



**Karolinska
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Acne, isotretinoin, depression and suicide risk

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Isotretinoin and suicide attempts: Background

- Systemic treatment severe acne since early 1980ies
- Highly teratogenic
- Not licensed in Sweden – compassionate use
- Cohort established late 1980ies
 - Exposure during pregnancy?
 - Malformations?
- Late 1990ies: psychiatric side-effects?

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- Late 1990s Källen B. Restriction of the Use of Drugs With Teratogenic Properties: Swedish Experiences With Isotretinoin. *Teratology* 60:53 (1999)

Psychiatric side effects – evidence

- Case reports (Hazen 1983)
- Spontaneous ADR-reports
- Animal studies
- Decreased metabolism in orbitofrontal cortex in humans:
 - No differences in depressive symptoms between isotretinoin-group (n=13) and antibiotics-group (n=15) before and after treatment.
- Observational studies.

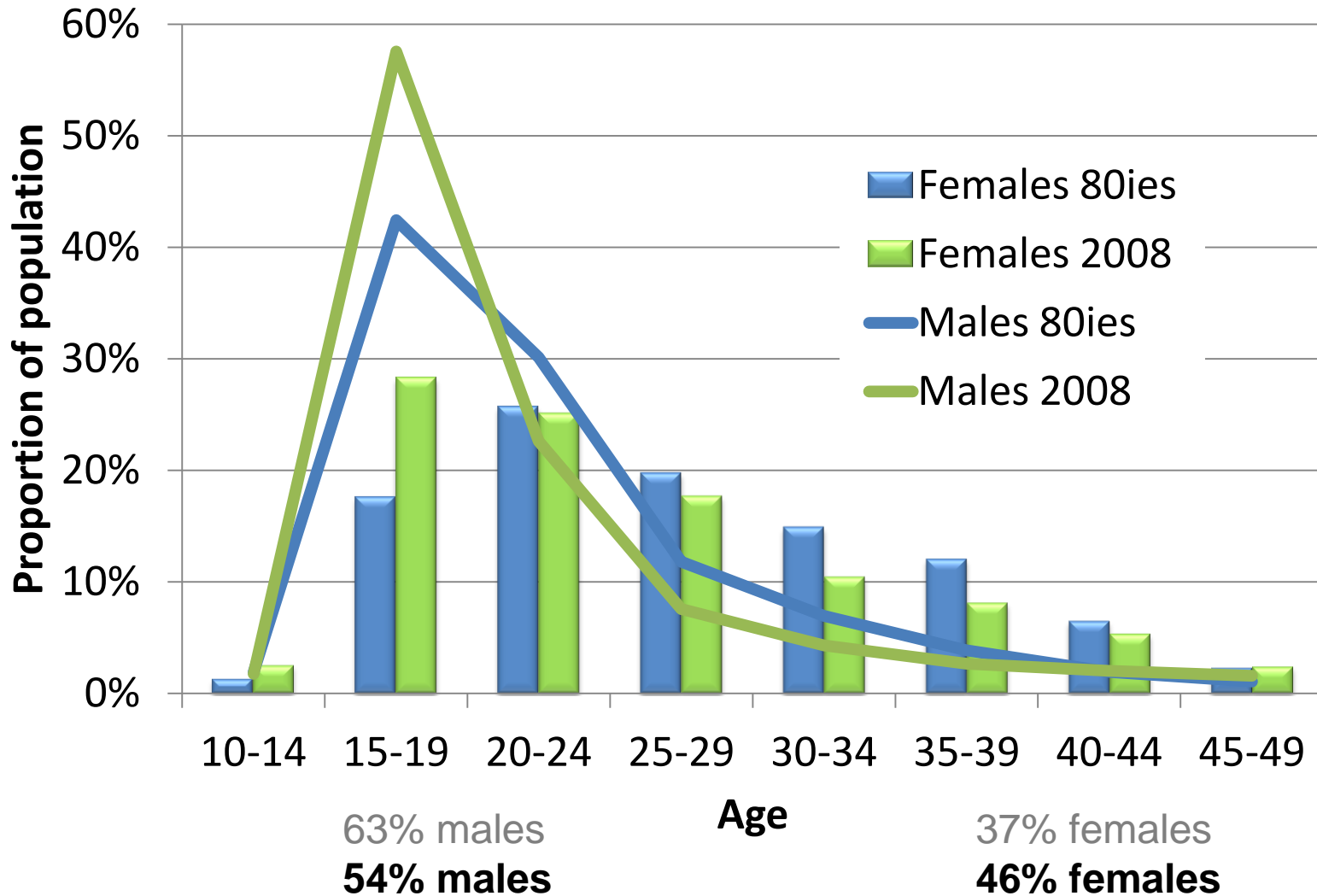
The Swedish isotretinoin cohort *characteristics*

