

Seveso Women's Health Study: Purpose

To investigate the relationship of serum TCDD and reproductive health outcomes:

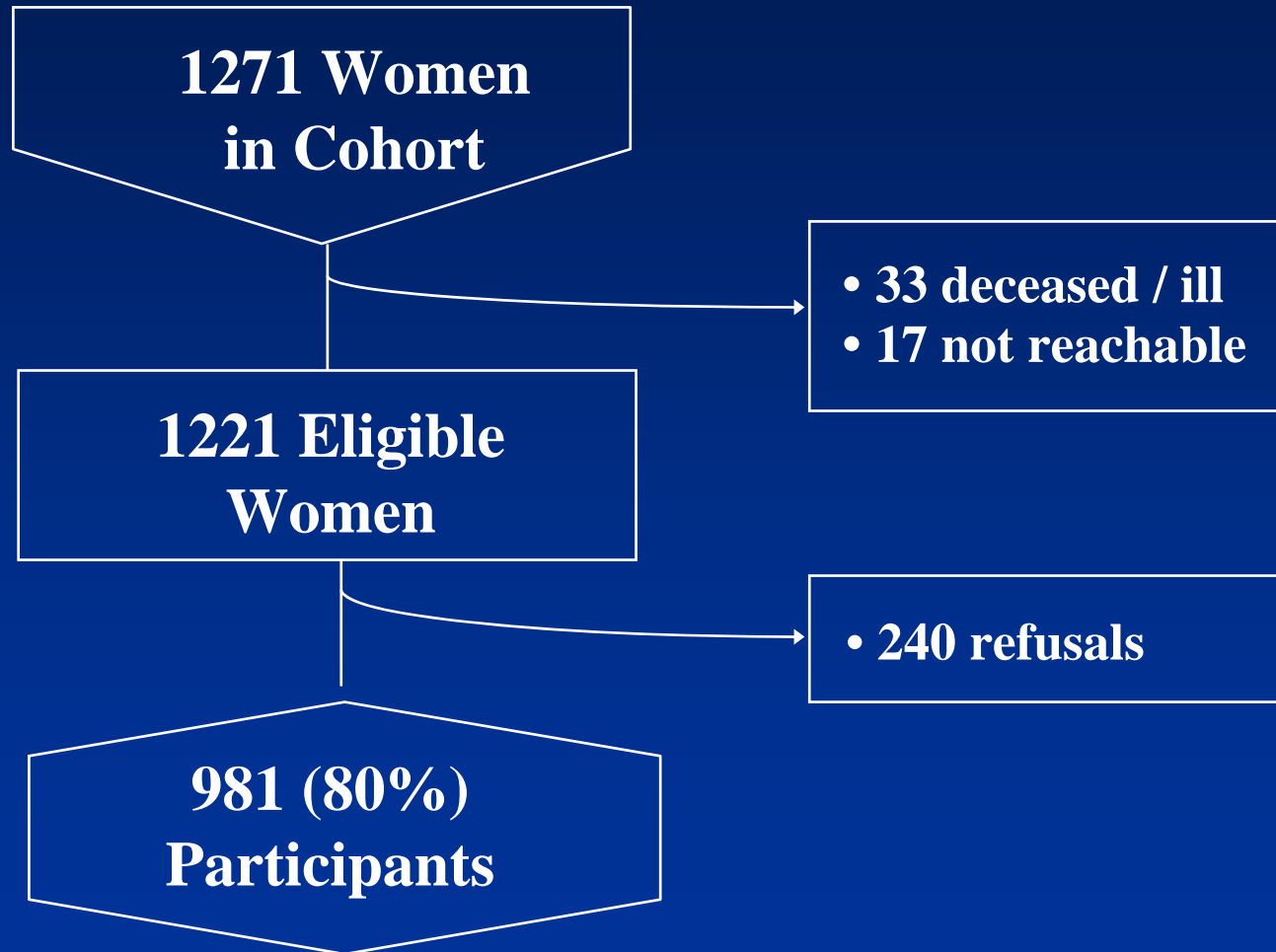
- Birth Outcomes*
- Age of Menarche*
- Menstrual Cycle*
- Age of Menopause*
- Endometriosis*
- Breast Cancer*
- Uterine Leiomyoma
- Ovarian Function/Hormones
- Benign Breast Disease
- Fertility and Time to Conception

Seveso Women's Health Study: Eligibility Criteria

Women who:

- **Were 0 - 40 years old in 1976**
- **Were residents of Zones A or B in 1976**
- **Had adequate stored serum collected between 1976 and 1980**

