

# Environmental and behavioral risk factors for subfertility:

*Findings from web-based preconception cohort studies*



Lauren A. Wise, Sc.D.

Professor, Department of Epidemiology  
Boston University School of Public Health  
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# Overview

- Trends in Fertility
- Prospective time-to-pregnancy studies in Denmark
  - 1) *Snart-Gravid*: “Soon Pregnant” Study (2007-2011)
  - 2) *Snart-Foraeldre*: “Soon Parents” Study (8/2011-present)
- Prospective time-to-pregnancy study in North America
  - 3) *PRESTO*: Pregnancy Study Online (6/2013-present)
- Methodologic and substantive findings

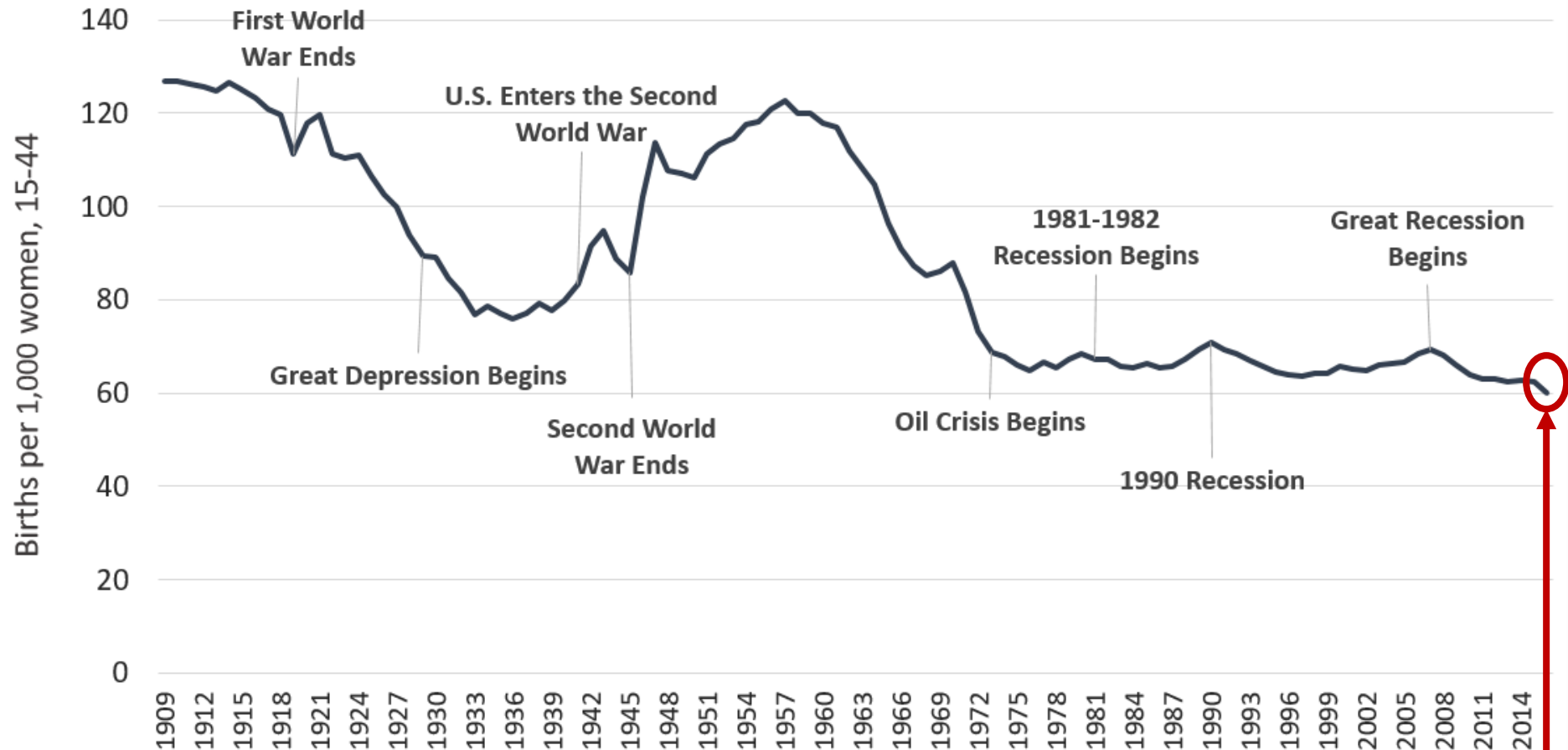


# Infertility

- About 10-15% of couples experience infertility
- Fertility rates are at an all-time low in United States
- Use of Assisted Reproductive Technology (ART) is increasing
- ART is associated with \$5 billion in annual health care costs, psychological and financial hardship among couples, and adverse pregnancy and birth outcomes