	Males	Females
Patients, N (%)	3613 (63%)	2143 (37%)
Age (years) at first prescription		
Mean	22.3	27.1
Duration of treatment (months)		
Mean	6.0	6.1
Total number of person-years on treatment	1819	1091

The Swedish isotretinoin cohort *highly selected*

- Prescription by dermatologists only
- Requirement for prescription:
 - Treatment with antibiotics for up to 6 months without improvement
- Selection of those with the worst acne, that also managed to pass through the health-care system to a specialist.

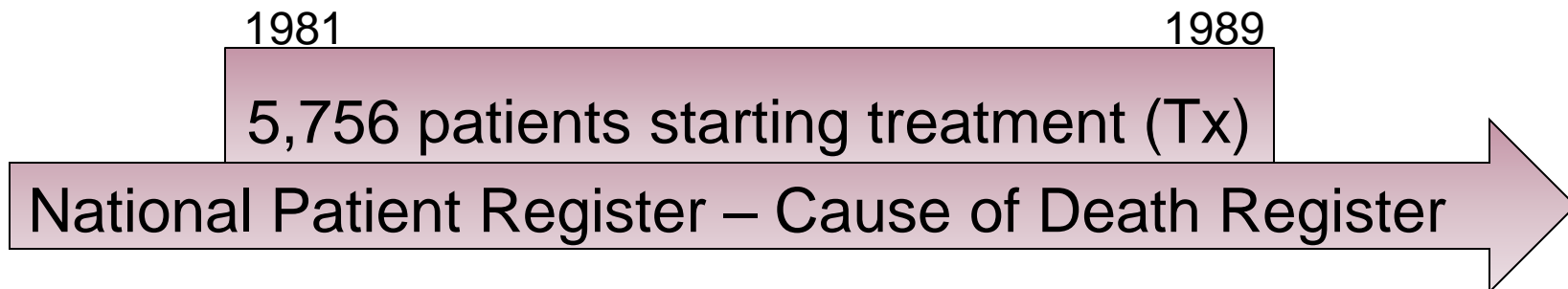
Distribution of sex and age: *then and now*