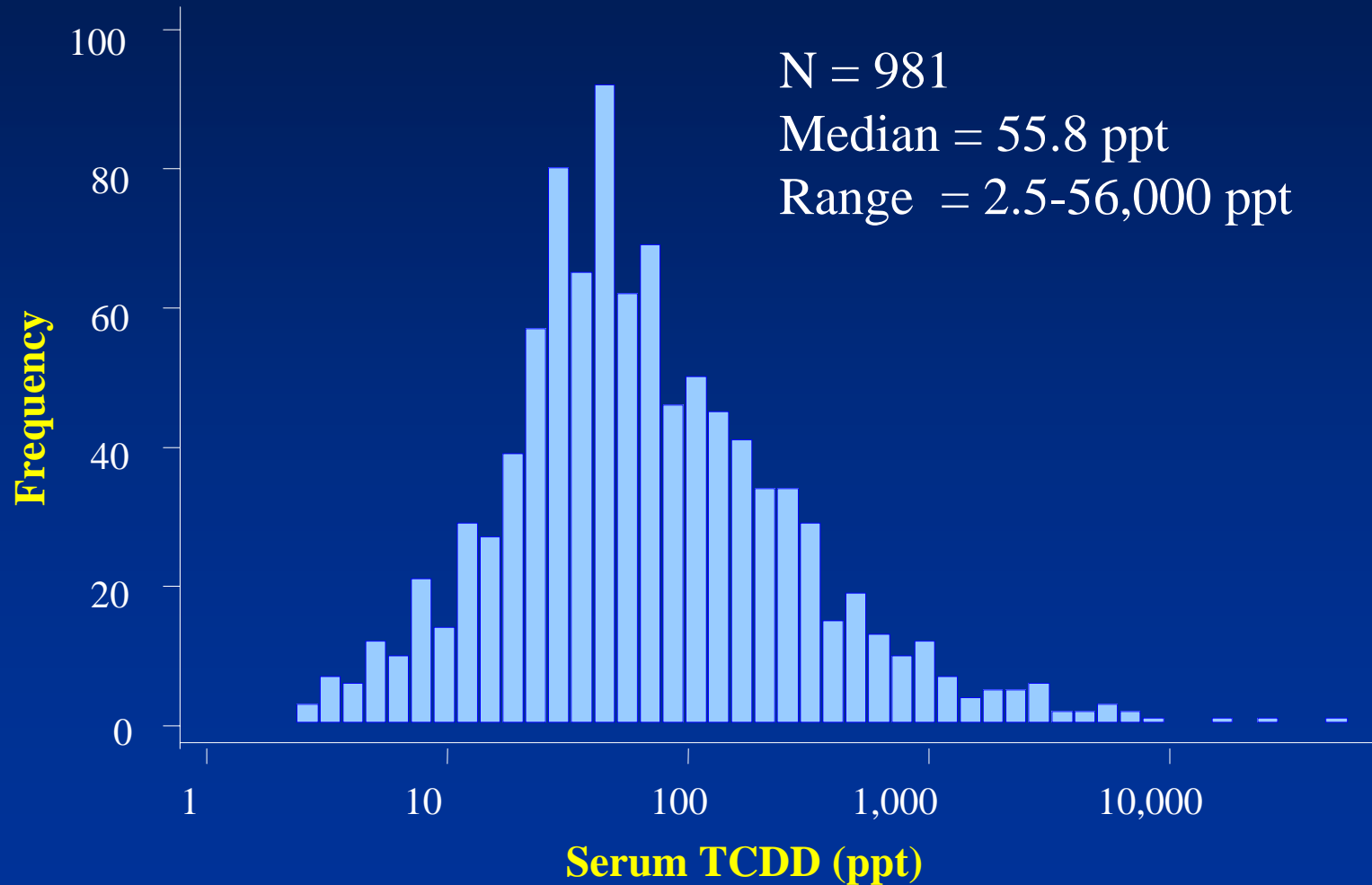
Participation Statistics



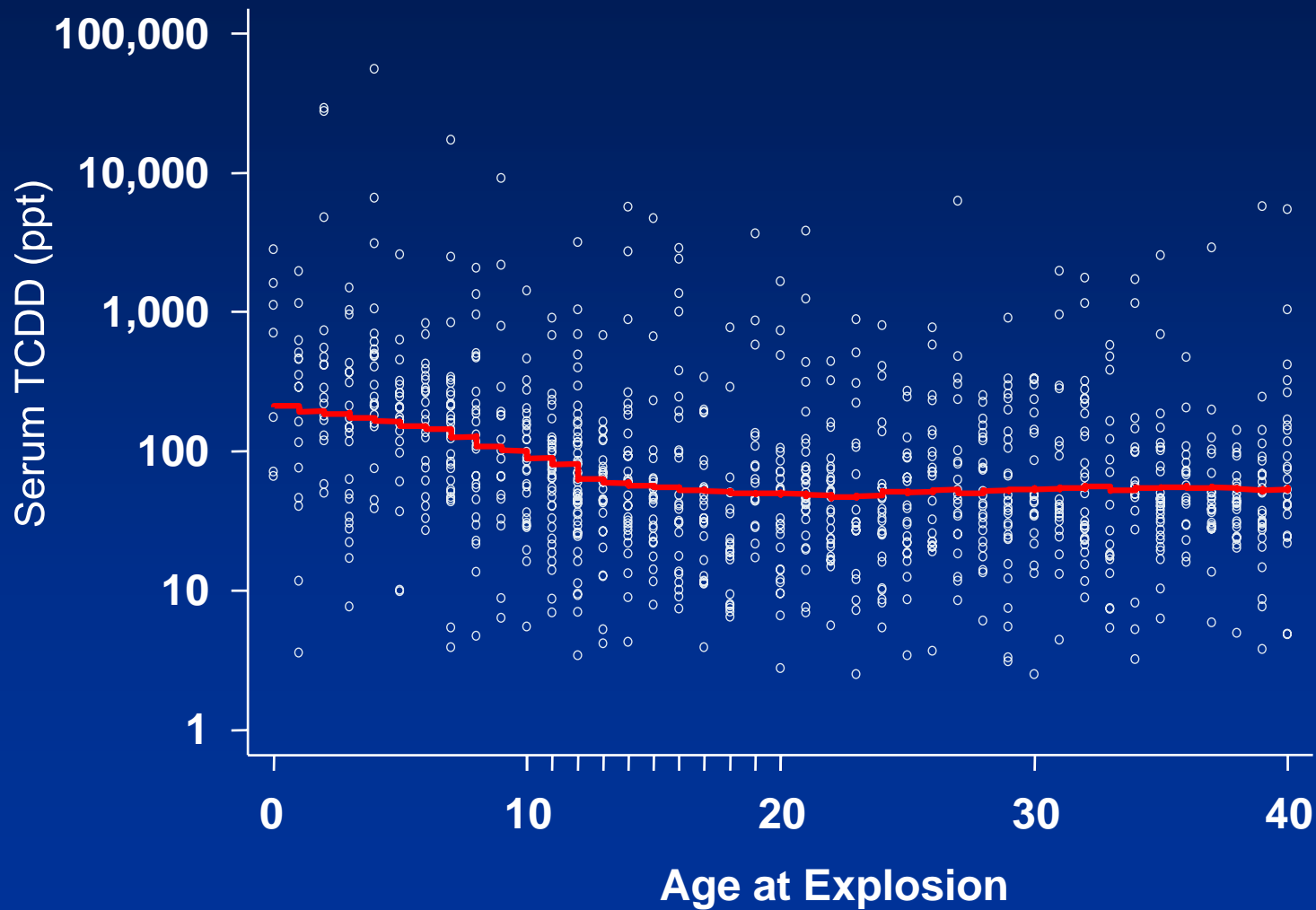
Data Collection

- **Personal Interview**
- **Blood Sample**
- **Gynecologic Examination**
- **Transvaginal Ultrasound**
- **Daily Menstrual Diary (3 cycles)**
- **Medical Records**
- **Laparoscopy if indicated**

Distribution of 1976 TCDD Serum Levels



