The impact of untreated parental MEN 1 on fertility and offspring childhood survival

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Background: MEN 1

- Hereditary neoplasia syndrome
  - Primary hyperparathyroidism
  - Pituitary adenoma, particularly prolactinoma
  - GI, respiratory, thymic neuroendocrine tumours
- Heterozygous loss of function MEN 1 gene
  - Autosomal dominant, ~95-100% penetrance
  - Onset mid teens to early 20s
- Tasman 1 MEN 1 kindred = largest globally
  - >2500 descendants of a common ancestor

Background: MEN 1 in pregnancy

- Published experience limited to
  - Case reports (2) on MEN 1-associated pregnancy
  - Inference from single organ endocrinopathy
- MEN 1 endocrinopathy develops in childhood
- Phenotype differs
  - Multiglandular PHPT with early skeletal impact
  - Aggressive prolactinoma

Background: MEN 1 in pregnancy

Case Report

Obstetric Medicine

Obstetric Medicine
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SAGE

Pregnancy in multiple endocrine neoplasia type I equals multiple complications

Megha Mistry, Manish Gupta and Mandeep Kaler

In conclusion, there are no sufficient studies or references that would guide us in terms follow-up and treatment of pregnant women diagnosed with MEN-1.

Objective & methods

- Objective
  - Define the natural history of untreated parental MEN 1 on:
    1. Fertility
    2. Offspring childhood survival
- Design
  - Retrospective cohort analysis Tasman 1 kindred
    - Kindred identified mid 1980s, tracing into early 1990s
    - Descendents born 1825-1950 included

Methods

- Tasmanian advantages
  - Limited population migration (island state)
  - Robust record keeping in colonial Tasmania
- Pedigree to founding ancestor established
  - Cross referenced with
    - Births, deaths, marriages registries
    - Medical & archival records
    - Biochemistry and genotype when available
  - Strict criteria to define *MEN 1* positive (*MEN 1*$^{+}$) status (63)
  - Controls: *MEN 1* negative (*MEN 1*$^{-}$) siblings (75)

    Era-matched Tasmanian population averages

Outcomes

- Primary outcomes
  1. Total number of births
  2. Offspring survival to 15 years of age
- Secondary outcomes
  1. Stillbirths, live births, maternal & paternal births
  2. Number of *MEN 1*$^{+}$ offspring
  3. High risk parental phenotypes
- Controls: *MEN 1*$^{-}$ siblings & population averages