The Swedish isotretinoin cohort

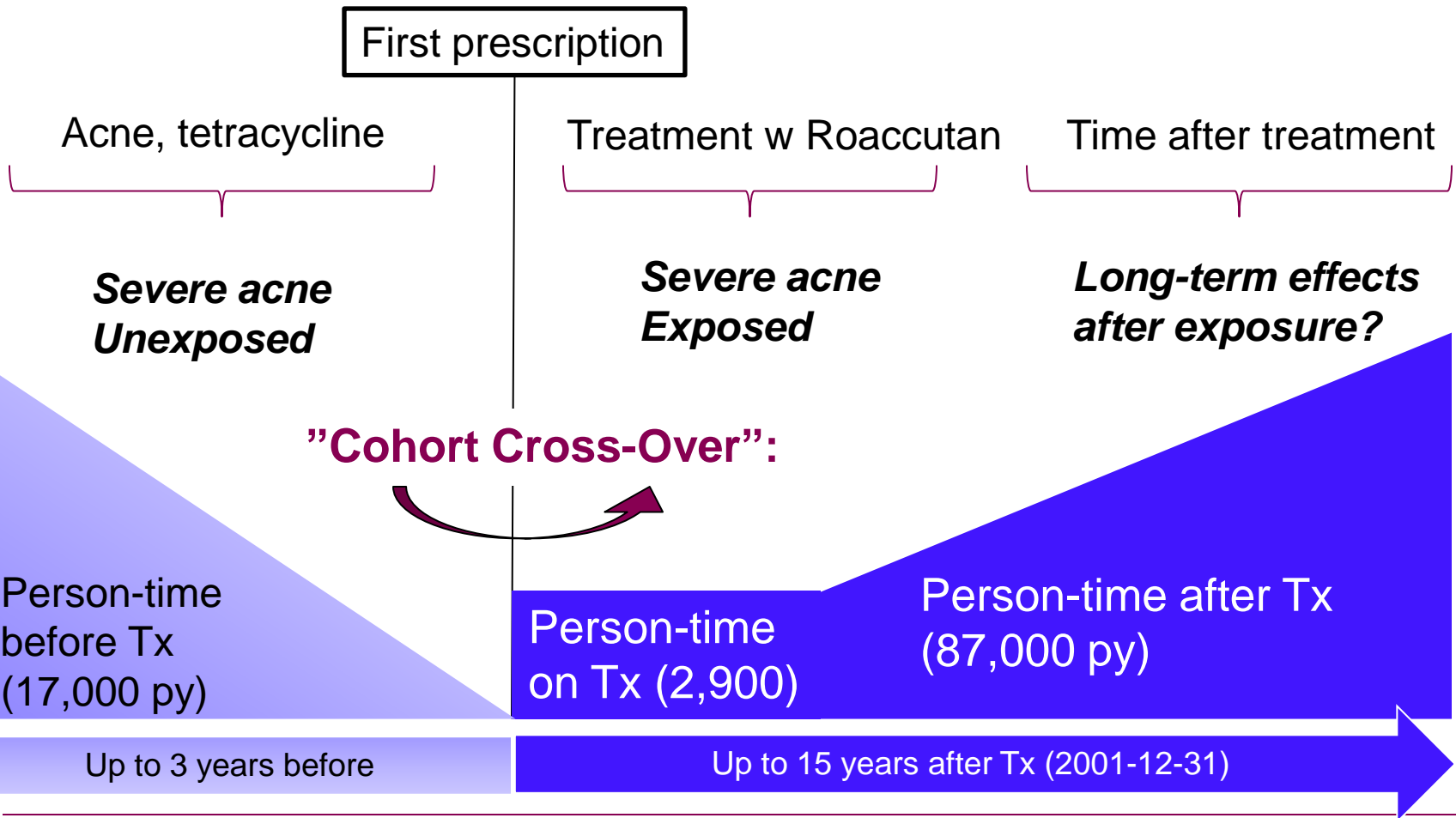
Who should be controls?

- Severe acne → psychiatric morbidity
- Other treatments as control? → different severity of acne



Population before Treatment: its own control

"Cohort Cross-Over":