TCDD by Age at Explosion

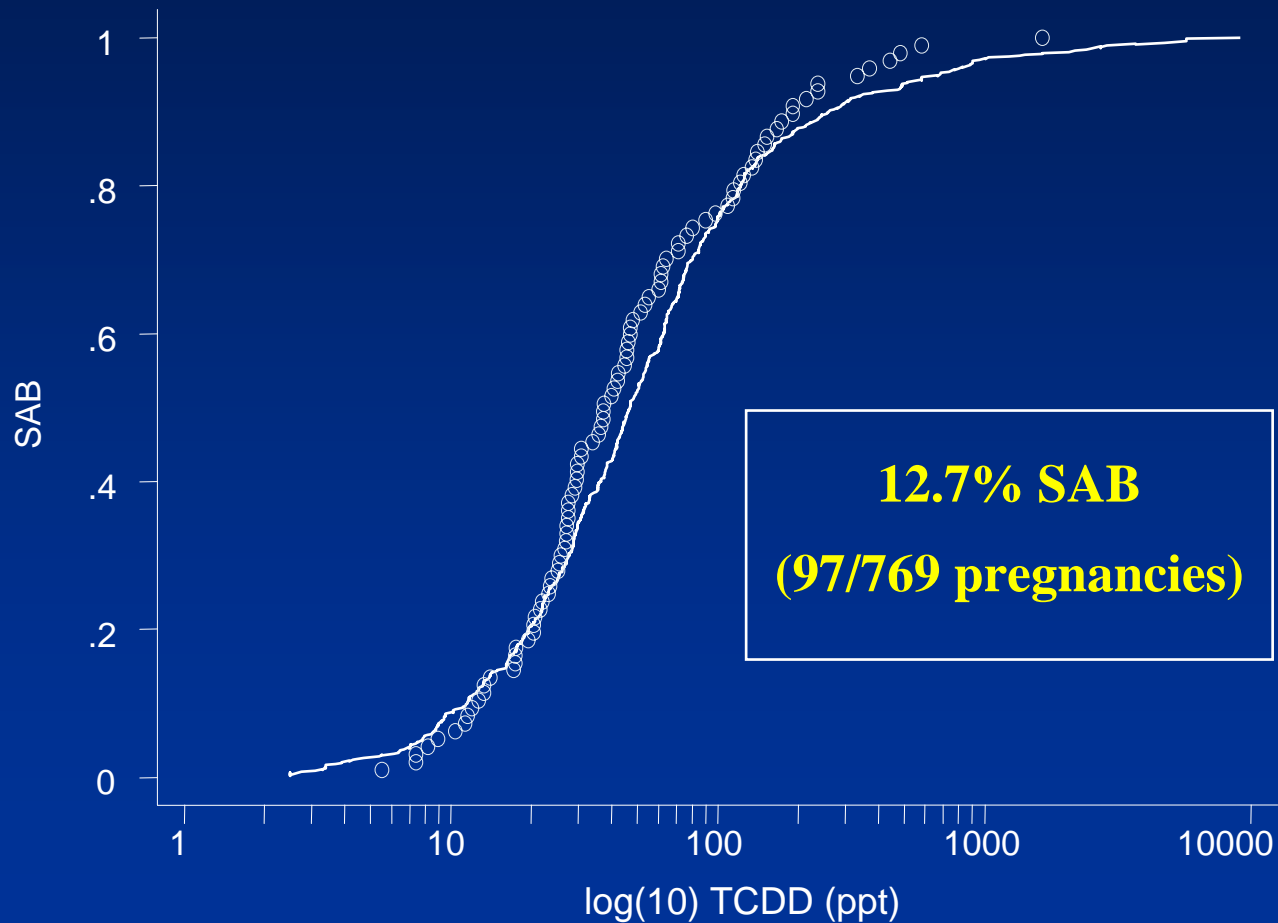


1976 background TEQ levels (ppt) in female residents of non-ABR, ages 0-40

Congener	Mean (SD)*	Range
TCDD	20.2 (12.9)	8.7 - 47.6
Other PCDDs / PCDFs / PCBs	80.2 (18.9)	52.8 - 117.4
Total TEQ	100.4 (17.7)	92.3 - 126.1

* Mean (SD) of 9 pools

Birth Outcomes: SAB



Birth Defects

(n=672 pregnancies)