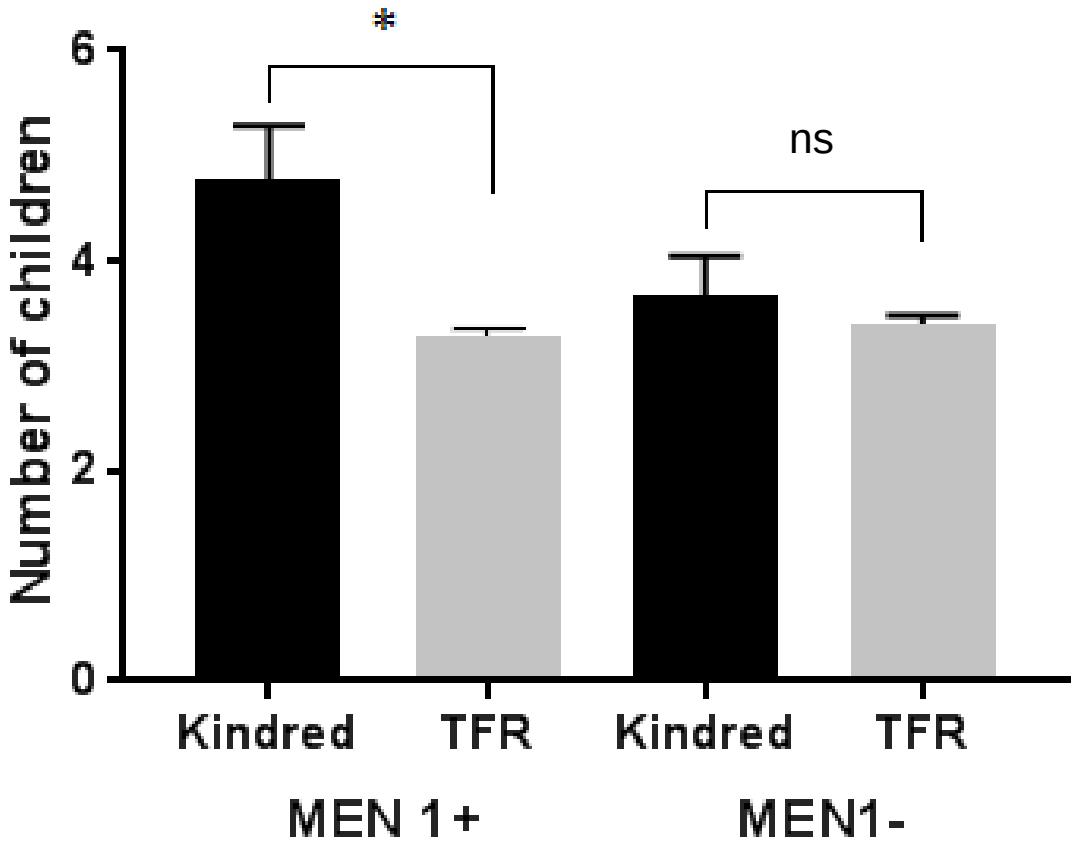
Table 1. Multivariable fertility outcomes of *MEN 1*$^{+}$ kindred members referenced against *MEN 1*$^{-}$ kindred members

	RR† (95% CI)
Number of births	**1.28 (1.00-1.64)**
• Live births	**1.30 (1.01-1.66)**
• Stillborn children	1.24 (0.24-6.36)
• Number of paternal births	**1.42 (1.02-1.99)**
• Number of maternal births	1.16 (0.81-1.65)

Boldface denotes statistically significant result.

†Adjusted for parental date of birth and gender.

Figure 1. Tasman 1 kindred fertility referenced against era-matched Tasmanian average fertility