Hospitalizations for suicide attempt

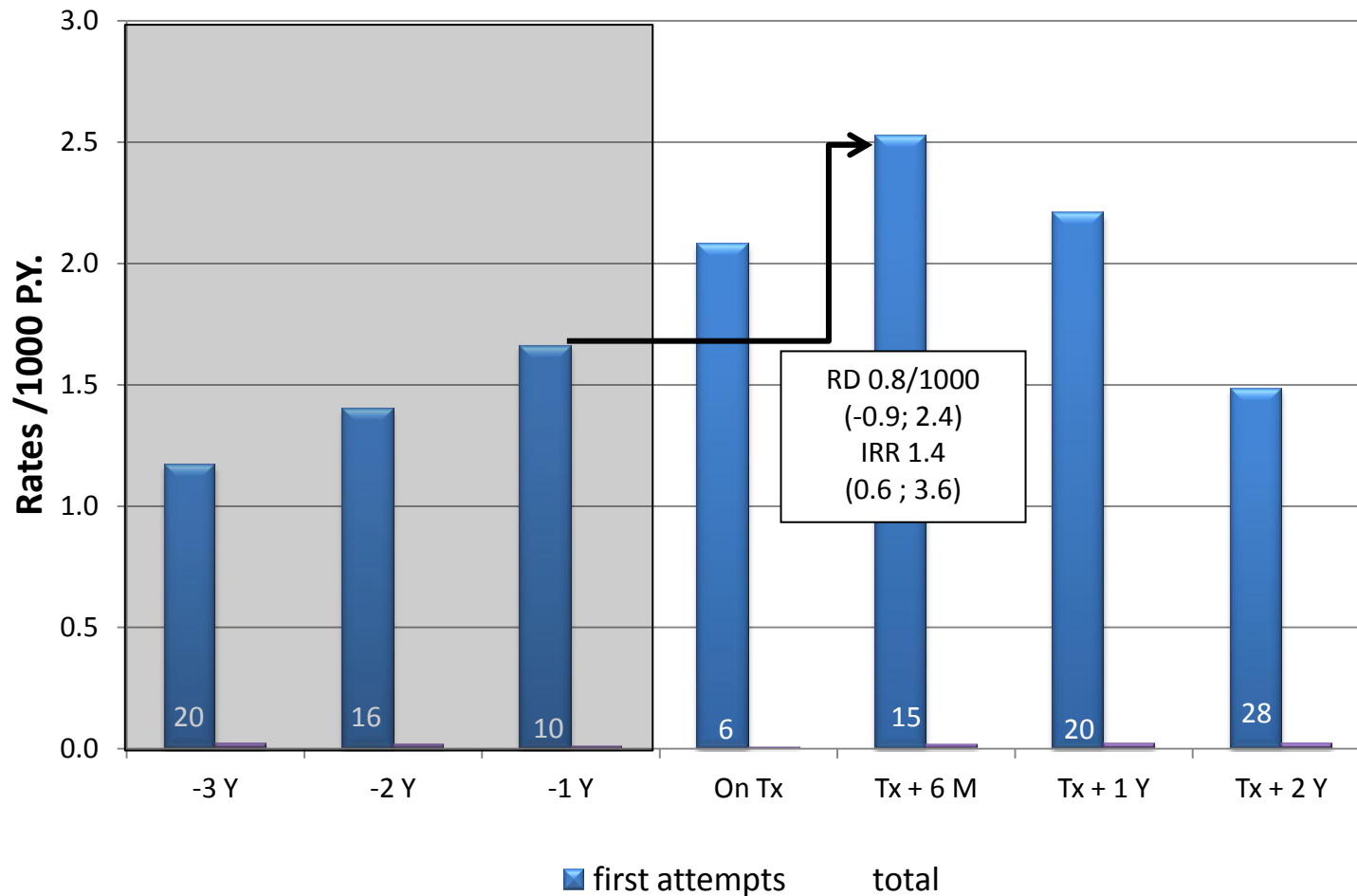
128 individuals (2.2%)