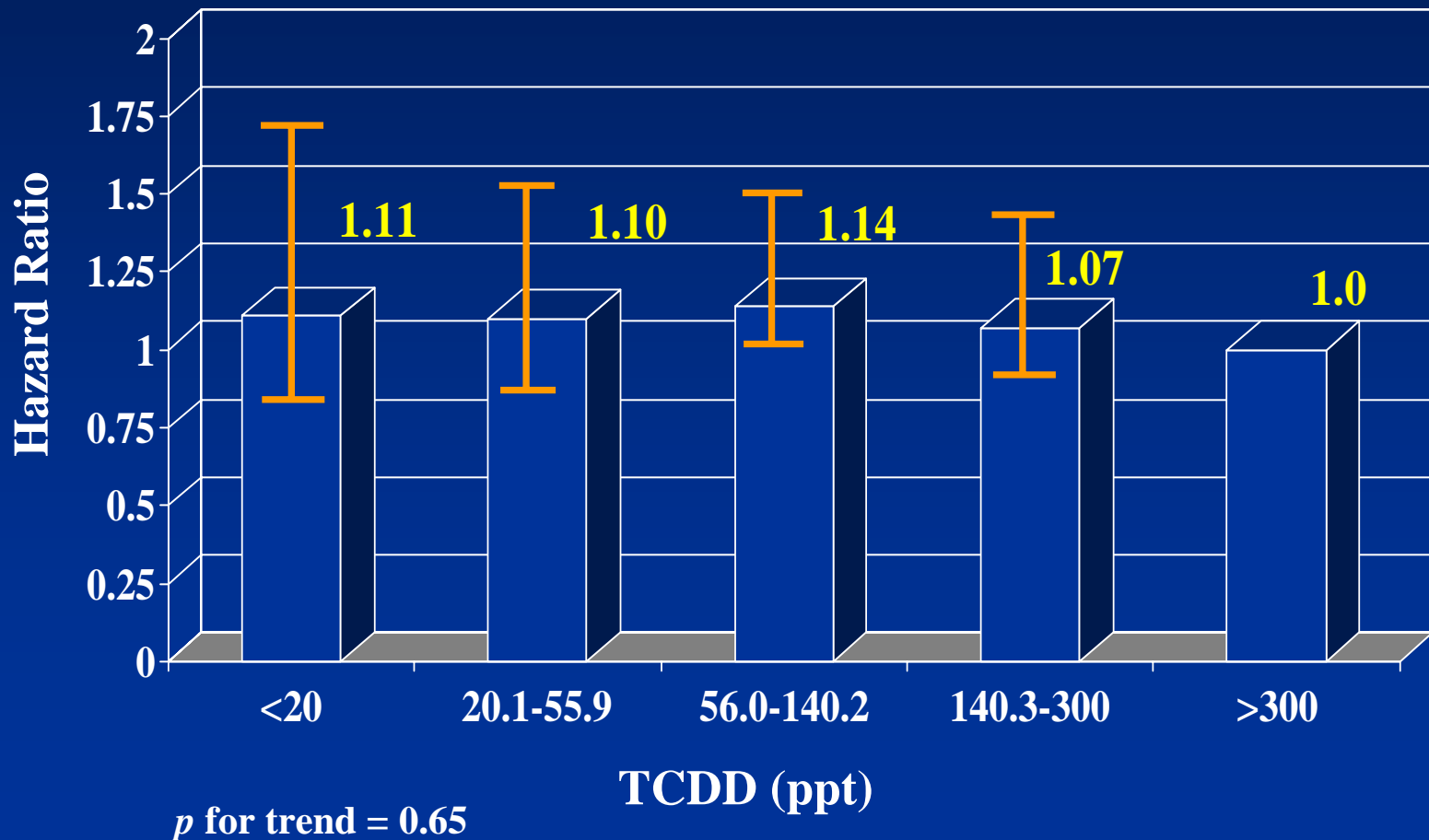
Birth Defect	Observed Frequency in Seveso	Expected Frequency in NE Italy	Serum TCDD level (ppt)
Anencephaly	1	0.02	19.5
Cleft lip	1	0.33	29.9
Hypospadias	2	0.26	74.7 61.2
Molar Pregnancy	1		61.1

Birth Outcomes: Birthweight / SGA

<u>Pregnancies</u>	<u>Years</u>	<u>N</u>	<u>Birthweight (g)</u> <u>β^* (95% C.I.)</u>	<u>SGA</u> <u>aOR* (95% C.I.)</u>
All eligible	1976-1998	608	-4 (-68, 60)	1.2 (0.8, 1.8)
<u>1st eligible</u>	<u>1976-1984</u>	<u>221</u>	<u>-89 (-203, 25)</u>	<u>1.8 (0.7, 4.3)</u>

* Change in β / O.R. per 10-fold increase in serum TCDD

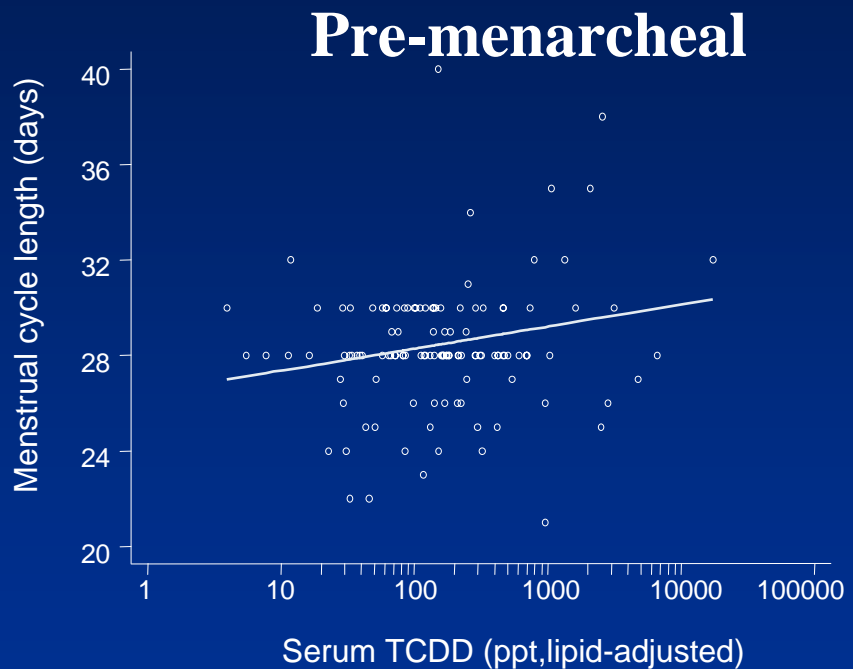
Cox PH Results: Risk of Earlier Menarche by TCDD Category among Premenarcheal Women (n=282)