* *p<0.05*

Data expressed as mean ± SEM

TFR, total fertility rate
NS, not significant

Figure 2. Observed offspring MEN 1 status referenced against expected frequency

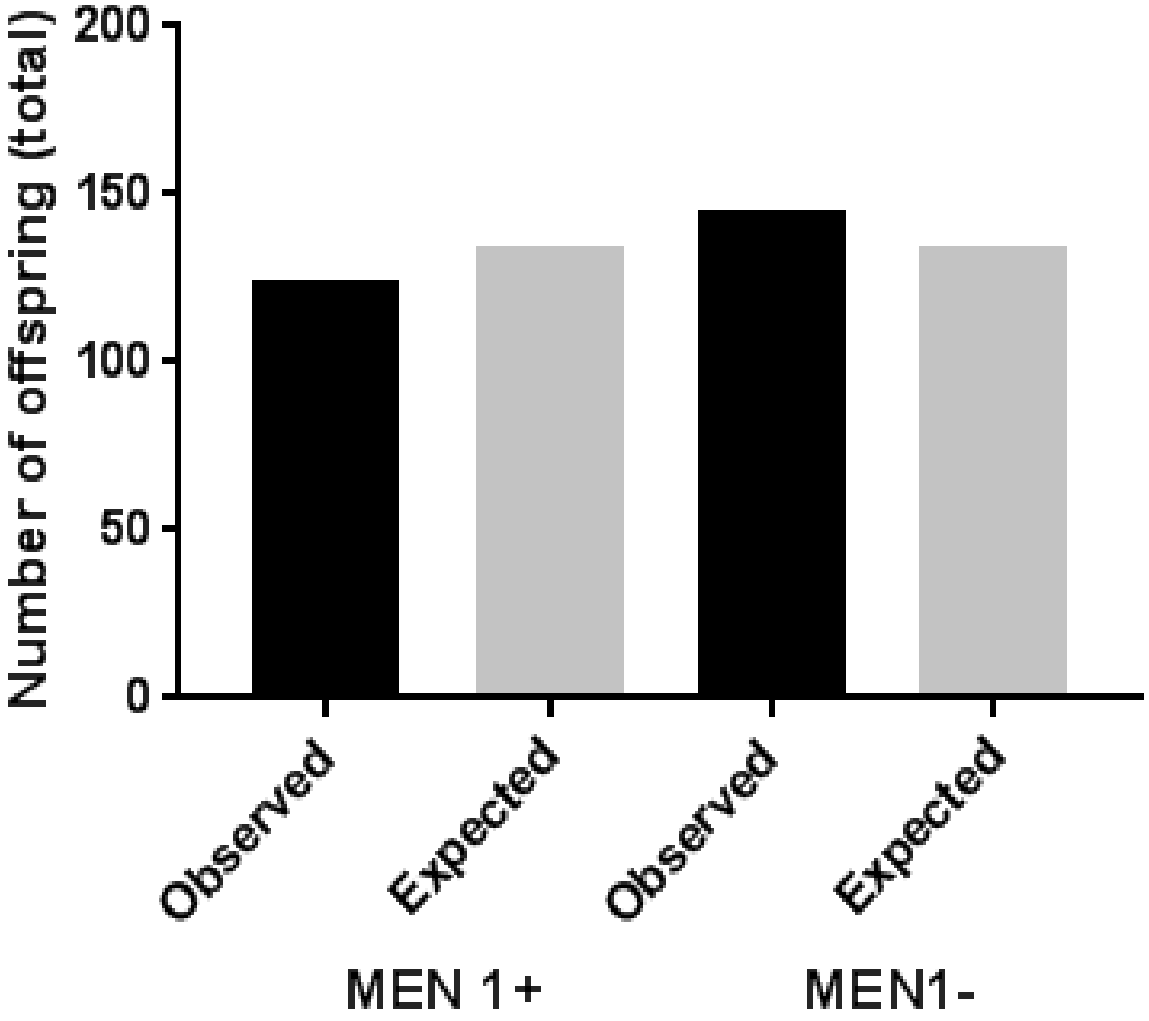
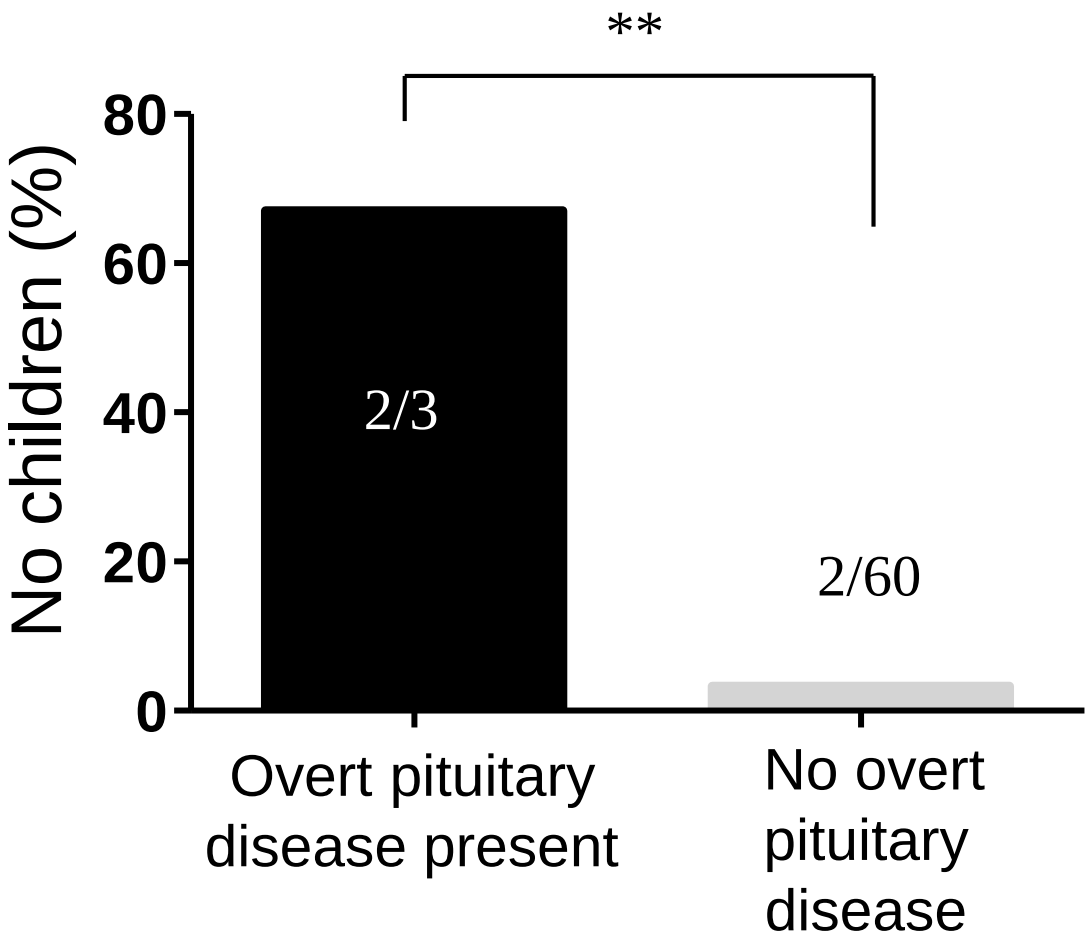
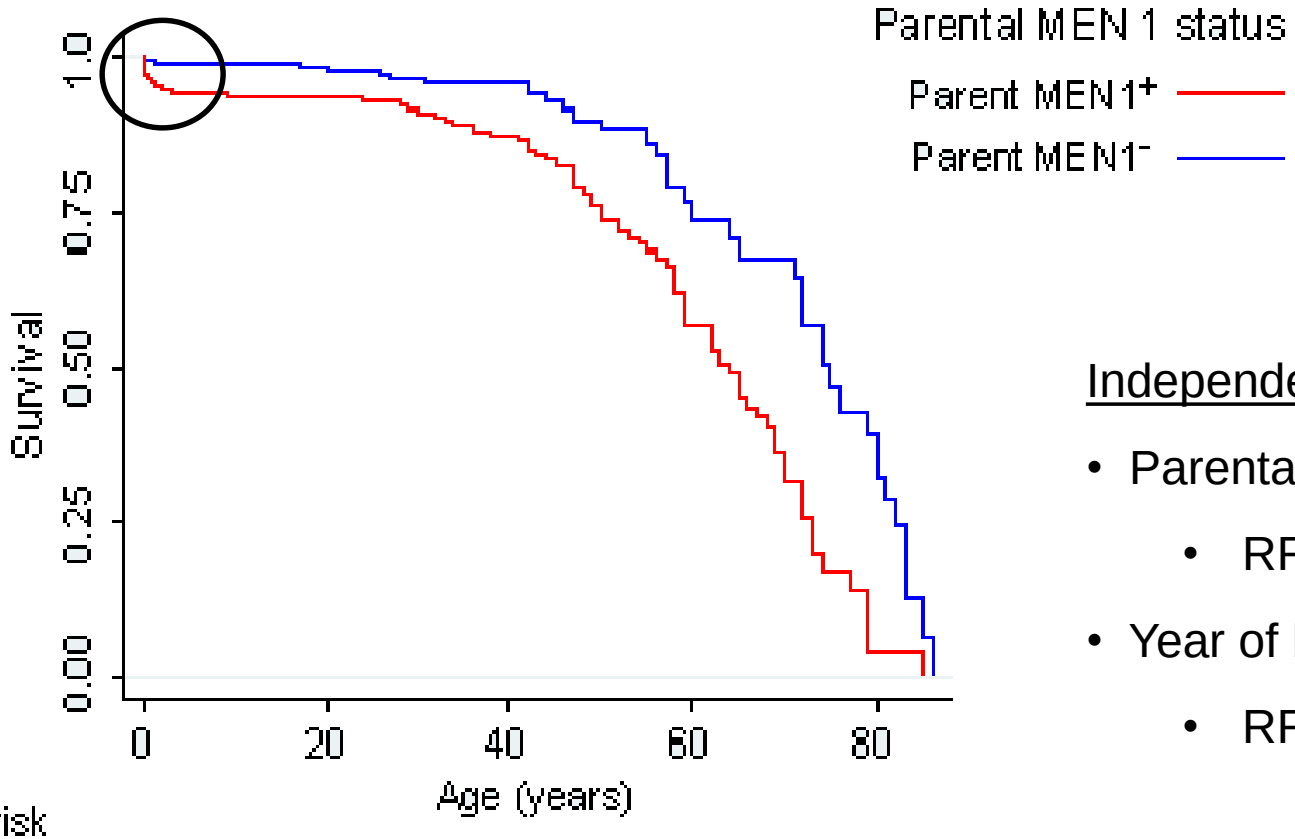


