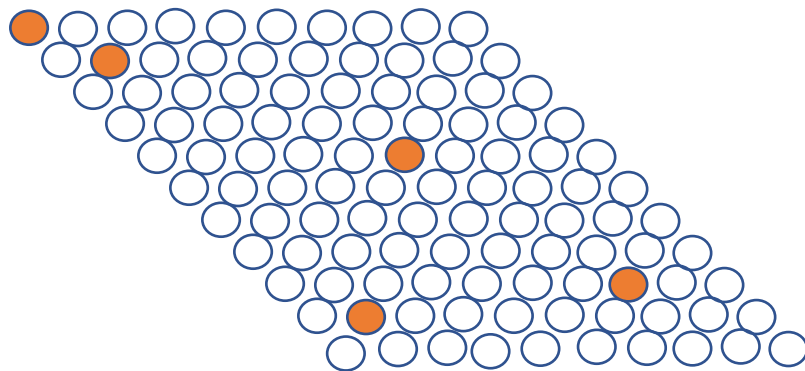
*N* = 24,682



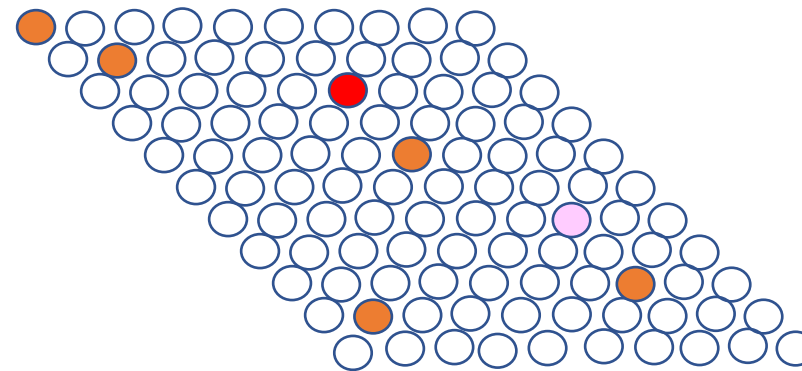
**6 Human Research Ethics Committee approvals needed and received for our record linkage study**

# Congenital anomalies: comparing IVF/ICSI with non-ART controls

- Non-ART (4.8%)



- With IVF or ICSI (6.5%)