210 hospitalizations

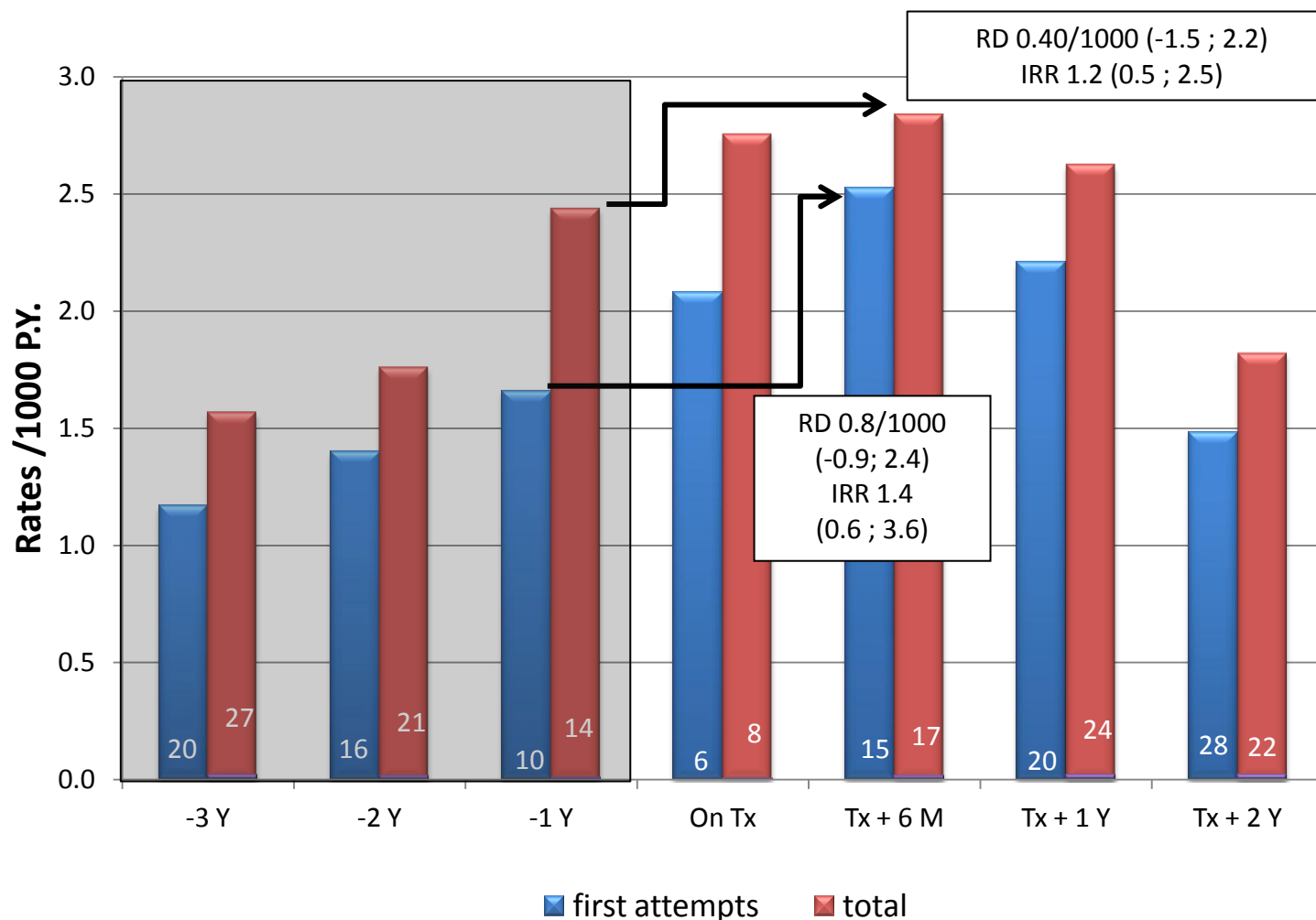
	Ever before treatment	During treatment plus 1 year	> 1 to 15 Y after treatment
Number of individuals	32	20	76
Subsequent suicides*:			
<i>Previous attempts</i>	3	4	6
<i>No previous attempt</i>		11	

*) Completed suicides at *any time* during follow-up; N=24

Rates of first and all suicide attempts per 1000 person-years before, during and after Tx



Rates of first and all suicide attempts per 1000 person-years before, during and after Tx



”Number needed to harm”