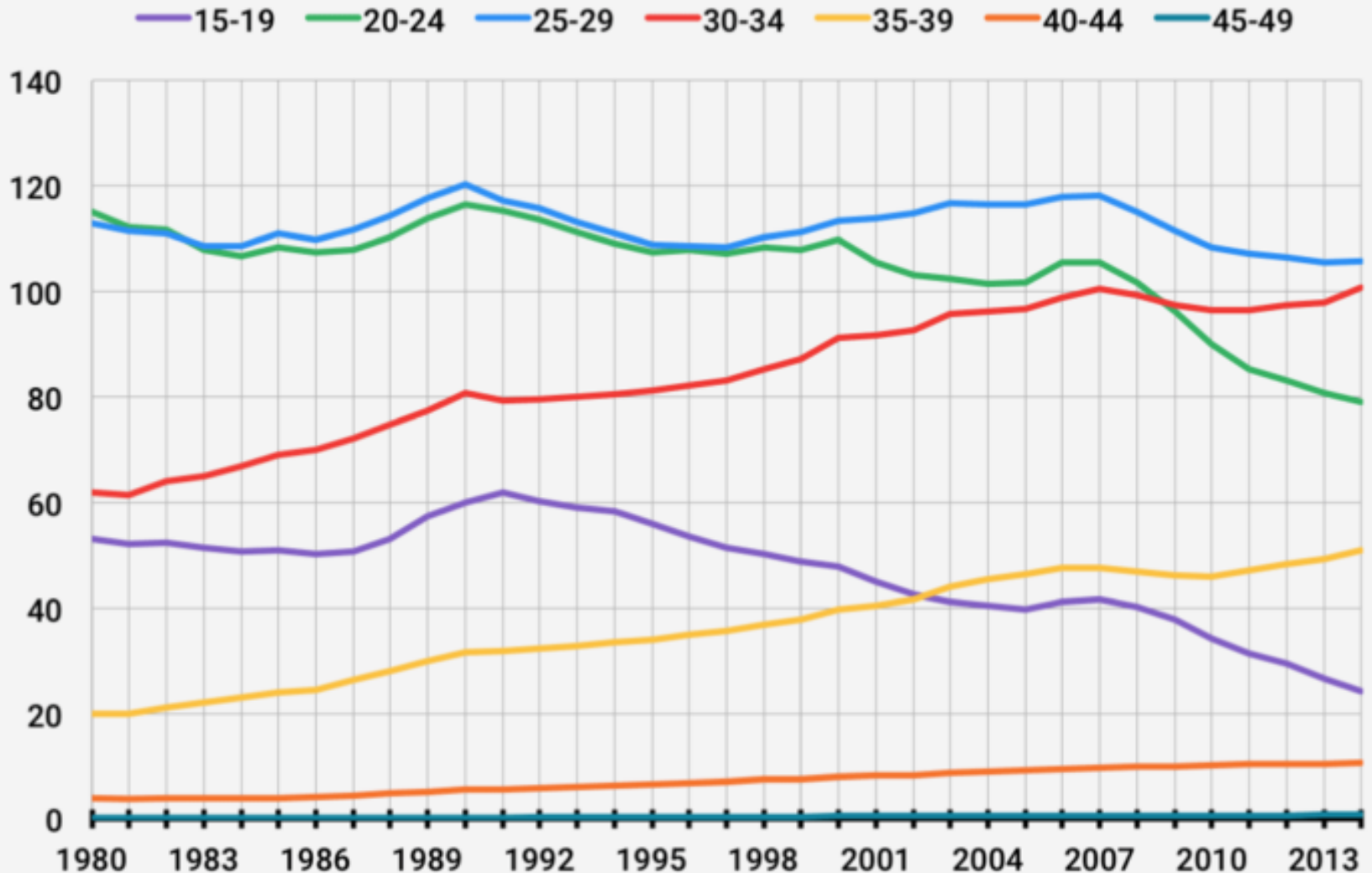


# Fertility Rate: United States, 1909-2016



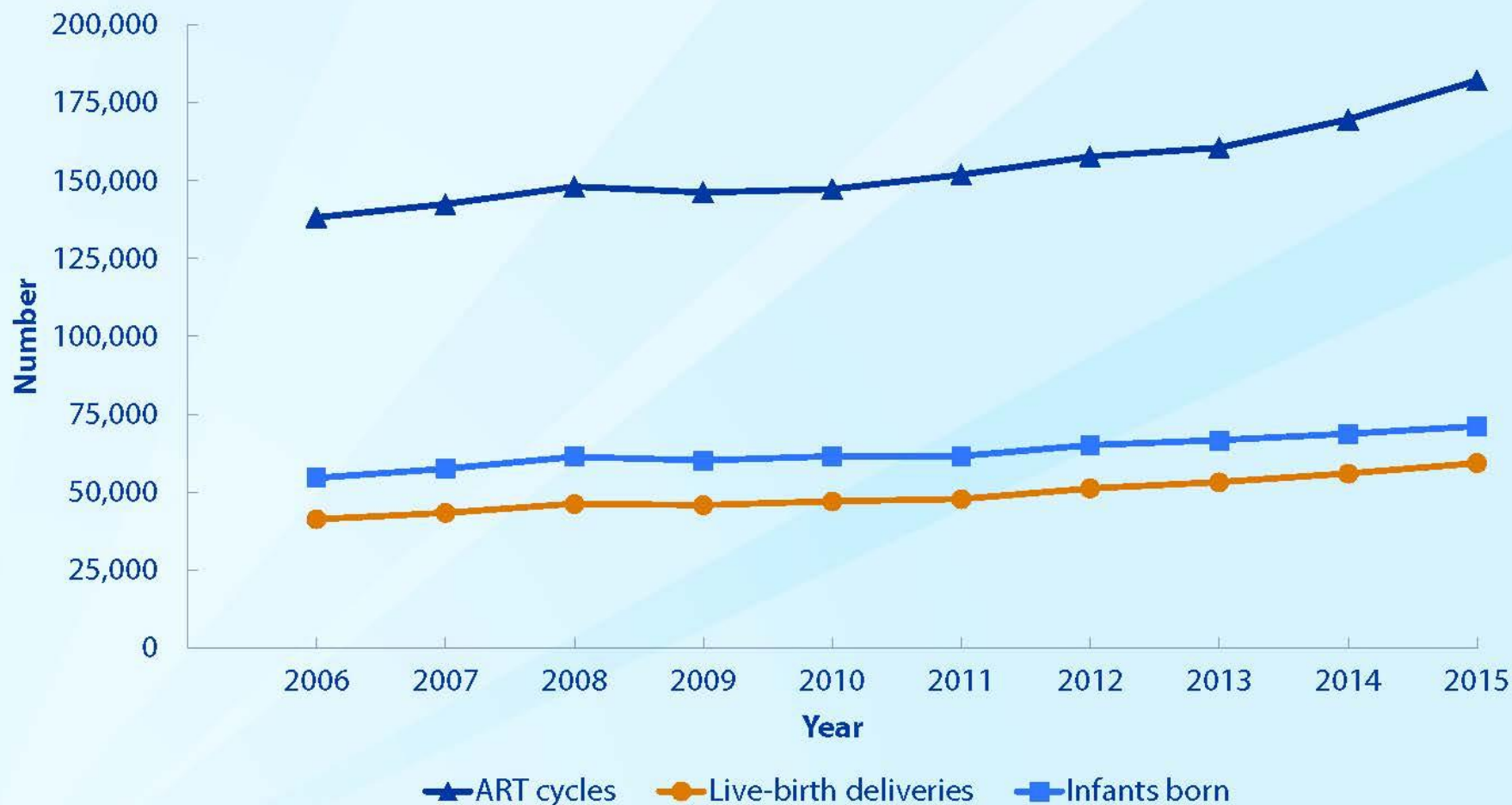
In 2016: fertility rate in US was the lowest it has ever been (60.2 births/1,000 women aged 15-44), down 1% from 2015.

# Birth rates by mother's age



SOURCE: National Vital Statistics Reports, "Births: Final data for 2013" and "Births: Preliminary data for 2014"

## Numbers of ART Cycles Performed, Live-Birth Deliveries, and Infants Born Using ART, 2006–2015



# Fertility Measures and Definitions

- Fecundity
  - Biologic capacity to reproduce, irrespective of pregnancy intention
- Fertility
  - Demonstrated fecundity
  - Term used most frequently by demographers, e.g. 'total fertility rate'
- Fecundability
  - Probability of conceiving in given time interval (e.g., menstrual cycle), with regular unprotected intercourse. Measure for study of fecundity.



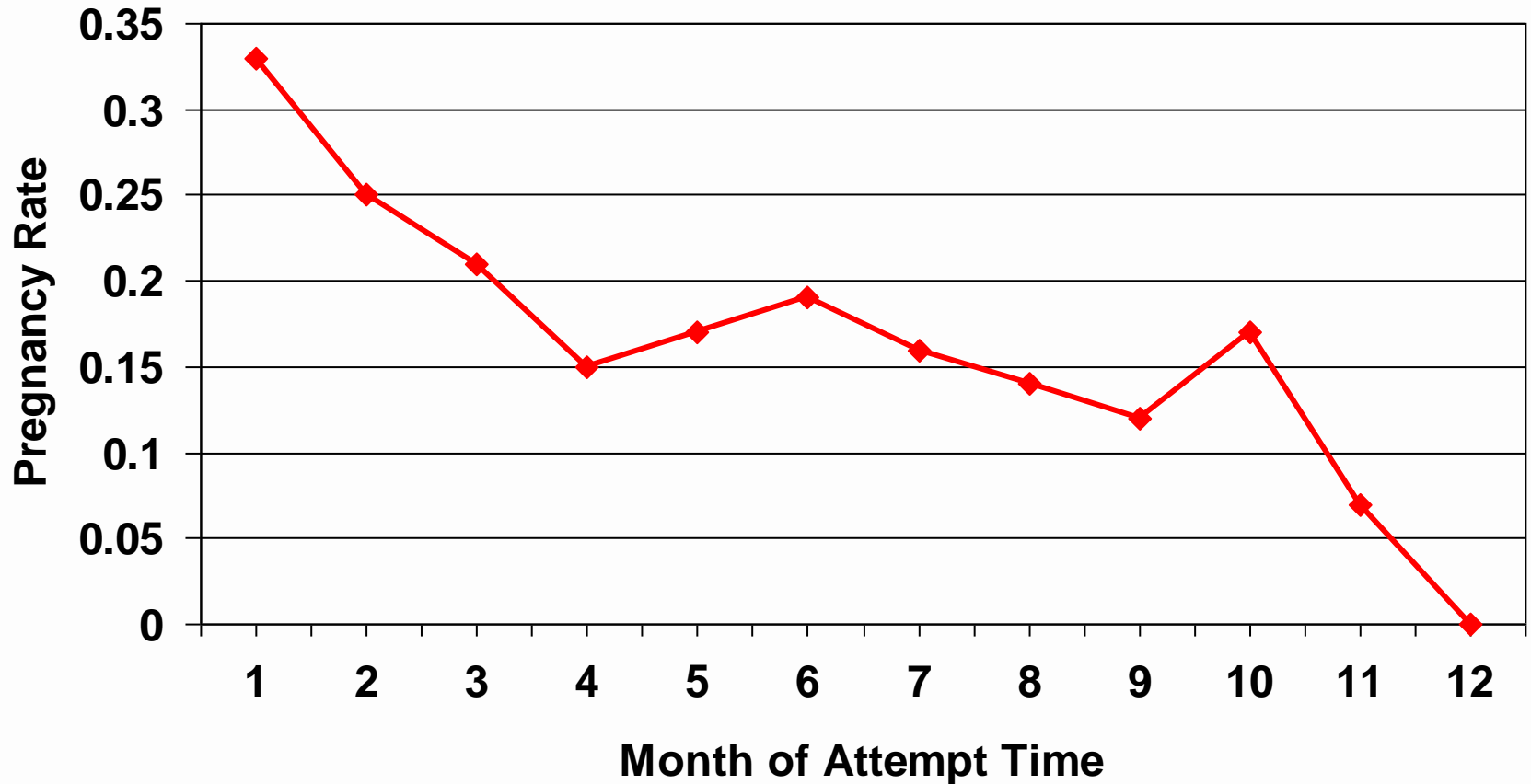
# Fecundability

- Probability: ranging from 0 to 100%
- Measured indirectly by number of menstrual cycles it takes to conceive, or **time-to-pregnancy (TTP)**
- TTP likely includes many cycles where conception occurs but there is early loss (e.g., before implantation)
- Integrated measure of all factors affecting fertility
- Function of biological processes in both male and female