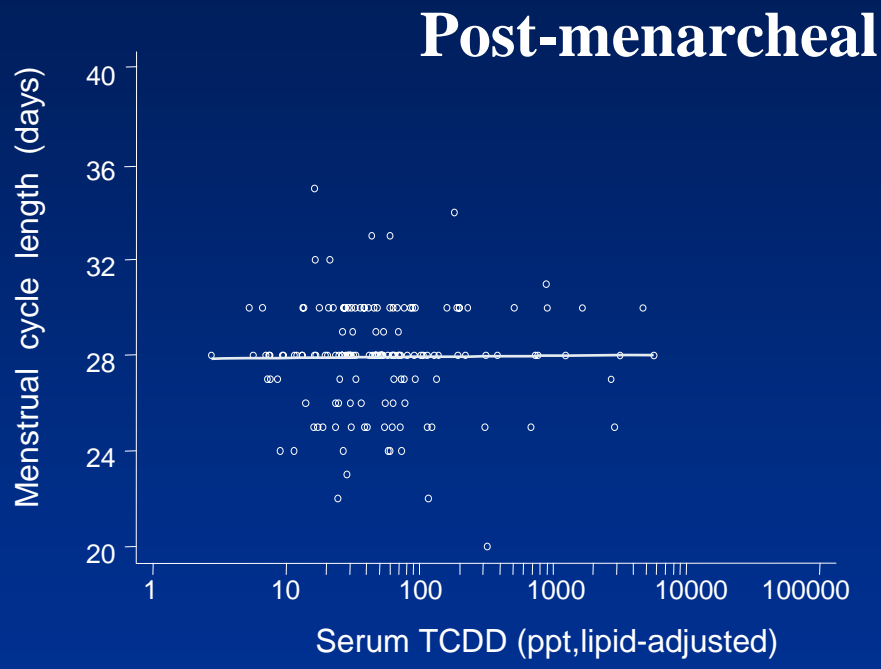
Cox PH Results: Risk of Earlier Menarche with Continuous $\text{Log}_{10}\text{TCDD}$

Sample	n	Hazard Ratio (95% C.I.)	<i>p</i> -value
Premenarcheal at explosion	282	0.95 (0.83 – 1.09)	0.46
< 8 years at explosion	158	1.08 (0.89 – 1.30)	0.71
< 5 years at explosion	84	1.20 (0.98 – 1.60)	0.07

TCDD vs Cycle Length by Menarcheal Status (n=301)



β (95% C.I.) = 0.93 (-0.01, 1.86)



β (95% C.I.) = -0.03 (-0.61, 0.54)

p-value for interaction = 0.08

No association between TCDD and:

- **Length of flow (days)**
- **Regular vs. irregular cycle length**
- **Heaviness of flow (scanty, moderate, heavy)**