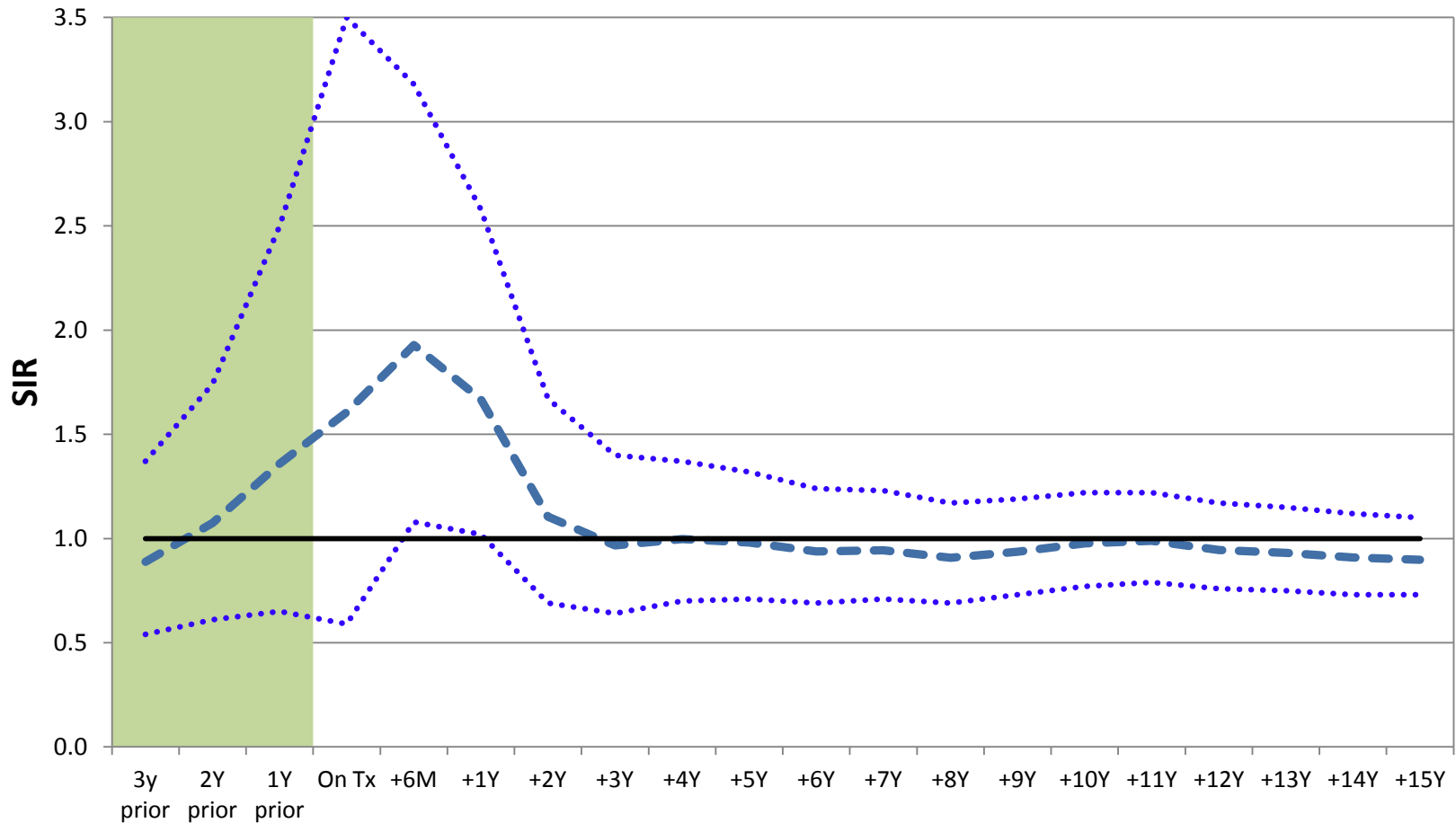
Number of new six-months’ treatments per year needed for one additional suicide attempt to occur:

- 2300 (first suicide attempt)
- 5000 (repeat attempt)

Assuming that the entire additional risk could be attributed to the treatment.

Rates and rate differences were higher for female patients than for male patients.