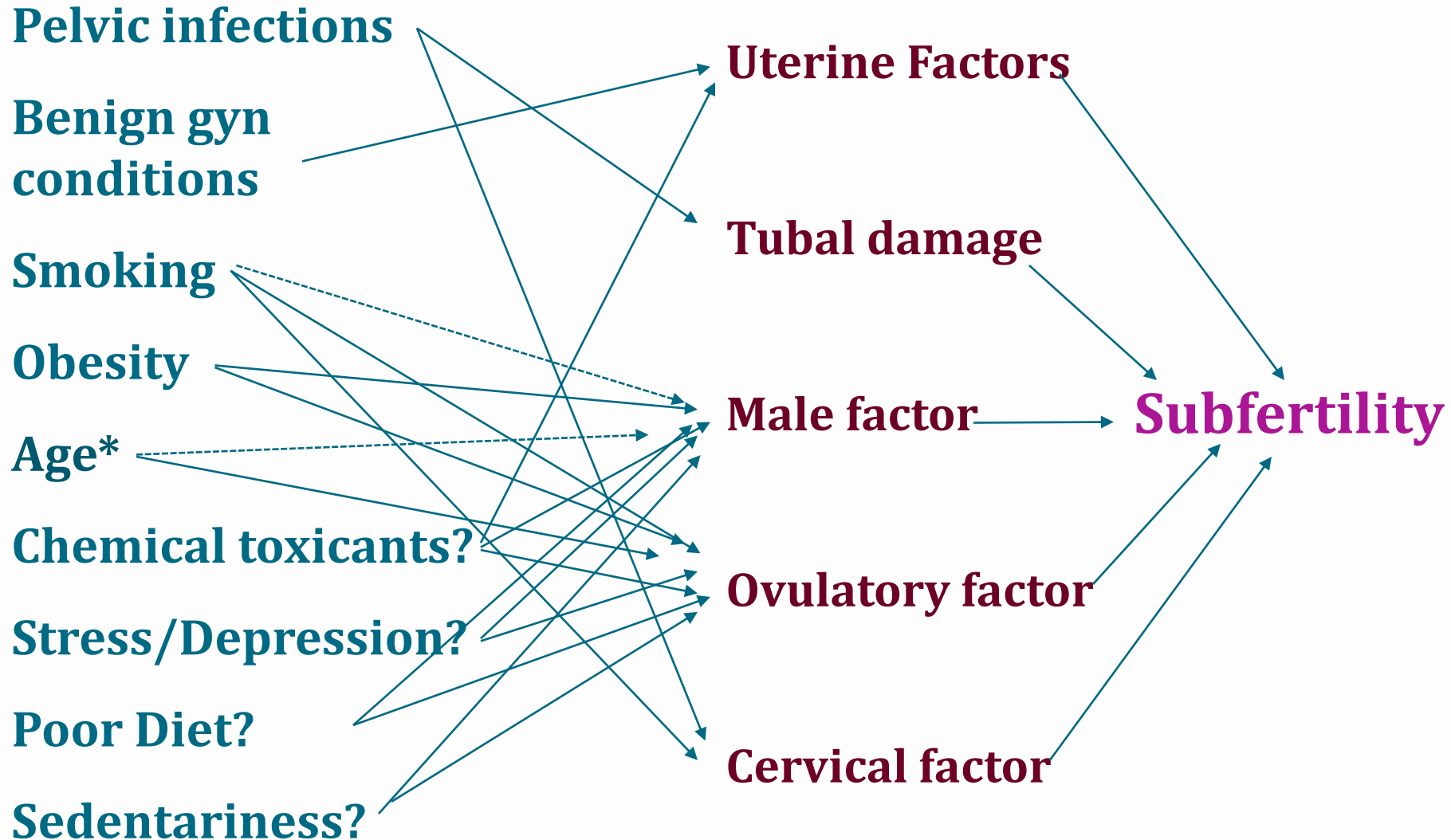


# Fecundability in a given population



Decline in fecundability seen in population over time. These data are from 611 women having IUDs removed in order to conceive. As the more fecund couples conceive and drop out of the pool of waiting couples, the sample is overrepresented by couples with lower fecundability. (Tietze et al. 1968)

# Modifiable pathways to subfertility



\* Delayed childbearing

# Time-to-pregnancy study designs

- **Retrospective**

- Sampling unit: pregnancy or live birth
  - First, most recent, vs. all
- Women/couples asked to recall TTP/exposures

- **Prospective**

- Sampling unit: pregnancy attempt
  - Women/couples discontinuing contraception
  - Women/couples actively trying to conceive

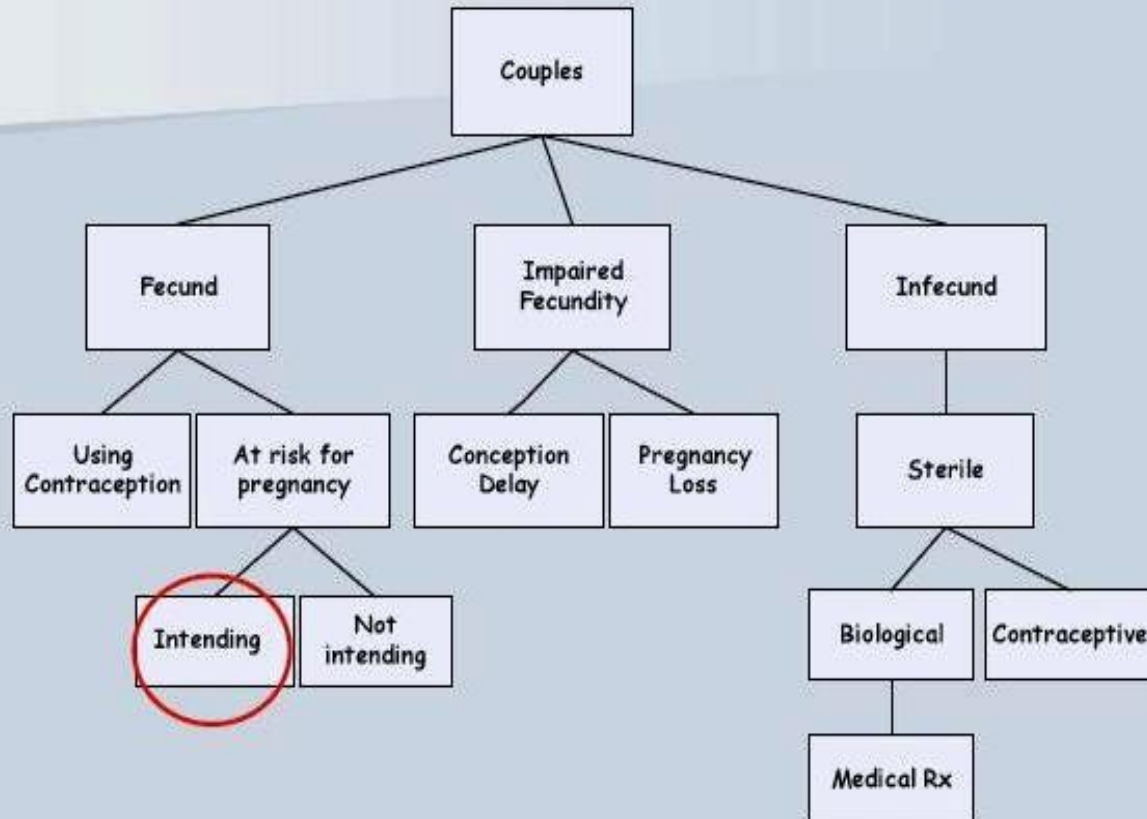
- **'Current duration approach'**

- Among those trying to conceive, ascertain length of pregnancy attempt (Slama *et al.* 2006)

If all women conceived, prospective and retrospective studies would generate equivalent data



# Population Fecundity



1-2% of reproductive age women planning or at risk for pregnancy in next few months  
(Bonde et al., 1988; Buck et al., 2004; Slama et al., 2006)

# Background: Snart-Gravid Study

- Prospective TTP study: Danish and U.S. Researchers
  - Aarhus University Hospital & Boston University School of Public Health
- Data collection
  - June 2007-August 2011 (follow-up ended in August 2012)
  - 6,033 women enrolled
- Main research questions:
  - Can internet be used for recruitment and follow-up in epidemiologic studies?
  - What are important lifestyle and behavioral determinants of TTP?



# Advantages of using the Internet?

- Cost efficiency
- Easier data collection and follow-up
- Flexibility
- Once infrastructure is set up, can collect data at low cost indefinitely
- Access to “hidden” populations
  - Couples planning a pregnancy
  - Individuals with HIV/AIDS



# Advantages of using the Internet?

- Some studies suggest equal or better data validity
  - Participants *may* be more truthful
  - Lower % missing data (pop-ups for missed questions)
  - Built-in data quality checks (validation rules)
  - Skip patterns → shorter survey → reduce “participant fatigue”
  - Can glean useful information from “break off”



# Snart-Gravid: study design

## Prospective cohort design

- Baseline questionnaire (randomized short vs. long)
- Follow-up questionnaire every 2 months for 12 months or until pregnancy occurs
- Early pregnancy questionnaire

## Eligibility requirements

- Danish women age 18-40 years
- Attempting to conceive
- Not using fertility treatments
- Willing to provide CPR number





# Baseline questionnaire

- Demographics
- Menstrual, contraceptive and reproductive history
- Frequency of intercourse
- Medical history
- BMI, waist & hip circumferences, physical activity
- Alcohol, caffeine, vitamins, medications
- Smoking (self, partner, *in utero*, passive)
- Perinatal factors: birth weight and gestational age
- Occupation



# Follow-up & early pregnancy questionnaires

- Follow-up
  - Pregnant?
  - Changes in lifestyle factors
- Early pregnancy
  - Method of pregnancy confirmation
  - Due date
  - Weight gain
  - Nausea and vomiting
  - Change in lifestyle factors since conception