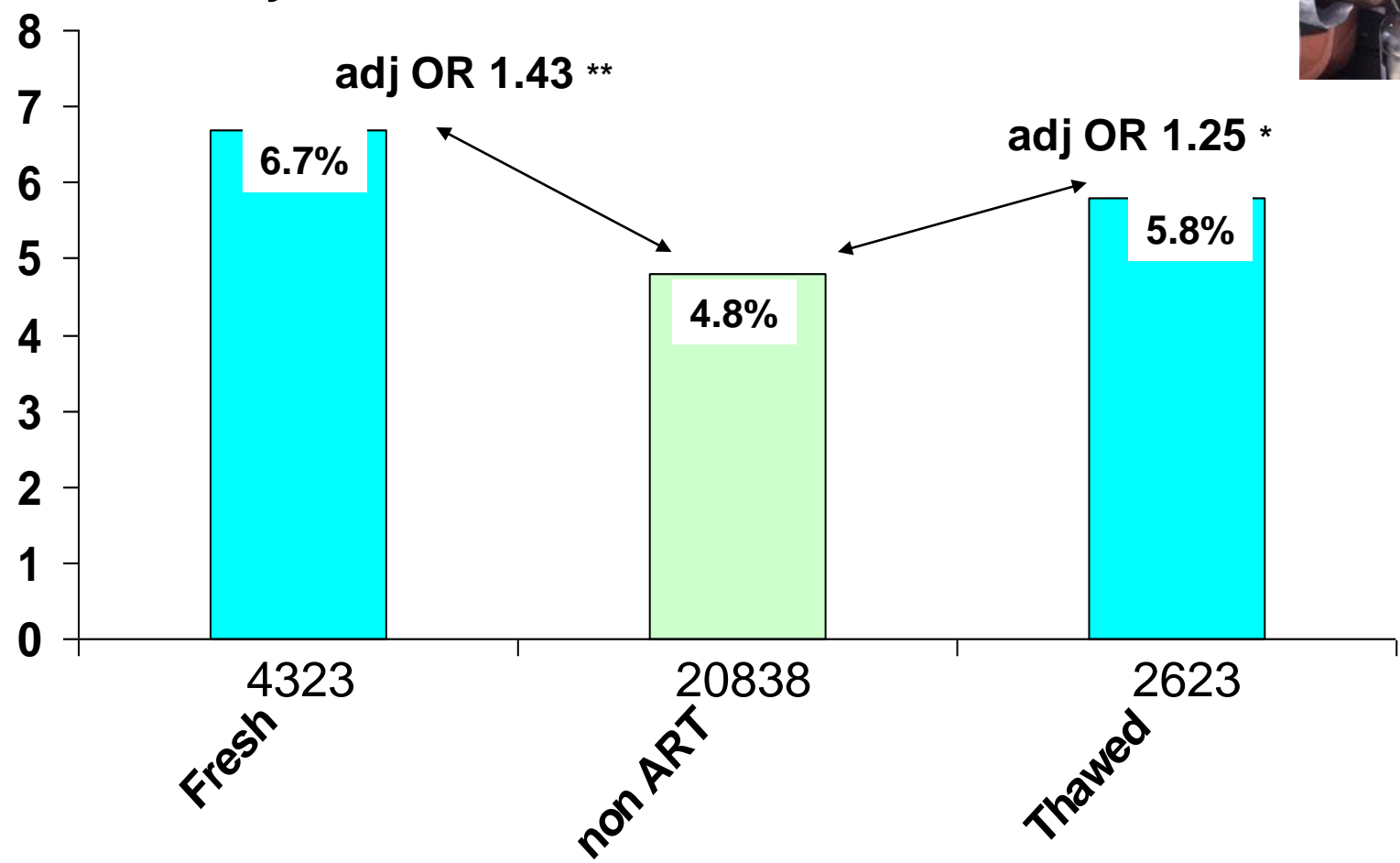


**Odds Ratio adjusted = 1.36**

# Congenital anomalies: comparing fresh or frozen-thawed embryo transfer with non-ART controls



% with congenital anomaly



# Where to next after baby outcomes?

*SK Kalra and KT Barnhart . 2011 Fert Stert 95(6):1887-9 (editorial)*

**“Many in the reproductive community consider it to be an act of self-sabotage to pursue the association of adverse outcomes and IVF. We suggest it is the opposite. The continued thoughtful and methodologically sound pursuit of the answer to these questions will preserve the sanctity of our field....”.**



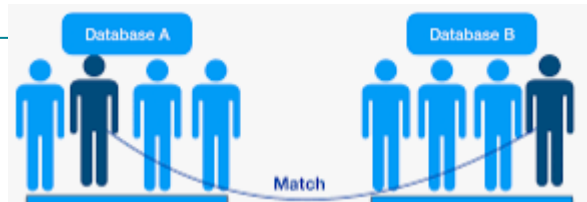
Glass desiccator used by Robert Edwards to incubate embryos



*Sarah Boseley. The Lancet Vol 392 August 4, 2018*



## 2009 onwards – move away from record linkage to real life

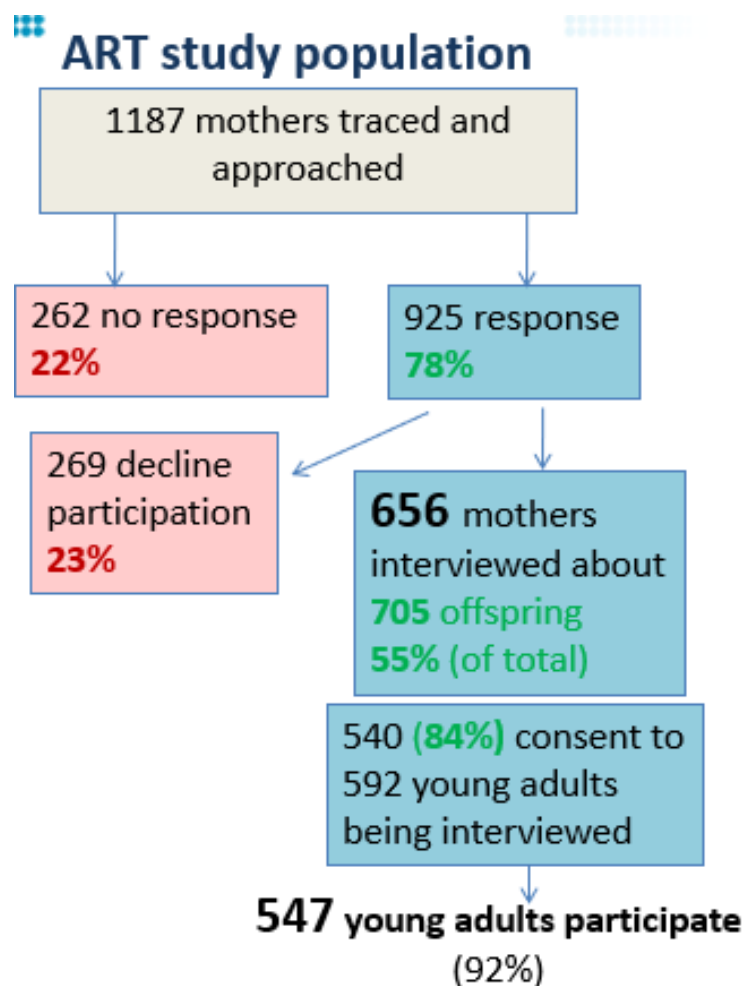


### Aim

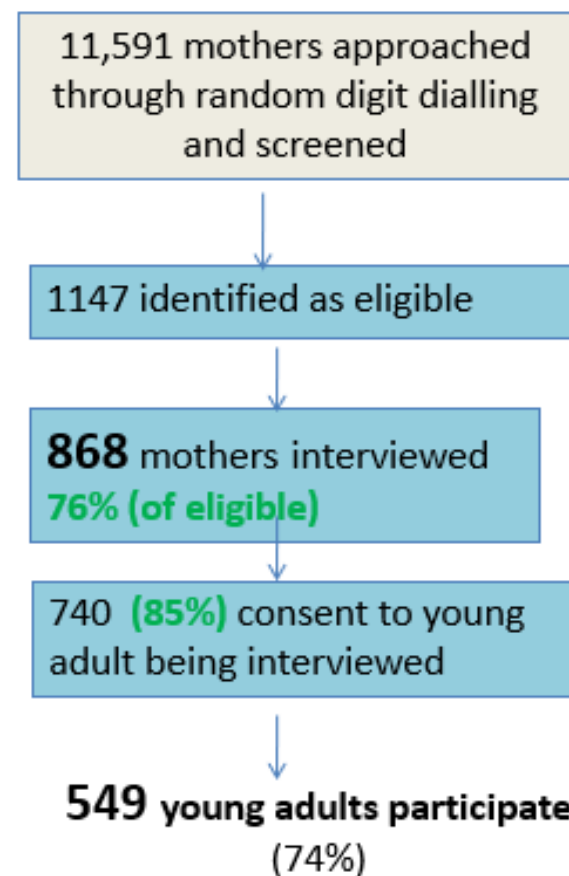
To compare the physical and mental health, educational and social development of young adults conceived through ART with age- and sex-matched, spontaneously conceived young adults