Serum TCDD Levels by Ovulation Status

*Unpublished results
presented:*

*Not for online
publication*

Risk of Ovulation with TCDD Exposure

*Unpublished results
presented:*

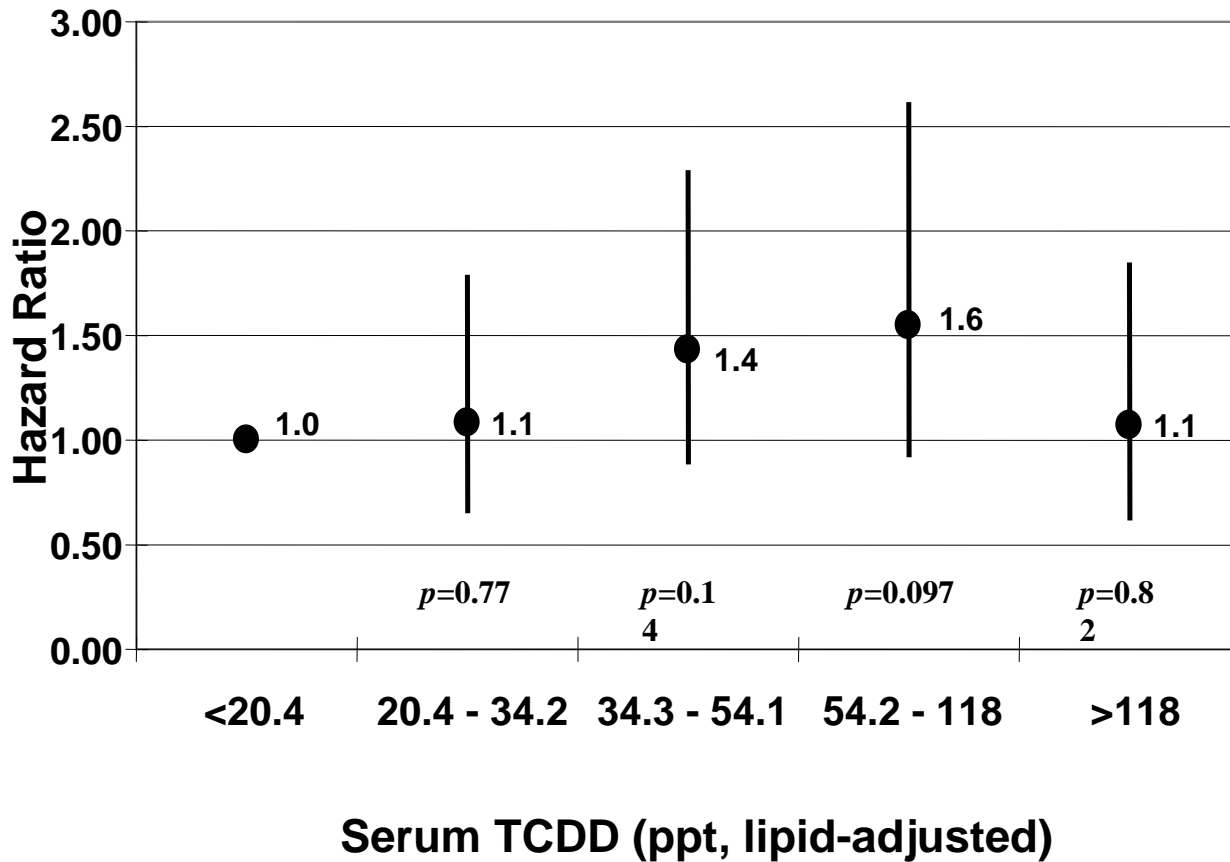
*Not for online
publication*

Change in hormone levels with TCDD exposure

*Unpublished results
presented:*

*Not for online
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Risk of Onset of Natural Menopause by TCDD Quintiles: Adjusted* Hazard Ratios (95% CI) (n=616)