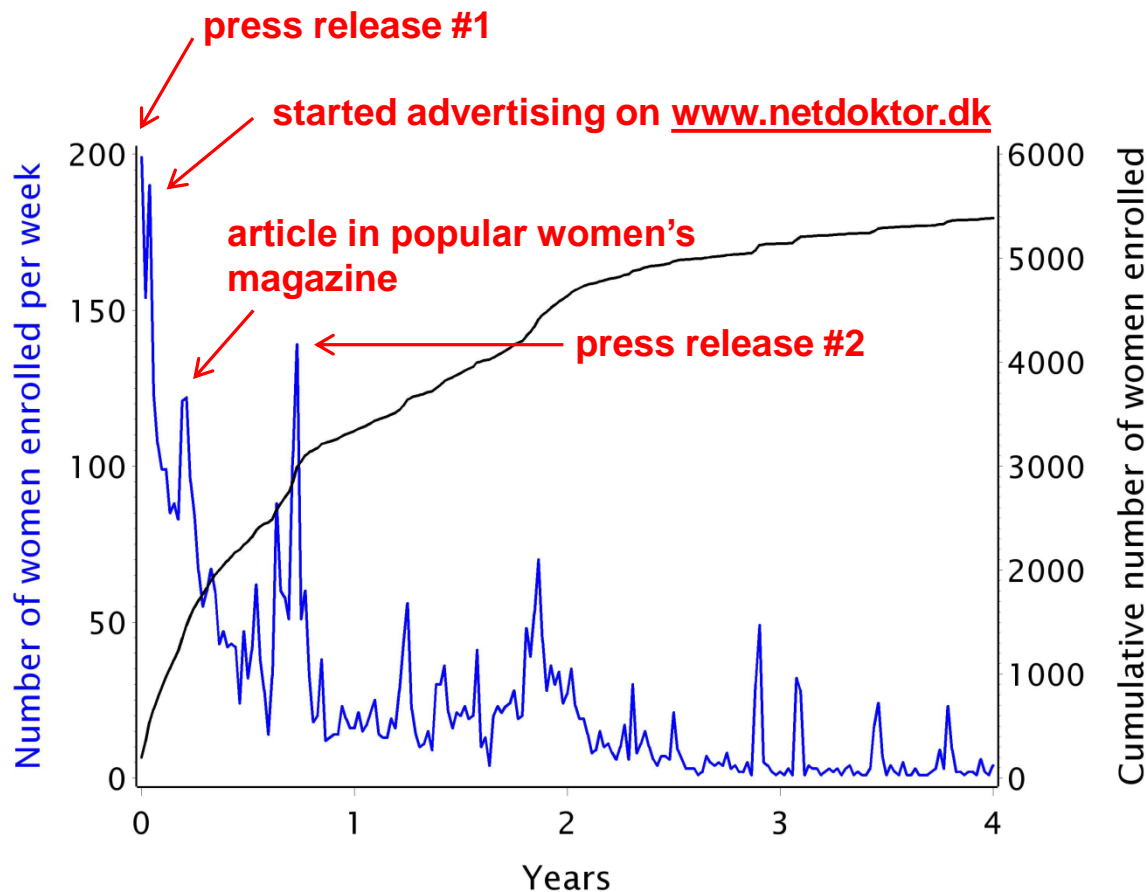


# Recruitment

- Ad on [www.netdokter.dk](http://www.netdokter.dk)
- Press releases resulting in:
  - Print articles: magazines, newspapers, on-line
  - TV and radio features
- Word of mouth
- **Target enrollment: 2,500 women**



# Recruitment



Adapted from Huybrechts K et al. *Eur J Epidemiol* 2010  
(follow-up extended through 4/12/2012)

# Follow-up

- 18% lost to follow-up at some point during year

BUT ....

- **registries** used to capture unobserved events (miscarriages or births for those lost to follow-up)

*Huybrechts K, et al. Eur J Epidemiol, 2010*



# Study costs

2008 US\$

## Study Cost Components

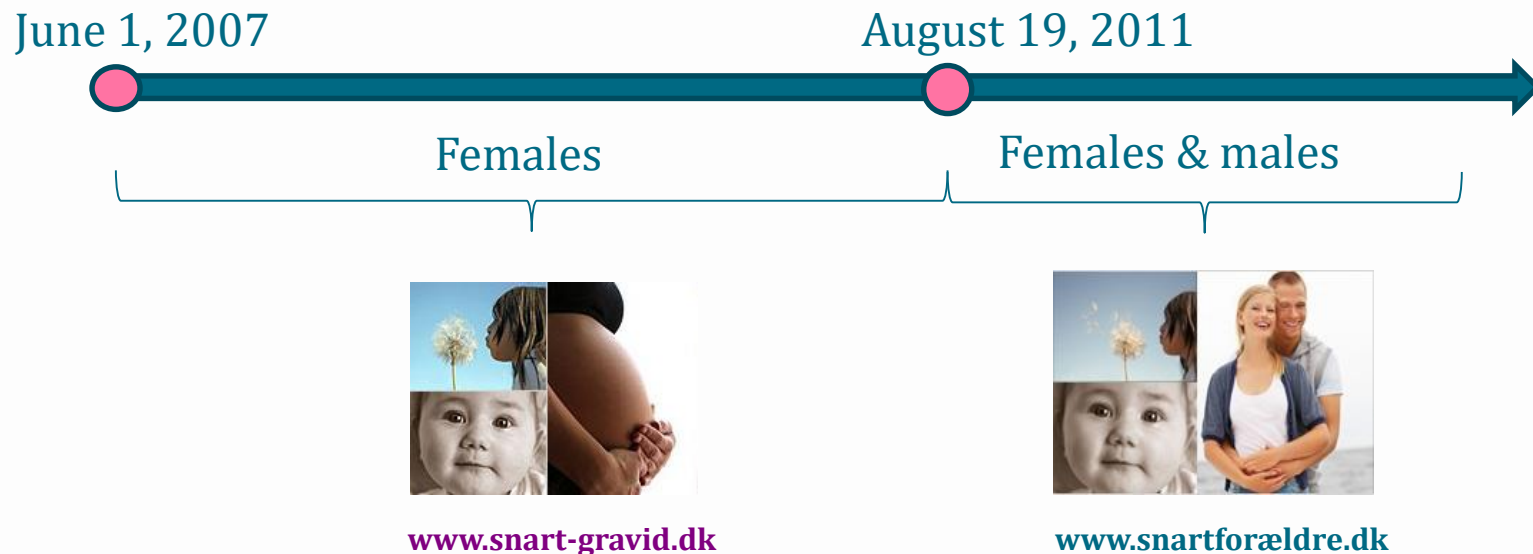
General set-up	
→ Website construction	\$34,625
→ Development e-mail reminder system	\$4,756
→ Other*	\$31,961
Subject recruitment (advertisements, media strategy)	\$40,508
Website maintenance and follow-up	\$9,850
Record linkage	\$9,512
Research personnel	\$268,287
<b>Total Cost</b>	<b>\$399,500</b>
→ Fixed	\$178,281
→ Variable	\$221,219
<b>Per subject cost</b>	<b>\$160</b>

Estimated per subject cost for conventional study design: **\$322**



# Snart Forældre Study

- Five-year R01 study funded by NICHD (PI: Hatch) to continue and expand Snart-Gravid Study ( $\geq 2011$ )
- General objectives:
  - Enroll additional women and their male partners over 3 years
  - Evaluate diet, exercise, medication use vs. TTP and miscarriage



# Internet-Based Time-to-Pregnancy Study in North America (June 2013 to present)



**PRESTO**

**Boston University Pregnancy Study Online**



Study website: [presto.bu.edu](http://presto.bu.edu)





# Study Design



- Internet-based preconception cohort studies of lifestyle, dietary, and medical risk factors for subfertility
- Eligibility requirements:

<b>Snart Gravid/Snart Forældre (2007-present)</b>	<b>PRESTO (2013-present)</b>
Resident of Denmark	Resident of U.S. or Canada
Age 18-45 years	Age 21-45 years
Willing to provide CPR number*	Willing to allow birth registry linkage
In stable relationship with male partner	
Attempting to conceive	
Not using fertility treatments	