# Young adult study population



## Non-ART study population



An in-depth analysis of information from structured telephone interviews shows:

**No difference in young adult reporting of:**

- Quality of life
- BMI
- Pubertal development
- Educational achievements

**A difference in maternal reporting of:**

- Hospitalisations across the 18 year time span (64% in ART offspring vs 51% in non-ART)
- Chronic respiratory atopy (30% in ART offspring vs 23% in non-ART)

# Comparing indicators of health and development of singleton young adults conceived with and without assisted reproductive technology

Jane Halliday Ph.D., Cate Wilson M.P.H., Karin Hammarberg Ph.D., Lex W. Doyle M.D., Fiona Bruinsma D.P.H., Robert McLachlan M.B.B.S., Ph.D., John McBain M.D., Turi Berg M.P.H., Jane R. Fisher Ph.D. and David Amor M.B.B.S., Ph.D.

Fertility and Sterility, 2014-04-01, Volume 101, Issue 4, Pages 1055-1063, Copyright © 2014 American Society for Reproductive Medicine



Fertility and Sterility  
Volume 101, Issue 4

## Adult IVF offspring doing well, study finds

**Study a relief for those involved in the ART of making babies**

Print delivery summary – 126 different media hits in one day!

But, we did find some differences and stated strongly the need for clinical review and further follow up

**IVF no  
bar to  
health**

**Babies  
created  
equal**

# From telephones to clinical review

Telephone interview study of young adults (19-30 years old) conceived by IVF/GIFT and their mothers – compared with non-ART controls



Clinical review and online survey of same adults a few years later, aged 22-35 years



2017-2018



**Australian Government**

**National Health and  
Medical Research Council**

## CHART Study

Clinical review of the Hhealth of young adults conceived following AART.





# Outcomes of interest – clinical review



*Height, weight, waist circumference,  
body fat*



*Cardiometabolic profile: lipids,  
fasting blood glucose and insulin;  
free fatty acids*



*Cardiovascular structure and function  
e.g. Carotid artery thickness, blood pressure*