Test for trend

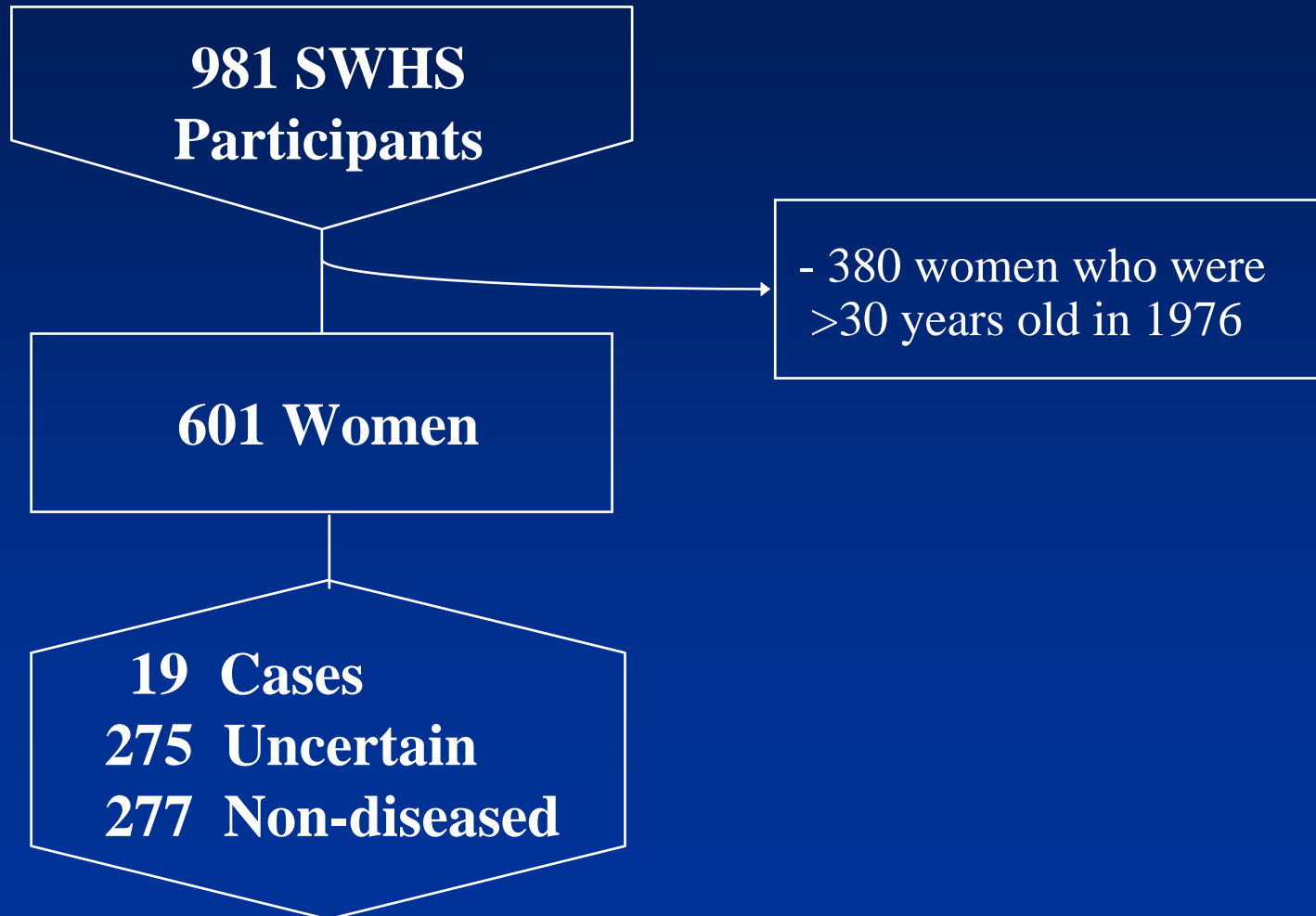
quintiles 1-5: $p = 0.44$

quintiles 1-4: $p = 0.04$

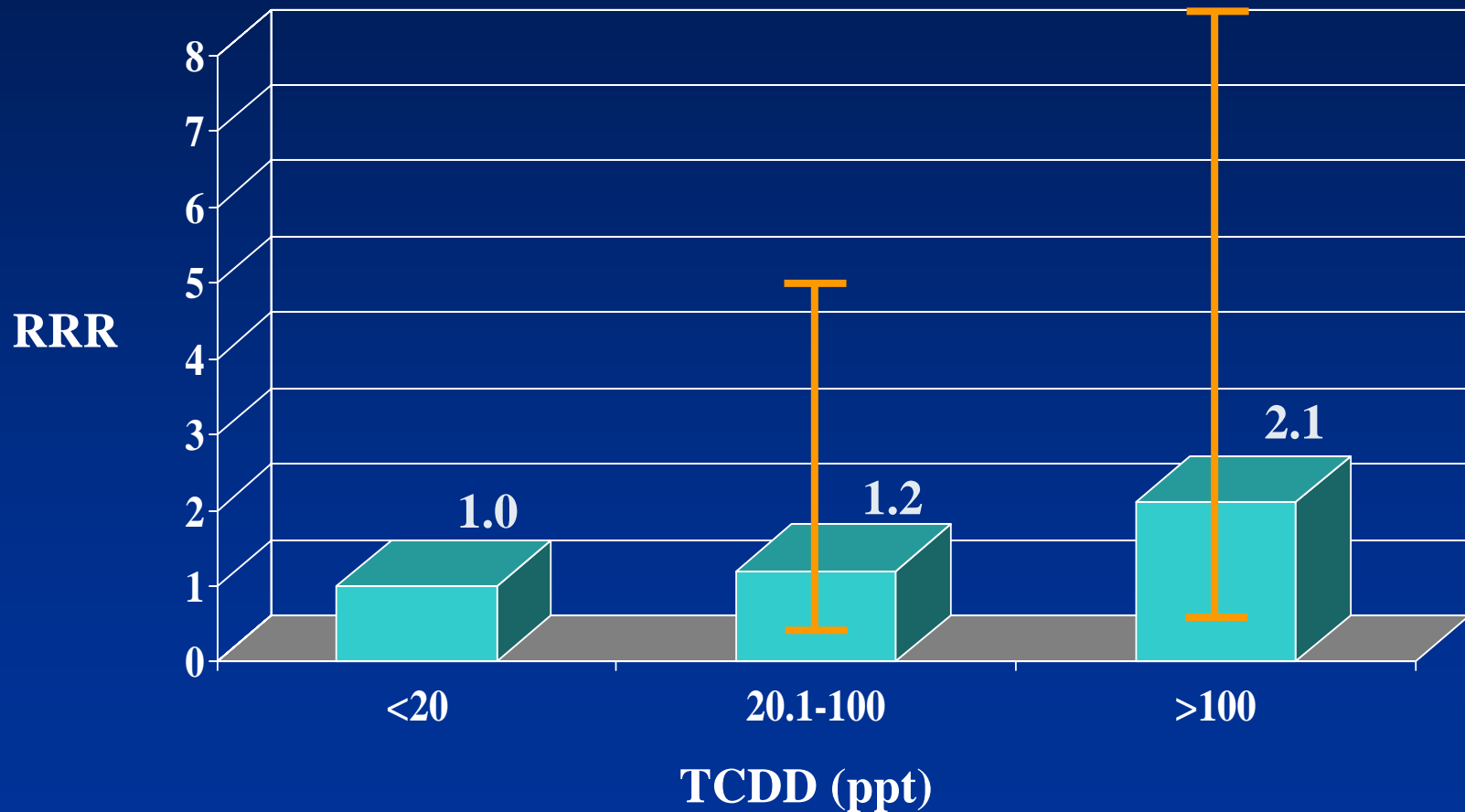
*Adjusted for education, parity, OC use, and other medical conditions.