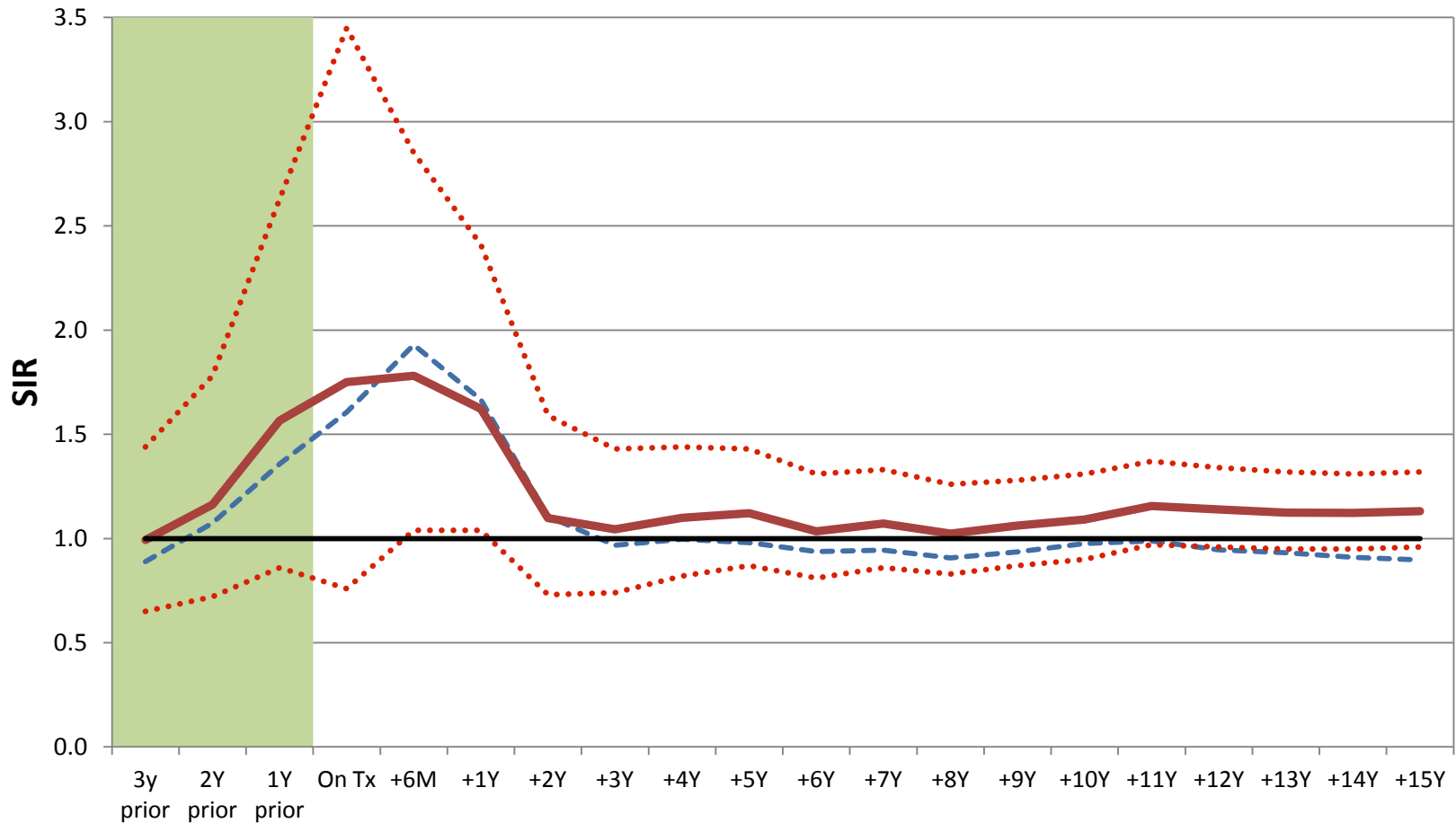
“Standardized Incidence Rates” of *first* suicide attempts standardized by age, sex and calendar-year



Acc N

1st	20	16	10	6	15	20	22	28	37	44	49	56	60	68	77	84	86	90	92	94
Total	27	21	14	8	17	24	28	38	52	65	71	85	92	106	119	136	143	149	155	161

Standardized Incidence Rates of *first* and *all* suicide attempts standardized by age, sex and calendar-year



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Interpretation

- Increasing frequency of suicide attempts already before treatment
- No definite additional risk attributable to isotretinoin, *on the population level*
 - No long-term effects on *initiating* suicidal behavior
- Certain *individuals* more sensitive to isotretinoin?
- Different risk patterns for females compared to males: higher vulnerability to acne *and/or to isotretinoin?*

No "reinforced" behaviour – but sensitive individuals?

- 32 patients made a first attempt before treatment:
→ **12 (38%)** (95% CI: 21% to 54%) made new attempt during follow-up
- 14 patients made a first suicide attempt during treatment or within six months thereafter:
→ **10 (71%)** (95% CI: 48% to 95%) made a new attempt during follow-up

Thank you!

Acknowledgment to my co-authors

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