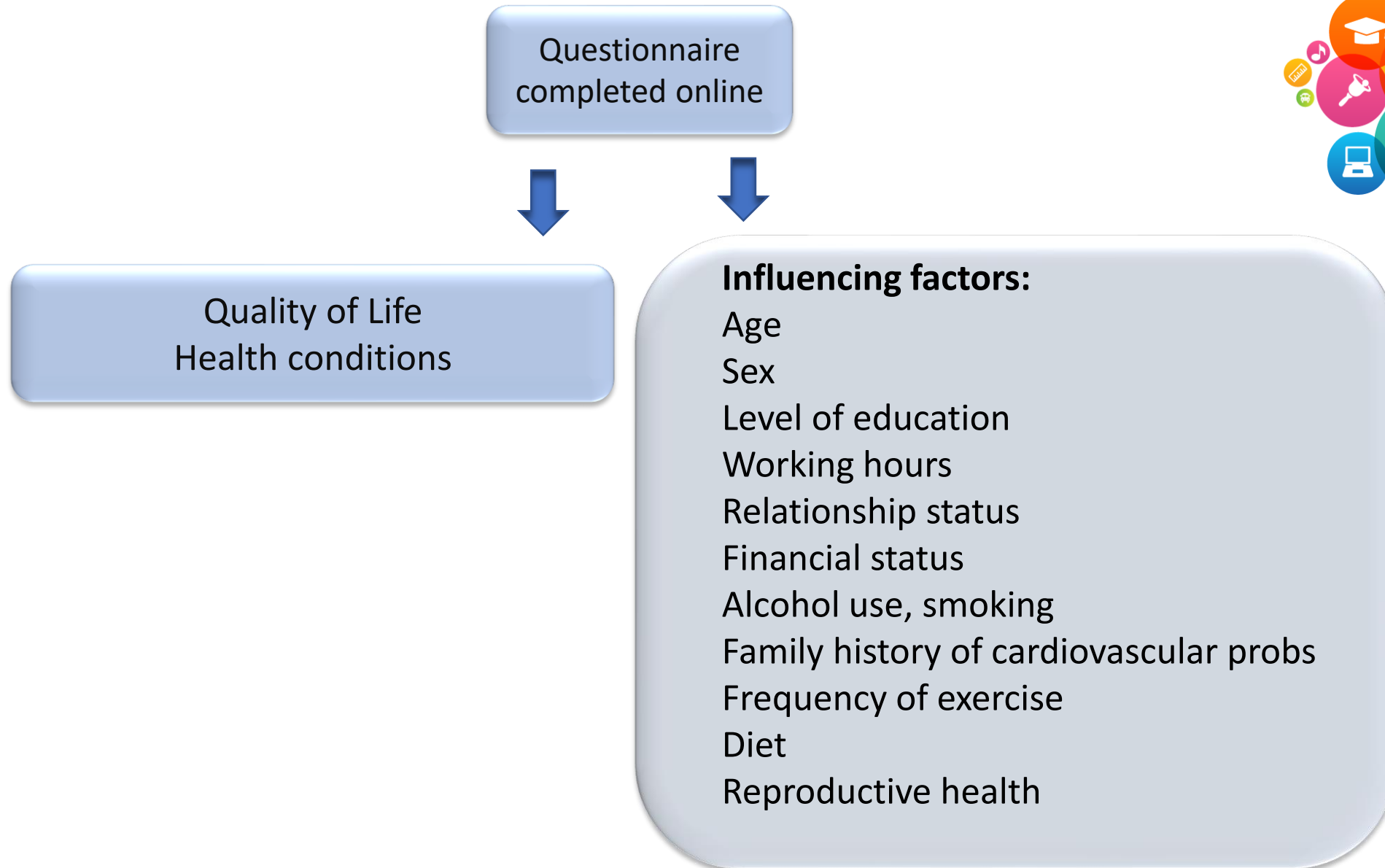


*Respiratory function:  
e.g. Spirometry*

Clinic appointment  
2-3 hours



# Outcomes of interest and influencing factors: self-report



## Results

### Health conditions from survey

|                                       | ART<br>N= 192 | Non-ART<br>N= 86 |
|---------------------------------------|---------------|------------------|
| Excellent physical health in general  | 29%           | 22%              |
| Medical advice for fertility concerns | 10%           | 6%               |
| Pregnancy attempted                   | 16%           | 12%              |
| Depression                            | 24%           | 26%              |
| Allergies/skin atopy                  | 27%           | 34%              |
| Asthma, lung or breathing prob (ever) | 41%           | 29%              |

| Age that asthma ceased<br>(years) | ART | Non-ART |
|-----------------------------------|-----|---------|
| <10                               | 15% | 0%      |
| 10-19                             | 24% | 17%     |
| 20-26                             | 3%  | 8%      |
| ongoing                           | 56% | 75%     |

### Respiratory health measurement from clinical review

(spirometry)



#### Respiratory measures

Forced expiratory volume  
Forced vital capacity

Results continued: most measures all 'normal'

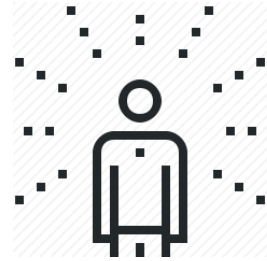
Height, weight, BMI, body fat



Quality of life



physical



psychological



social  
relationships



environment

Cardiovascular measures:  
BP, structural changes  
(artery thickness)



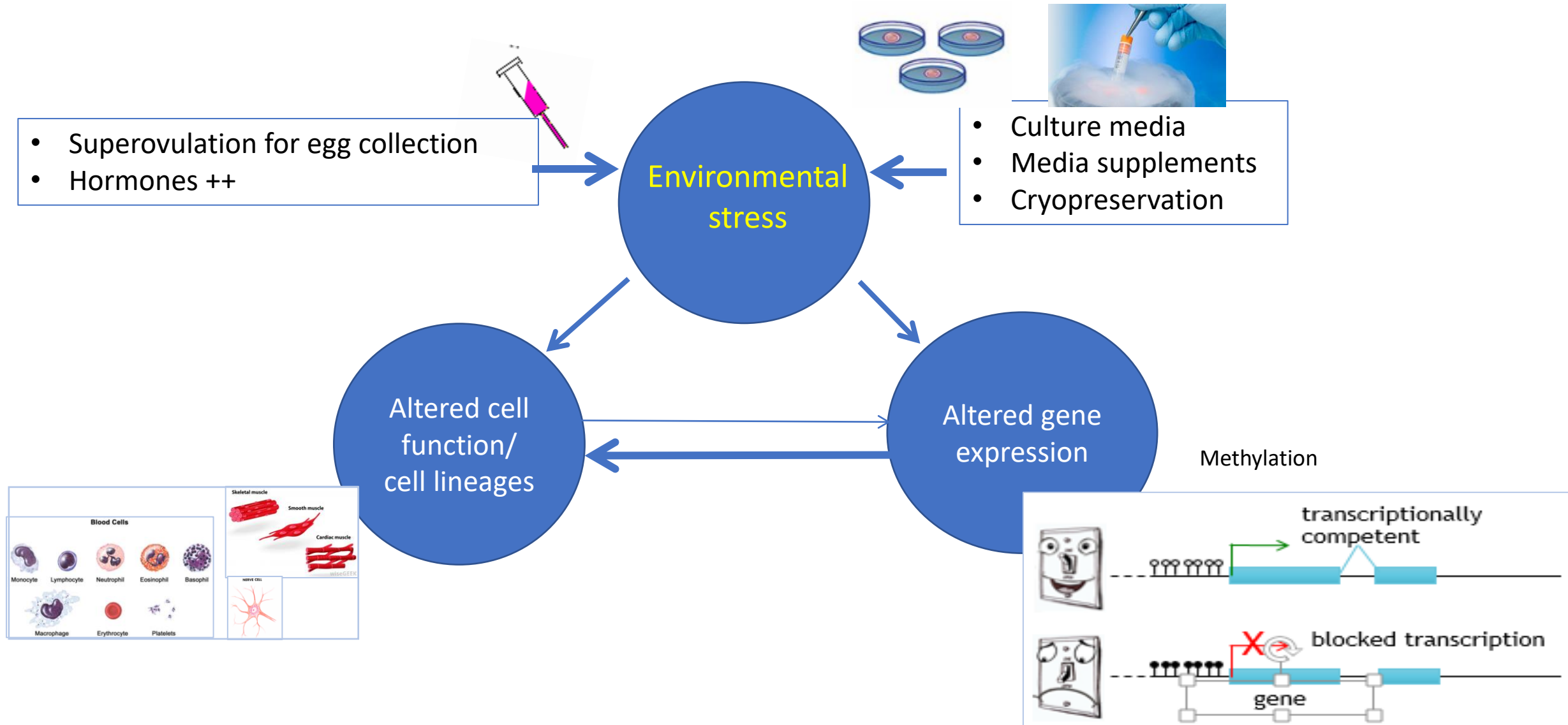
Fertility and Sterility® Vol. 112, No. 1, July 2019