Figure 3. High risk phenotypes



** $p<0.01$

Figure 4. Untreated parental MEN 1 is a risk factor for early offspring childhood mortality



Number at risk

Parent MEN1-	345	216	105	27	11
Parent MEN1+	357	254	126	46	1

<u>Independent risk factors</u>

- Parental MEN 1
  - RR 4.2, p=0.008
- Year of birth
  - RR 0.97, p<0.001

Summary

1. MEN 1 does *not* adversely impact fertility overall
   - However, high risk phenotypes
2. *MEN 1*$^{+}$ kindred members had more children
   - No excess maternal births or *MEN 1*$^{+}$ offspring
3. Untreated parental MEN 1 is a risk factor for offspring childhood mortality

Conclusions

- Periods of excess risk
  - Fertility/conception  Except high risk phenotypes
  - Pregnancy 
  - Postpartum/childhood 
- Risk stratified management warranted
- Need to define & manage high risk phenotypes

Acknowledgements

- Tasman 1 kindred members
- Professor John Burgess
- Professor Joseph Shepherd

Table 2. Aetiology of childhood death stratified by MEN1 status of parent

Aetiology of death	Parent MEN1 status		*p* value
	$MEN1^{+}$	$MEN1^{-}$	
Congenital malformation	2	0	1.0
Prematurity	3	1	1.0
Infectious	10	2	0.02
Neoplastic	1	1	1.0
Unclear	6	1	
Other	1	1	
Total	23	6	**<0.01**

Limitations

- Case definition
  - Slight excess of *MEN 1*$^{-}$ kindred members
- Resolution of dataset
  - Pregnancy complications
- Single genotype