*\*Permits linkage to all registries in Denmark*

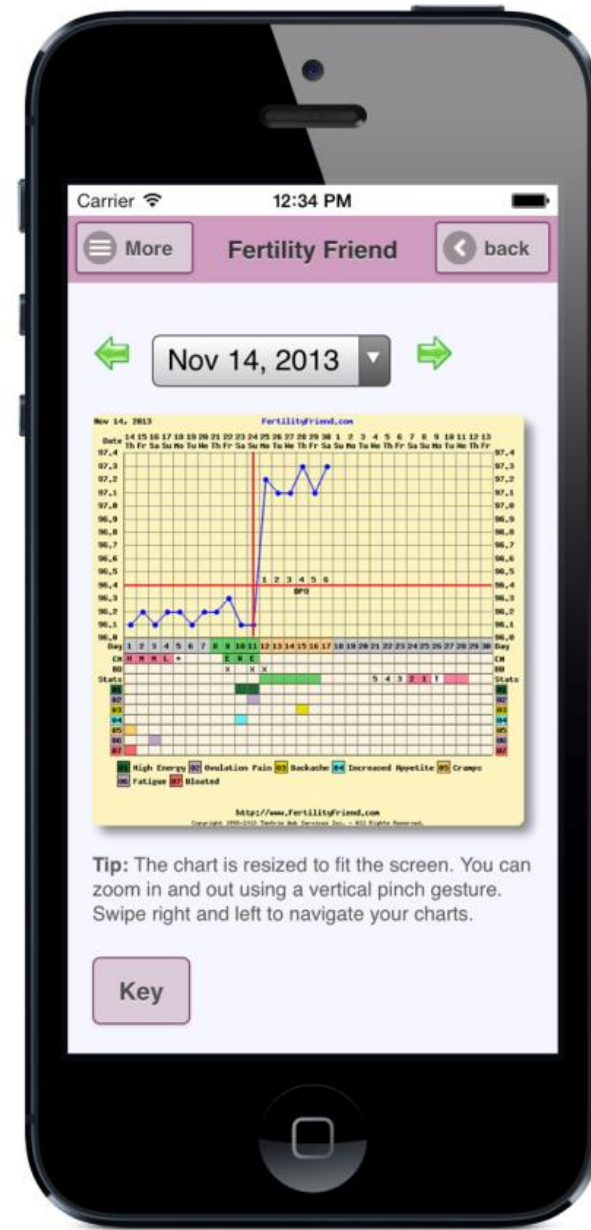
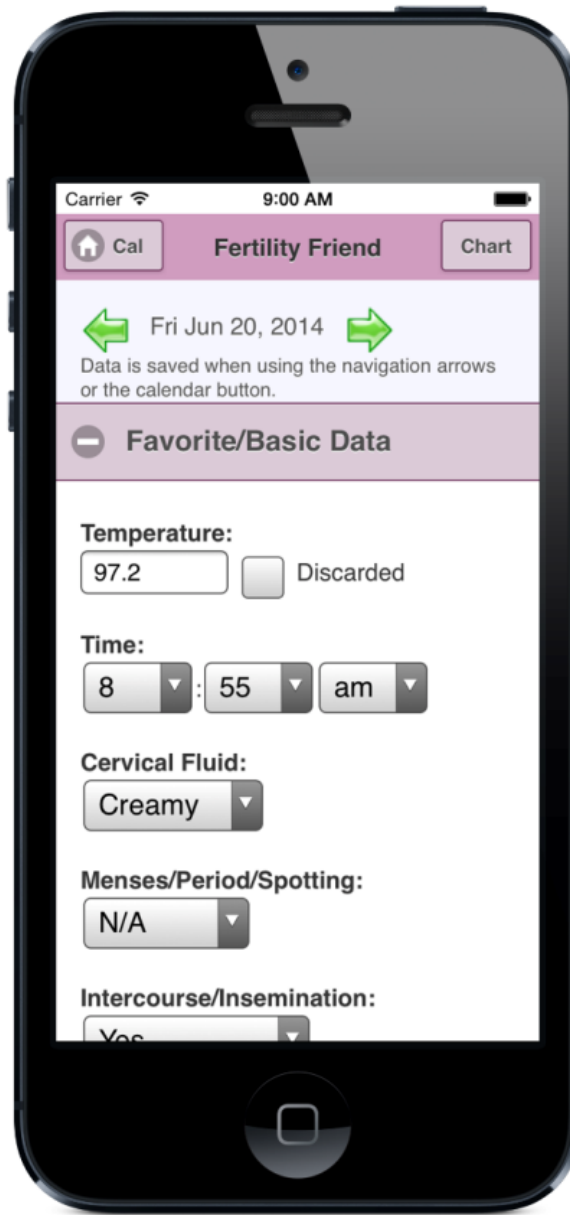
# PRESTO: Online Data Collection



- Screener questionnaire
- Baseline questionnaire
  - Randomization (50%) to [FertilityFriend.com](http://FertilityFriend.com)
  - Optional: male baseline questionnaire
- Food Frequency Questionnaire: 10 days after baseline
- Follow-up: every 8 weeks for 12 months or until pregnancy
- If participant becomes pregnant:
  - Early pregnancy questionnaire (6-10 weeks' gestation)
  - Late pregnancy questionnaire (32 weeks' gestation)
  - Postpartum questionnaire (6 months after due date)
- Birth registry linkage (MA, CA, PA, TX, MI, and FL)



# Smartphone app



# *Incentives*



- ✓ For enrolling in PRESTO:
  - ✓ Randomization (50%/50%) to VIP membership at [FertilityFriend.com](http://FertilityFriend.com)
- ✓ For completing dietary questionnaire:
  - ✓ Nutrient summary of intake
  - ✓ Lottery to win \$100 gift card to grocery store (1/500 women)
- ✓ For completing male questionnaire:
  - ✓ Lottery to win iPad mini (1/250 couples)
- ✓ For completing all required follow-ups:
  - ✓ Lottery to win \$200 gift card (1/500 women)
- ✓ For enrolling in E-PRESTO:
  - ✓ \$50 gift card (x2)