**Health of adults aged 22 to 35 years  
conceived by assisted  
reproductive technology**

Jane Halliday, Ph.D.,<sup>a,b</sup> Sharon Lewis, Ph.D.,<sup>a,b</sup> Joanne Kennedy, M.G.C.,<sup>a</sup> David P. Burgner, Ph.D.  
Markus Juonala, Ph.D.,<sup>a,e,f</sup> Karin Hammarberg, Ph.D.,<sup>g,h</sup> David J. Amor, Ph.D.,<sup>a,b</sup> Lex W. Doyle, M.  
Richard Saffery, Ph.D.,<sup>a,b</sup> Sarath Ranganathan, Ph.D.,<sup>a,b,d</sup> Liam Welsh, Ph.D.,<sup>a,d</sup> Michael Cheung,  
John McBain, M.D.,<sup>k</sup> Stephen J. C. Hearps, Ph.D.,<sup>a</sup> and Robert McLachlan, Ph.D.<sup>l,m,n</sup>

Media activities said to reach 3.07 million

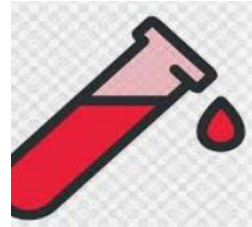
# Epigenetics: exposures related to ART



Adapted from Gardner DK, Lane M. Ex vivo early embryo development and effects on gene expression and imprinting. *Reprod Fertil Dev* 2005



# Epigenetic changes seen in newborn blood spots, but not in the adult blood sample



[http://upload.wikimedia.org/wikipedia/commons/1/16/Phenylketonuria\\_testing.jpg](http://upload.wikimedia.org/wikipedia/commons/1/16/Phenylketonuria_testing.jpg)



Sept 3, 2019

## ARTICLE

<https://doi.org/10.1038/s41467-019-11929-9>

OPEN

## Assisted reproductive technologies are associated with limited epigenetic variation at birth that largely resolves by adulthood

Boris Novakovic<sup>1,2</sup>, Sharon Lewis<sup>1,2</sup>, Jane Halliday<sup>1,2</sup>, Joanne Kennedy<sup>1</sup>, David P. Burgner<sup>1,2,3,4</sup>, Anna Czajko<sup>1</sup>, Bowon Kim<sup>1</sup>, Alexandra Sexton-Oates<sup>1</sup>, Markus Juonala<sup>1,5,6</sup>, Karin Hammarberg<sup>1,7,8</sup>, David J. Amor<sup>1,2,4</sup>, Lex W. Doyle<sup>1,2,9,10</sup>, Sarath Ranganathan<sup>1,2,4</sup>, Liam Welsh<sup>1,4</sup>, Michael Cheung<sup>1,2,4</sup>, John McBain<sup>11</sup>, Robert McLachlan<sup>12,13,14</sup> & Richard Saffery<sup>1,2</sup>

## IVF changes babies' genes but these differences disappear by adulthood

September 3, 2019 5:52am AEST



# Conclusions

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- Record linkage revealed some adverse outcomes at birth after IVF or ICSI, such as increased congenital anomalies, but the absolute risk remains low.
- Self-reported and clinically measured health and wellbeing outcomes are positive in the young adults conceived by IVF.
- Epigenetic data reveal some changes at birth associated with IVF, which are resolved by adulthood.
- **More research is needed:**
  - reproductive health of older offspring – *a further survey of the adult cohort is underway*
  - later onset chronic health conditions – *watch and wait*
  - epigenetic changes in young children and teenagers – *new cohort required*
- **What about outcomes after ICSI?**

# Acknowledgements

Access Australia and IVFlings  
All the mothers and young adults



David Amor  
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Boris Novakovic  
Sarath Ranganathan  
Richard Saffery  
Obi Ukomunne  
Liam Welsh  
Cate Wilson



Gordon Baker  
Sue Breheny  
Dhanushi Fernando  
Shavi Fernando  
Karin Hammarberg  
Gab Kovacs  
Luk Rombauts  
Viv McLachlan  
Rob McLachlan



Franca Agresta  
Claire Garret  
David Healy  
John McBain  
Kay Oke  
Debbi Rushford