Eskenazi et al., EHP 2005

Endometriosis Analysis: Participants

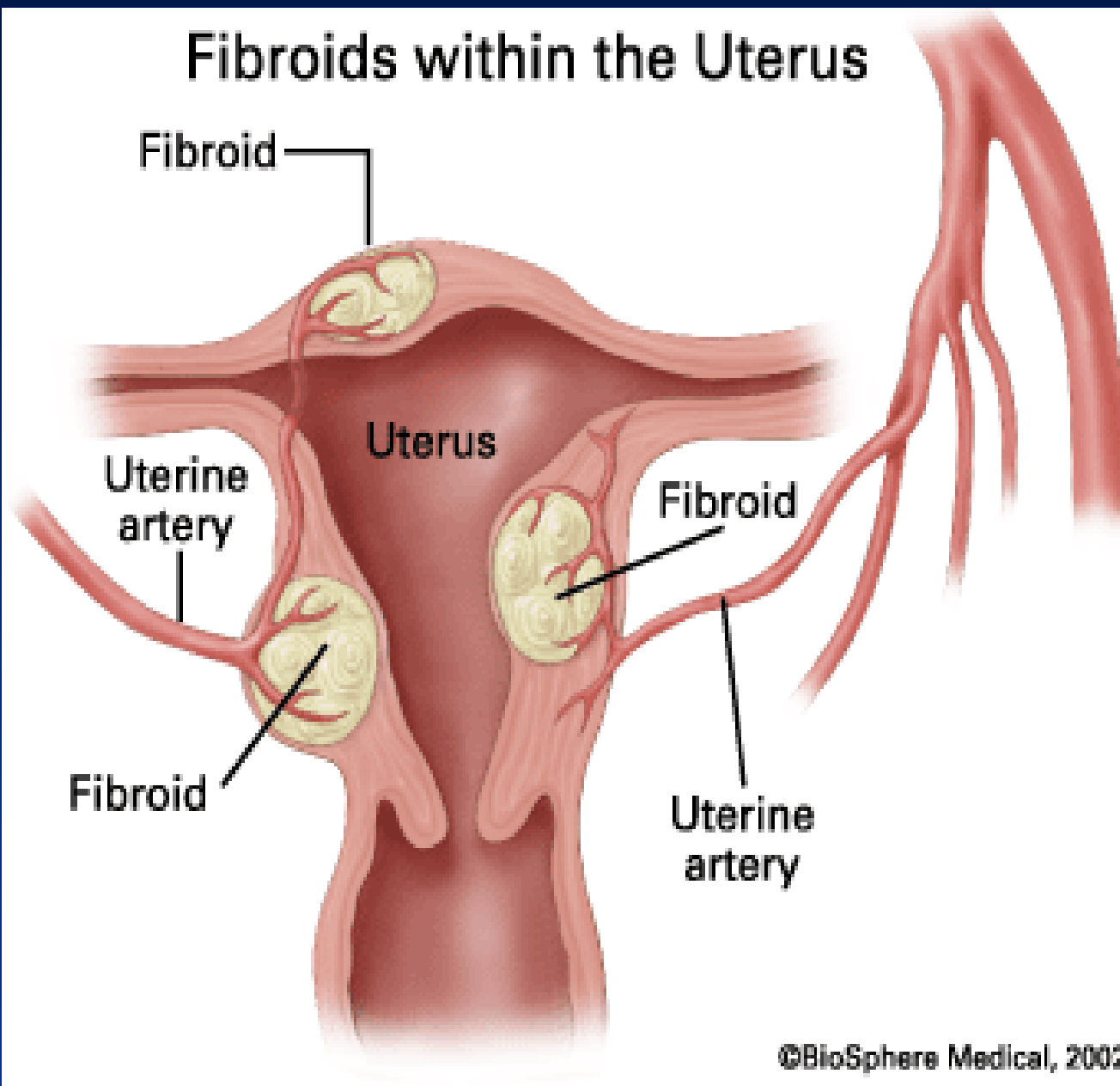


Age-adjusted Relative Risk Ratio of TCDD Exposure and Endometriosis



p for trend = 0.25

Fibroids within the Uterus

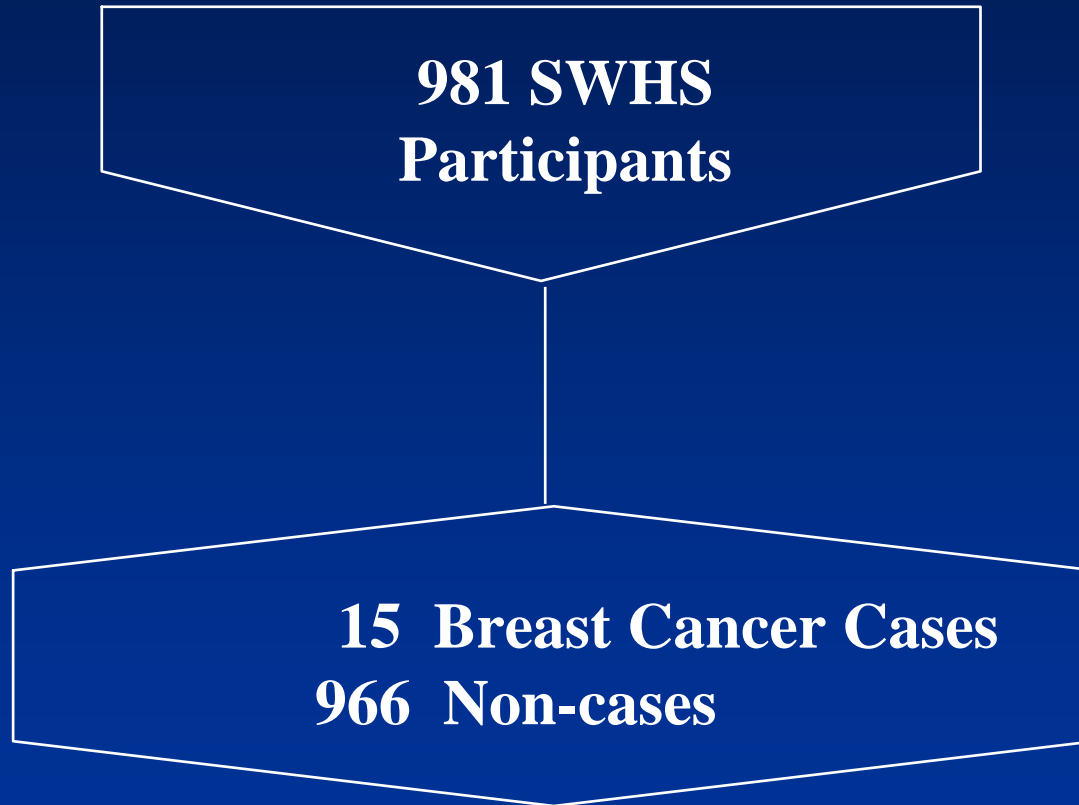


**Smoothed estimate of relationship between
 \log_{10} TCDD and log hazard of fibroids onset,
adjusted for age**

*Unpublished results
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Breast Cancer Analysis: Participants



Relation of Breast Cancer Incidence with continuous TCDD

TCDD	Cases / Total	Hazard Ratio (95% C.I.)
\log_{10} TCDD	15 / 981	2.1 (1.0 – 4.5)

(test for trend, $p = 0.05$)

Summary

*Unpublished results
presented:*

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Considerations

- Underestimate of effects possible due to potentially high background TEQ
- Highest exposed women were the youngest at follow-up
- Animal evidence suggests *in utero* exposure may be the more sensitive route for the developing fetus.
- It is possible the effects of TCDD are yet to be observed.

Continued follow-up of the SWHS cohort and their offspring is needed.