It’s not just Tassie

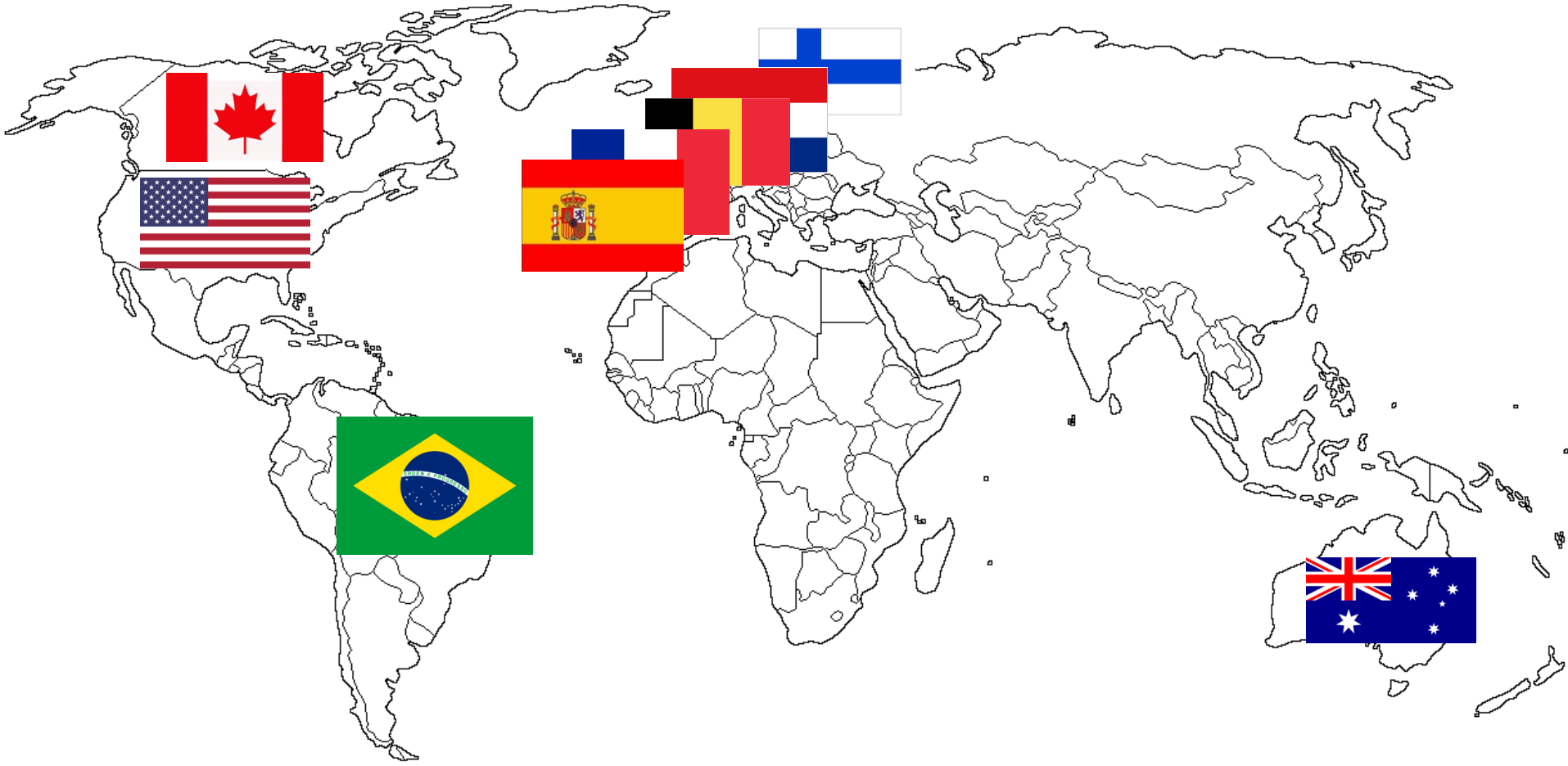


Table 4. Pregnancy outcomes for *MEN 1*$^{+}$ parents stratified by parent gender

	MEN 1^{+} parent		
	Father (*n*=27)	Mother (*n*=35)	*p* value
Parental year of birth*	1928 (16.8)	1930 (25.5)	0.96
Average births (total)	5.3 (4.7)	4.4 (3.5)	0.40
Live births	5.3 (4.7)	4.3 (3.5)	0.35
Stillborn children, % of total births	0.6	1.3	0.52
MEN 1^{+} births	2.2 (1.9)	1.9 (1.9)	0.56
MEN 1^{-} births	2.7 (2.6)	2.2 (2.1)	0.42

Boldface denotes statistically significant result.