## Significant others

Jane Fisher  
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Penny Smithers  
Julie Hoy  
James King

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NHMRC  
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Jack Brockhoff Foundation  
Monash Research and Education Foundation  
Reproductive Biology Unit Sperm Fund, Melbourne IVF  
MCRI



# Health of young men born after ICSI

Dr Sarah Catford

Endocrinologist | Post-doctoral research fellow



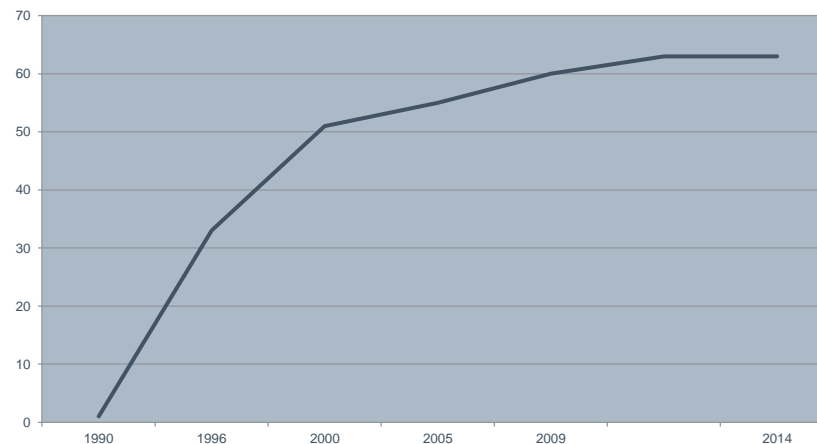
# Intracytoplasmic sperm injection (ICSI)

- Single sperm injected into an egg
- Introduced in 1992
- To overcome poor semen quality
- Main type of assisted reproductive treatment worldwide



## Australia & NZ

% ART embryo transfer cycles using ICSI

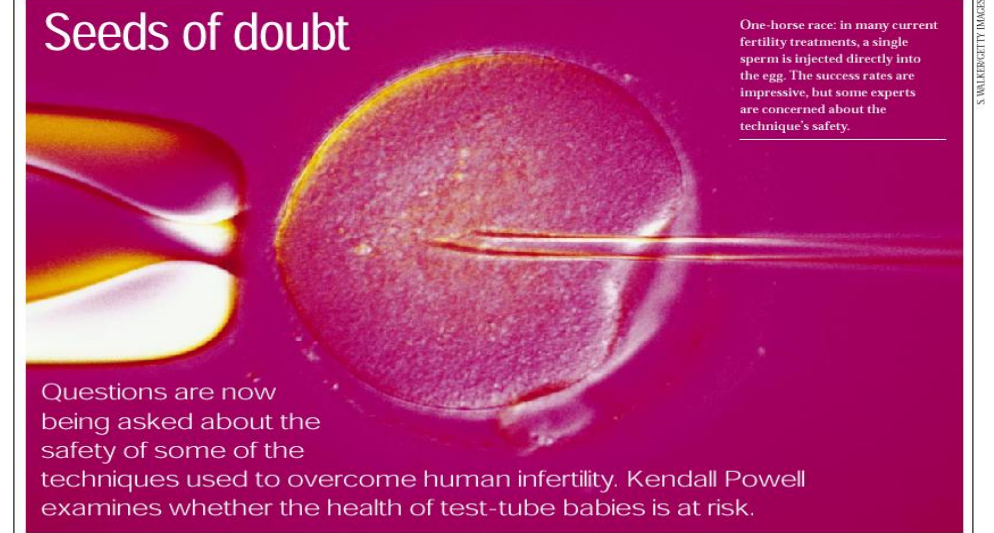




# Safety of ICSI

1. Heritability of infertility
  - Can infertility be passed on?
2. Effects of using poor-quality sperm
  - Does poor quality sperm have negative effects on other body systems?
3. Effects of procedure itself
  - Does the extra handling of the sperm and egg have negative effects?