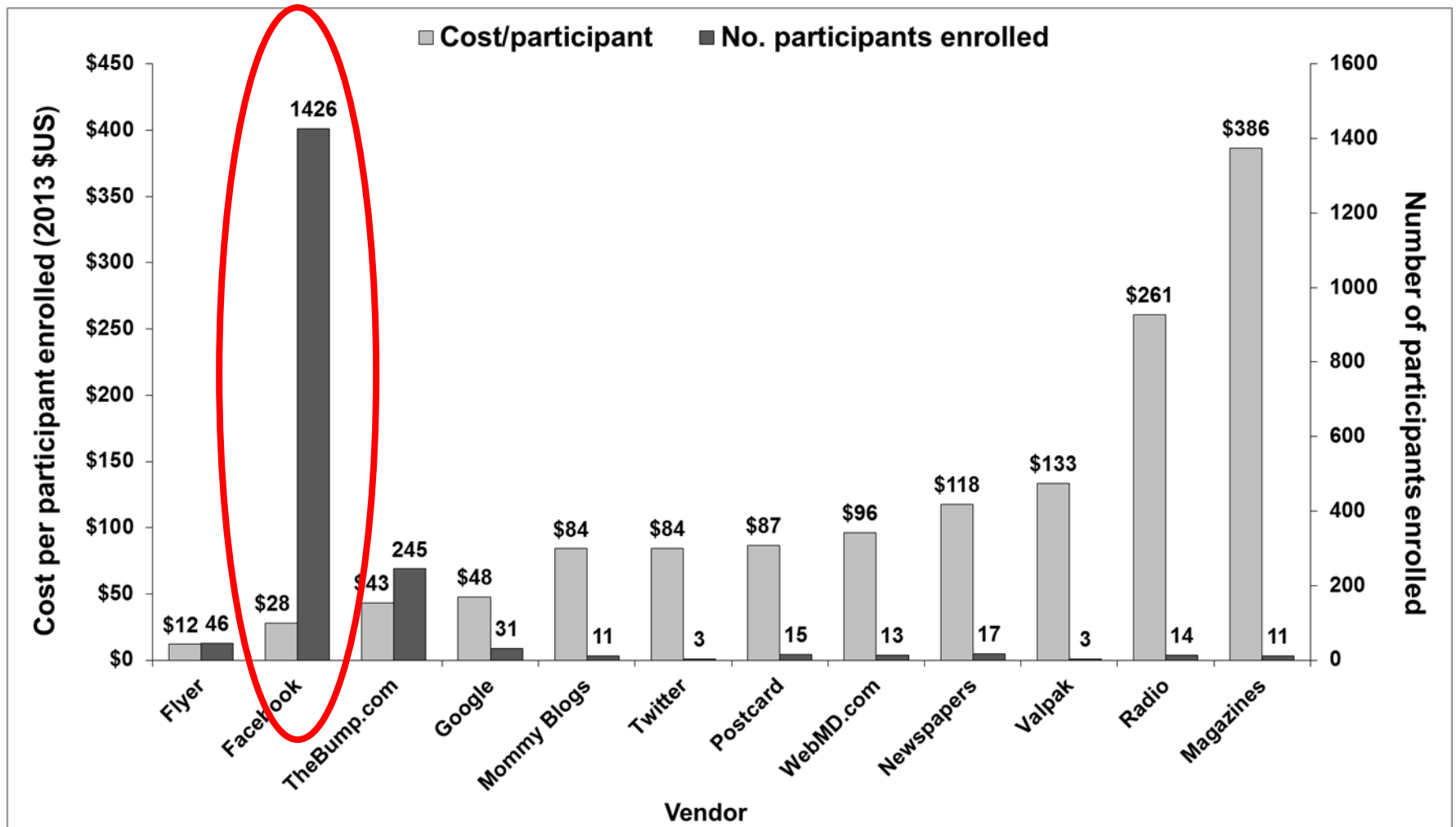
# *Incentives*



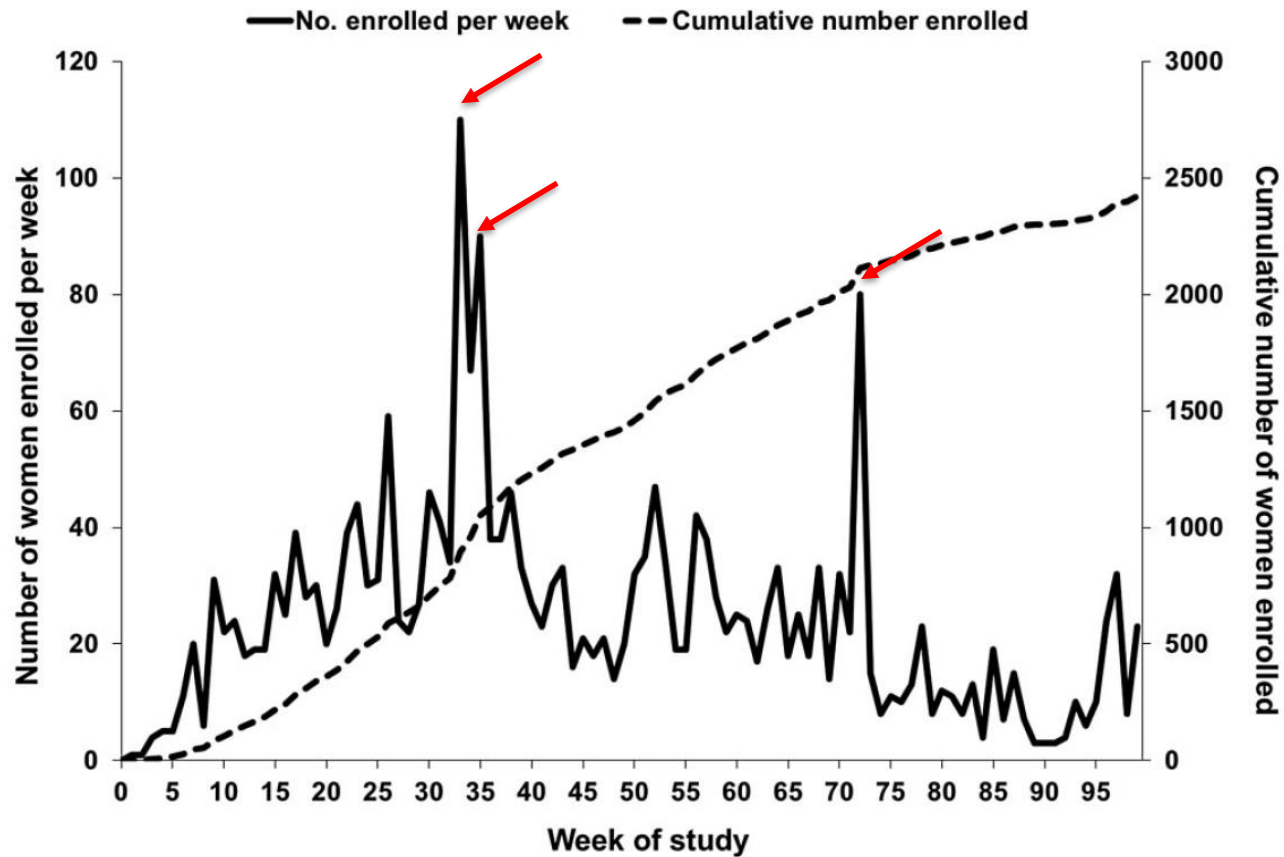
- ✓ For enrolling in PRESTO:
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- ✓ For enrolling in E-PRESTO:
  - ✓ \$50 gift card (x2)



# Cost per participant enrolled and total number enrolled, by vendor



# Total number of participants enrolled



**Figure 2.** Total number of female participants enrolled in PRESTO (2013–15). Peaks at 33 ( $n = 110$ ), 35 ( $n = 90$ ), and 72 ( $n = 80$ ) weeks are result of PRESTO participant posting on Reddit.com.

# Study costs: PRESTO vs. traditional cohort study

Table 4. Costs of recruiting and following 2,421 female PRESTO participants

Study cost components	
General set-up	
Website construction	\$20,183
Development of e-mail reminder system	\$3,441
Other <sup>a</sup>	\$20,321
Subject recruitment (advertisement, media strategy, incentives <sup>b</sup> )	\$67,898
Website maintenance and follow-up	\$16,831
FertilityFriend.com VIP memberships (in-kind donation: \$45 x 935)	\$42,075
Research personnel <sup>c</sup>	\$187,432
<b>Total costs</b>	<b>\$353,181</b>
<b>Per subject cost (2013 US\$)</b>	<b>\$146</b>

<sup>a</sup> Includes costs associated with quality assurance, system documentation, and coordination between research and system development teams.

<sup>b</sup> Includes lotteries but not FertilityFriend.com memberships. FertilityFriend.com memberships were donated in-kind and no NIH funds were used to cover this expense.

<sup>c</sup> Includes for unpaid internships completed by undergraduate and graduate students at Boston University.

**Estimated per subject cost for conventional study design: \$322**



# Selected findings



# Cohort enrollment



June 1, 2007

August 19, 2011

July 1, 2013



Females

Females & males



[www.snart-gravid.dk](http://www.snart-gravid.dk)

6,033♀



[www.snartforældre.dk](http://www.snartforældre.dk)

6,365♀ + 928♂



Boston University Pregnancy Study Online

9,565♀ + 2,198♂

**21,963♀ + 3,126♂**

## Substudies:

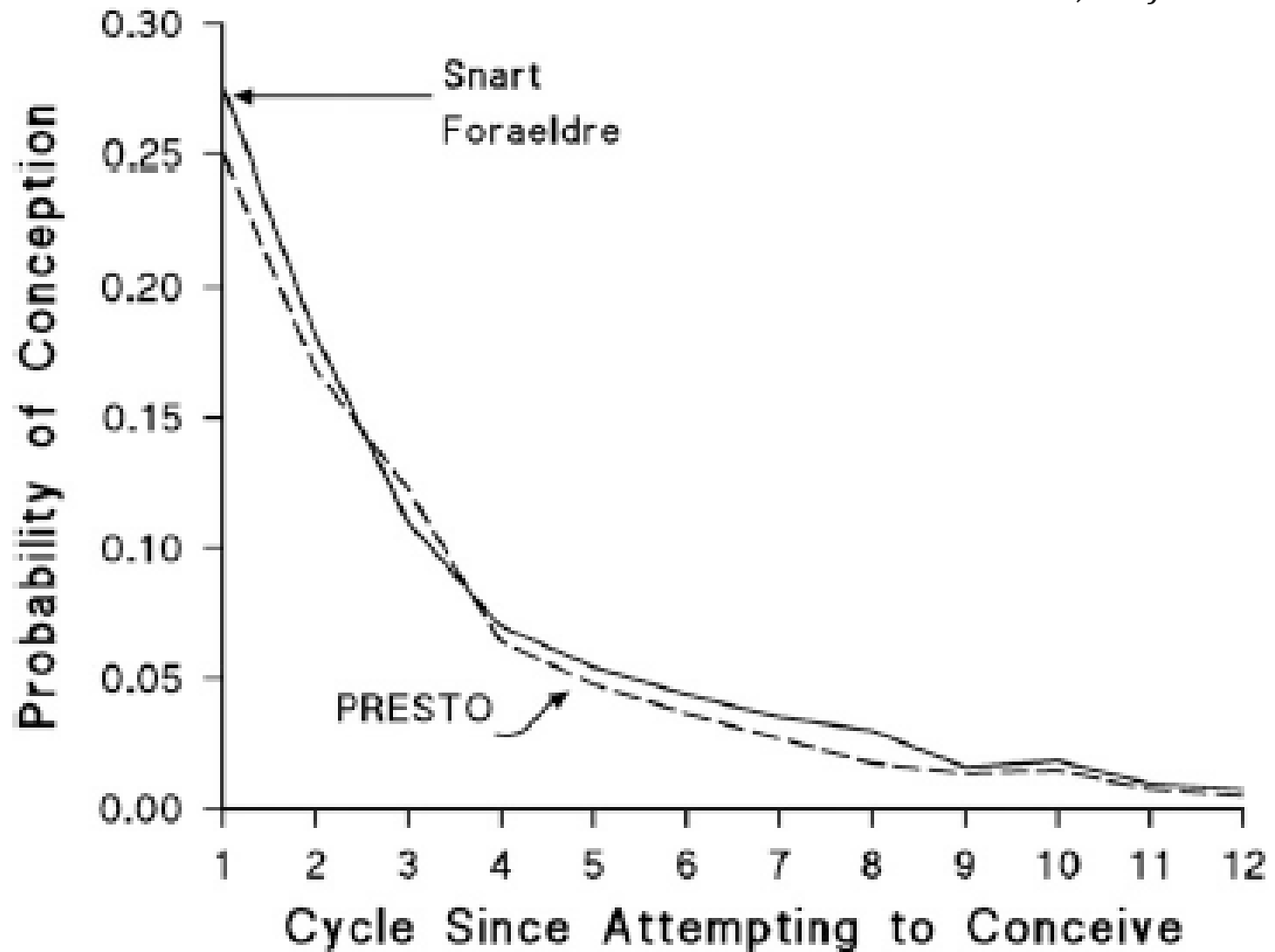
- ✓ Blood & urine collection: 129 women (SF) + 159 women (PRESTO)
- ✓ In-home semen testing: ≥290 samples (PRESTO)