## news feature



*Nature 2003*

# Health of children born after ICSI

*Compared to children conceived naturally*



↑ adverse perinatal events  
↑ birth defects



Similar in most domains



Some differences in  
metabolic health

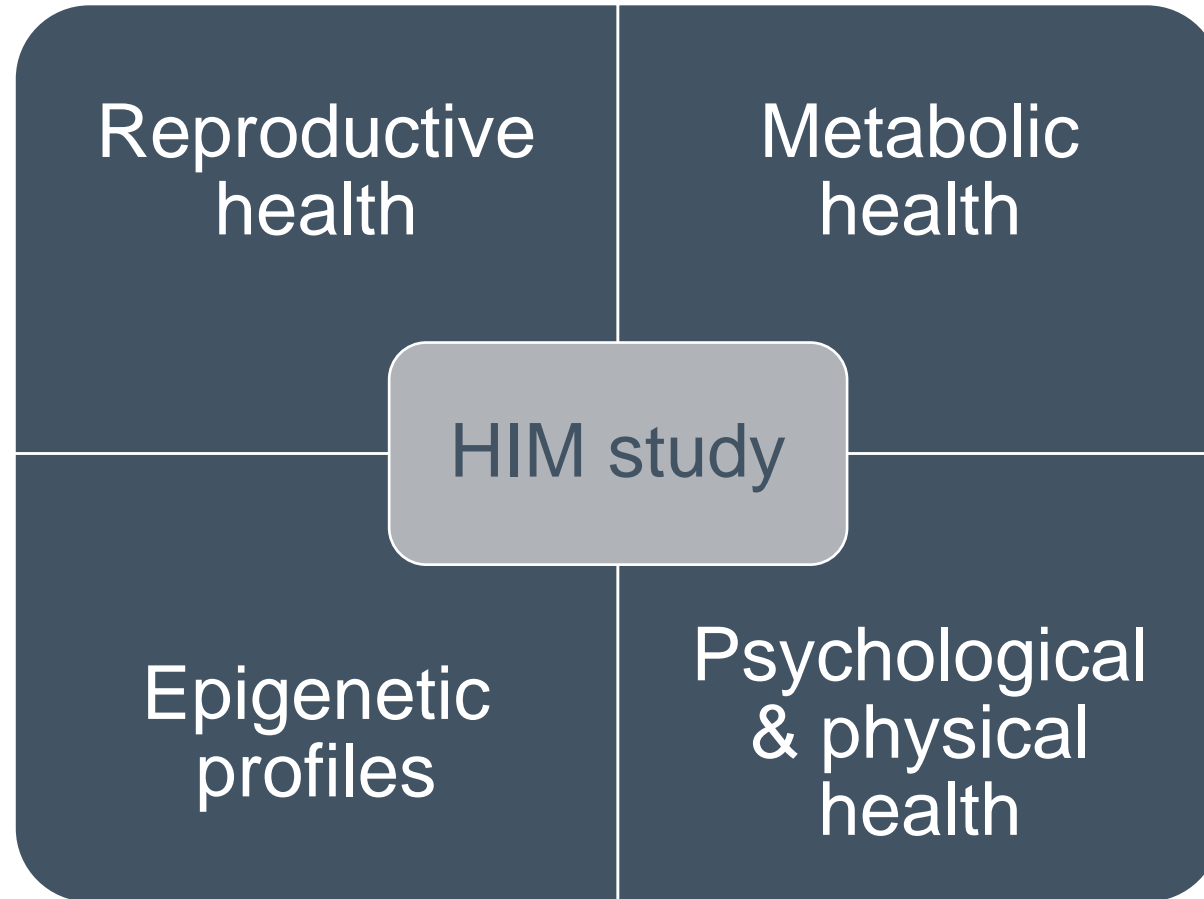


? Lower sperm count  
? Poorer sperm quality

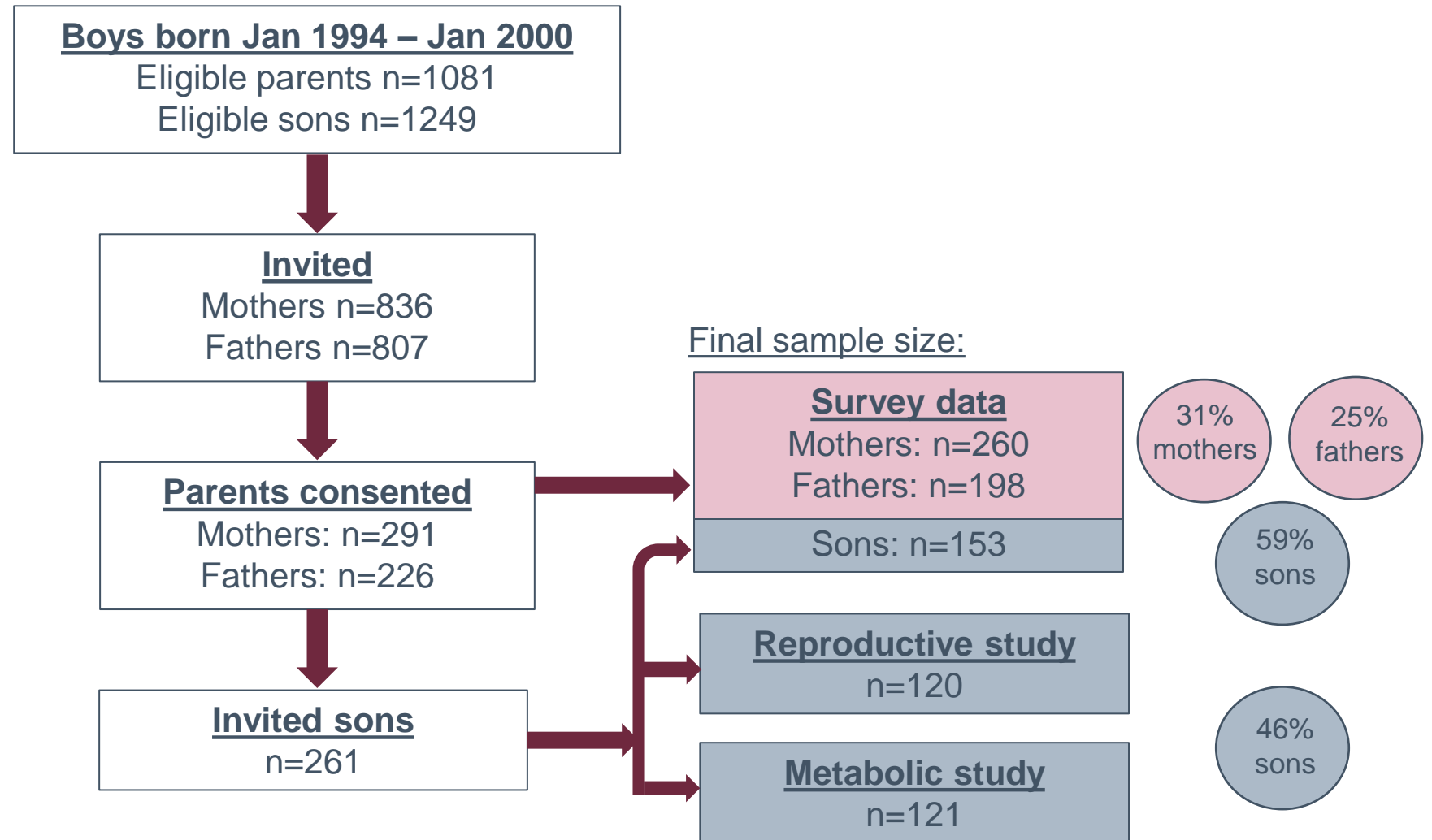


# Health and fertulity of young men conceived using ICSI

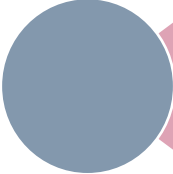
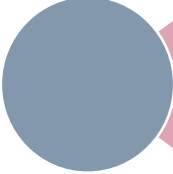
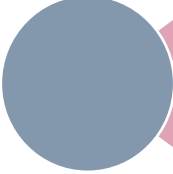
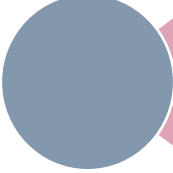
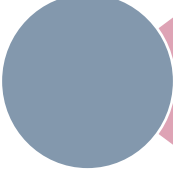
Men 18-24 years of age



# Recruitment of sons born after ICSI

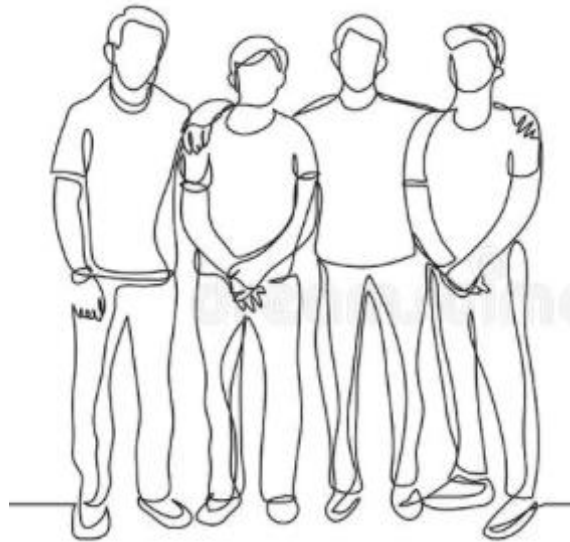


# Measurements

-  Questionnaires
-  Medical records
-  Physical examination
-  Blood fertility hormones & metabolic markers
-  Semen analysis



# Study groups



**Men conceived  
with *ICSI***

*n*=120 (reproductive data)  
Average age = 22 years  
*n*=121 (metabolic data)



**Men  
conceived  
with *IVF***

Derived from Victorian  
CHART study  
*n*=74  
(metabolic data)



**Men  
conceived  
*naturally***

*n*=356  
(reproductive data)

Derived from WA  
Raine study  
*n*=688  
(metabolic data)

# Main results

## Reproductive health of men conceived with ICSI

- ***Compared to men conceived naturally***
  - No differences in sperm count
  - Slightly lower sperm motility – but still normal
  - Normal testosterone, fertility hormones and testicular size
  - No correlation between father and son's sperm parameters

## Reproductive function in men conceived with in vitro fertilization and intracytoplasmic sperm injection

Sarah R. Catford, Ph.D.,<sup>a,b,c</sup> Jane Halliday, Ph.D.,<sup>c,d</sup> Sharon Lewis, Ph.D.,<sup>c,d</sup>  
Moiria K. O'Bryan, Ph.D.,<sup>e</sup> David J. Handelsman, Ph.D.,<sup>f</sup> Roger J. Hart, CREI,<sup>g,h</sup>  
John McBain, M.D.,<sup>i,j,k</sup> Luk Rombauts, Ph.D.,<sup>b,l</sup> David J. Amor, Ph.D.,<sup>c,d</sup> Richard Saffery, Ph.D.,<sup>c,d</sup>  
and Robert I. McLachlan, Ph.D.<sup>a,b,l</sup>

# Metabolic health of men conceived with ICSI

- ***Compared to men conceived naturally***
  - Higher diastolic blood pressure
  - Higher scores of insulin resistance
  - No differences in systolic blood pressure, weight, height, cholesterol
- ***Compared to men conceived with IVF***
  - No major differences

# Summary

- Largest study to date on health of ICSI-conceived adults
- Reassuring results on reproductive health
- Preliminary data on metabolic health requires further study
- Further research still needed
  - Replicate results
  - Identify factors that are driving potential health differences



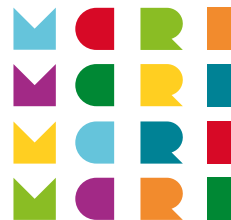


# Questions?



**VARTA**  
Victorian Assisted Reproductive  
Treatment Authority

**HUDSON**  
INSTITUTE OF MEDICAL RESEARCH



murdoch  
children's  
research  
institute



**Monash  
Health**





# Thank you.



## VARTA

Victorian Assisted Reproductive  
Treatment Authority

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