# Data Analysis

- ✓ Restriction:  $\leq 6$  cycles of attempt time at entry
- ✓ At-risk cycles contributed until report of pregnancy, fertility treatment, no longer trying, loss to follow-up, or end of follow-up (12 cycles), whichever came first
- ✓ Proportional probabilities regression: fecundability ratio (FR<sup>\*</sup>) and 95% confidence interval (CI)
- ✓ Multiple imputation

*\*FR = cycle-specific probability of conception among exposed divided by that among unexposed. FR < 1 indicates **reduced** fecundability*

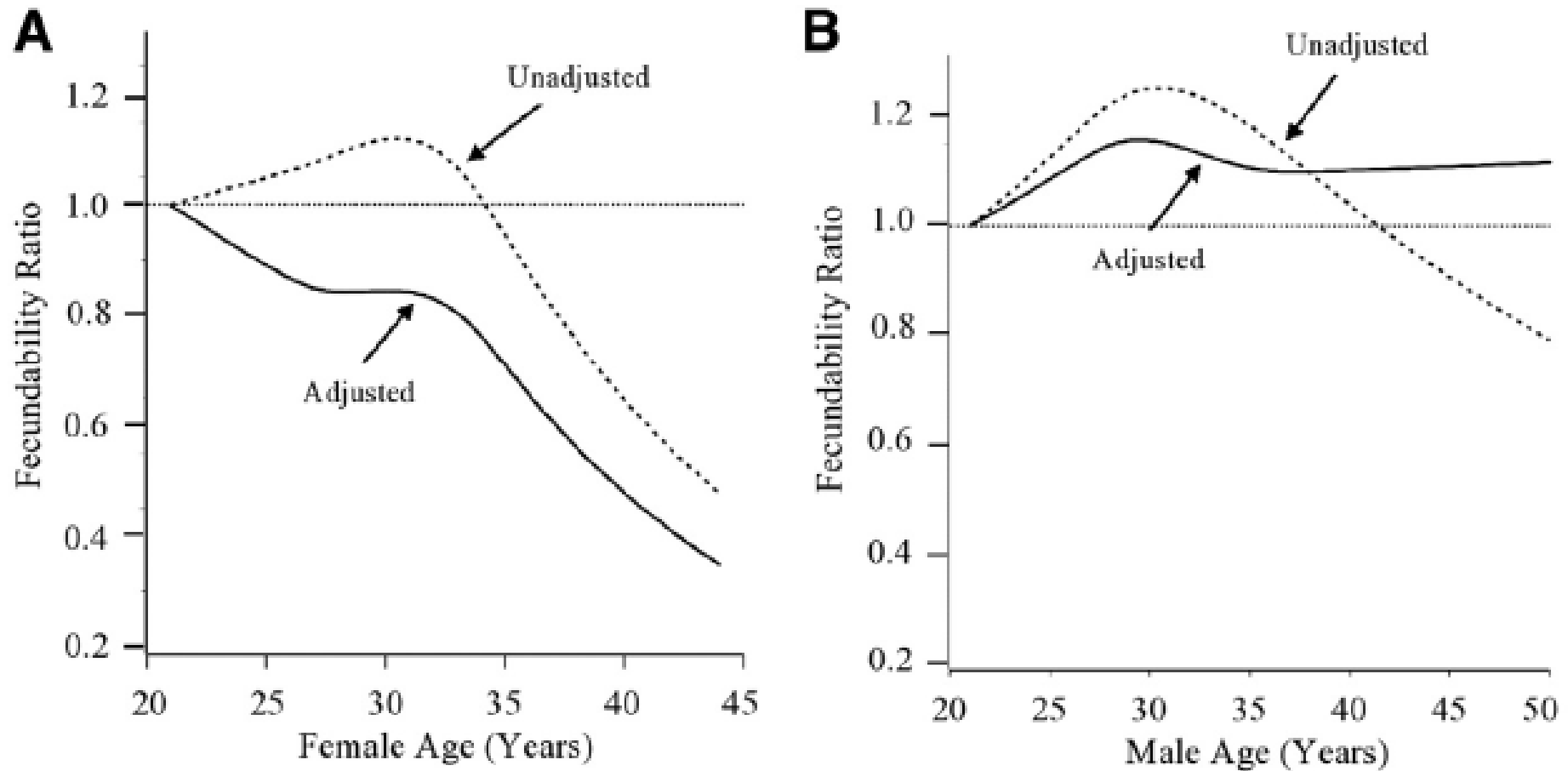




**FIGURE 2** Conditional probability of conception per menstrual cycle of attempt time stratified by cohort. PRESTO, Pregnancy Study Online.

## FIGURE

Association between female and male age and fecundability, fitted by restricted cubic splines, PRESTO, 2013-2017



## Body mass index and TTP

**Table II** Anthropometric measures at baseline and time to pregnancy

	No.	Cycles	Unadjusted model		Adjusted model <sup>a</sup>		Adjusted model <sup>b</sup>	
			FR	95% CI	FR	95% CI	FR	95% CI
BMI, kg/m <sup>2</sup>								
<20	161	843	0.95	0.78–1.15	0.94	0.77–1.15	1.02	0.83–1.27
20–24	666	3416	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
25–29	199	1178	0.83	0.70–0.99	0.83	0.70–1.00	0.72	0.58–0.90
30–34	85	569	0.73	0.57–0.94	0.75	0.58–0.97	0.60	0.42–0.85
≥35	38	334	0.55	0.39–0.78	0.61	0.42–0.88	0.48	0.31–0.74
Male partner's BMI, kg/m <sup>2</sup>								
<20	28	168	0.85	0.56–1.30	0.94	0.61–1.44	0.95	0.62–1.46
20–24	611	3200	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
25–29	432	2423	0.93	0.81–1.06	0.98	0.85–1.13	0.98	0.85–1.13
30–34	60	399	0.79	0.59–1.05	0.99	0.73–1.35	0.97	0.72–1.33
≥35	18	150	0.59	0.36–0.98	0.72	0.43–1.22	0.72	0.43–1.22

<sup>a</sup>Adjusted for age, partner's age, cycle regularity, cycle length, partner's BMI (in female BMI analysis only), physical activity, smoking, alcohol intake and intercourse frequency.

<sup>b</sup>Adjusted for factors in 'a' as well as waist circumference (in BMI analyses), female BMI (in all analyses except weight change) and BMI at age 17 (in weight gain analyses).



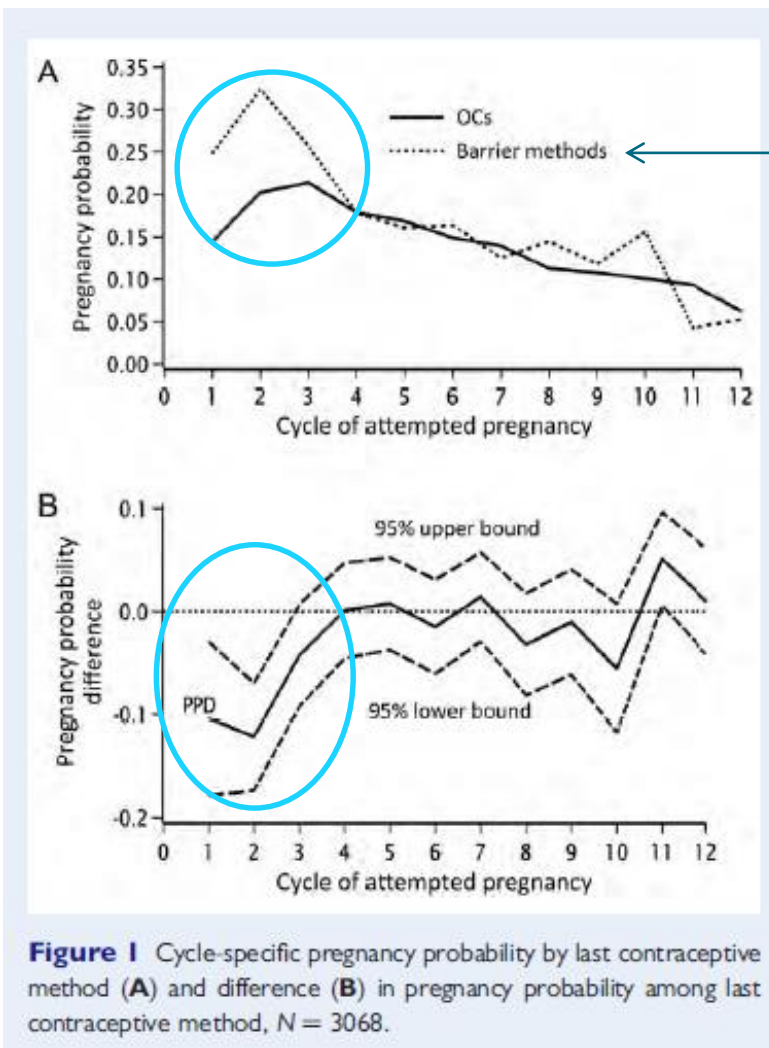
## Vigorous physical activity and TTP, stratified by BMI

Characteristic	Vigorous physical activity, hours per week					
	None	<1	1	2	3-4	≥5
Body mass index (kg/m <sup>2</sup> )						
<25						
Pregnancies	337	365	311	392	267	93
Cycles	1,700	2,148	1,798	2,355	1,627	688
FR	1.00 (ref.)	0.79 (0.66–0.93)	0.79 (0.66–0.94)	0.76 (0.64–0.89)	0.72 (0.60–0.87)	0.58 (0.45–0.75)
≥25						
Pregnancies	163	201	129	128	75	23
Cycles	1,156	1,344	809	801	668	131
FR	1.00 (ref.)	1.12 (0.89–1.41)	1.15 (0.88–1.48)	1.16 (0.89–1.51)	0.76 (0.56–1.03)	1.22 (0.74–2.02)

Note: FR adjusted for cycle number, age, partner's age, body mass index, alcohol consumption, pack-years of smoking, intercourse frequency, last method of contraception, and moderate physical activity (when applicable); 95% CI in parentheses. FR = fecundability ratio; CI = confidence interval.



# Pre-gravid oral contraceptive (OC) use and TTP

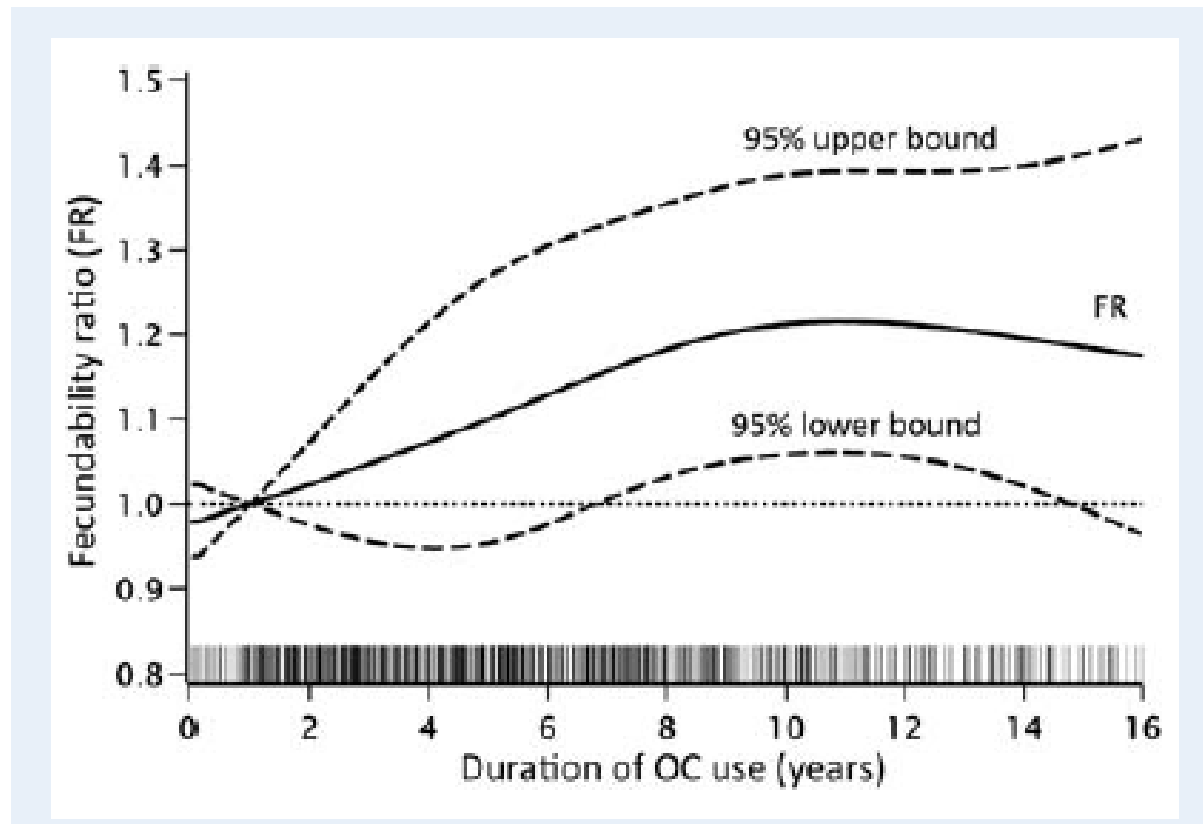


Reference group





# Duration of OC use and fecundability

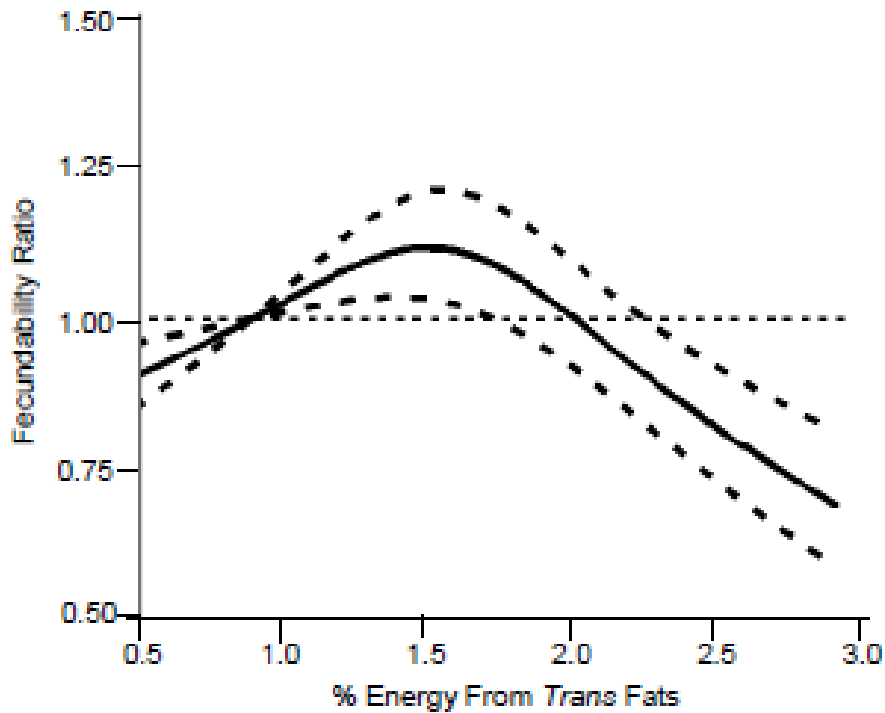


Mikkelsen *et al. Hum Reprod* 2013

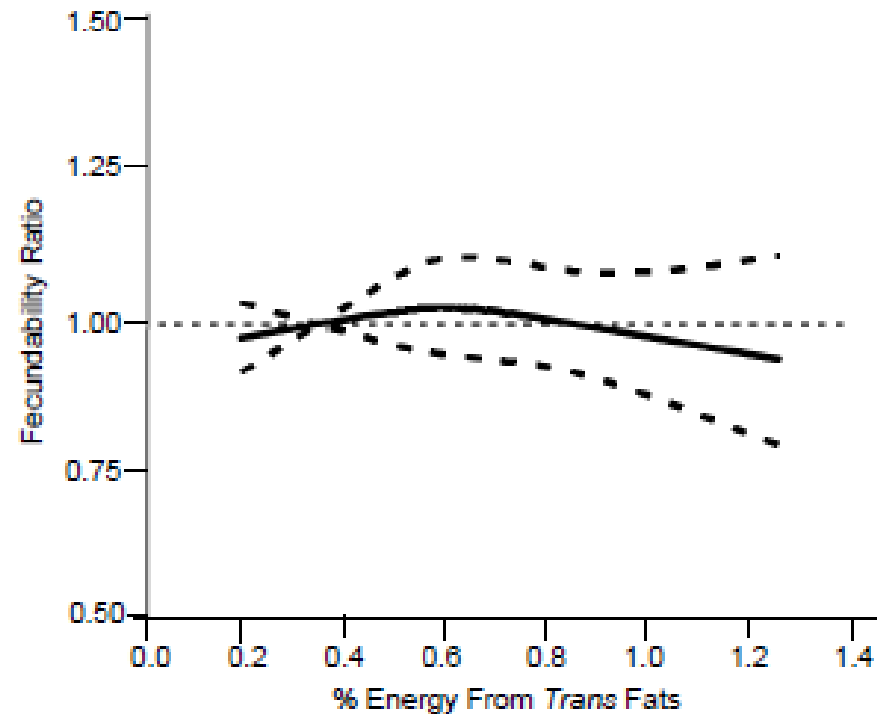
# Dietary factors



# Intake of trans fatty acids and fecundability

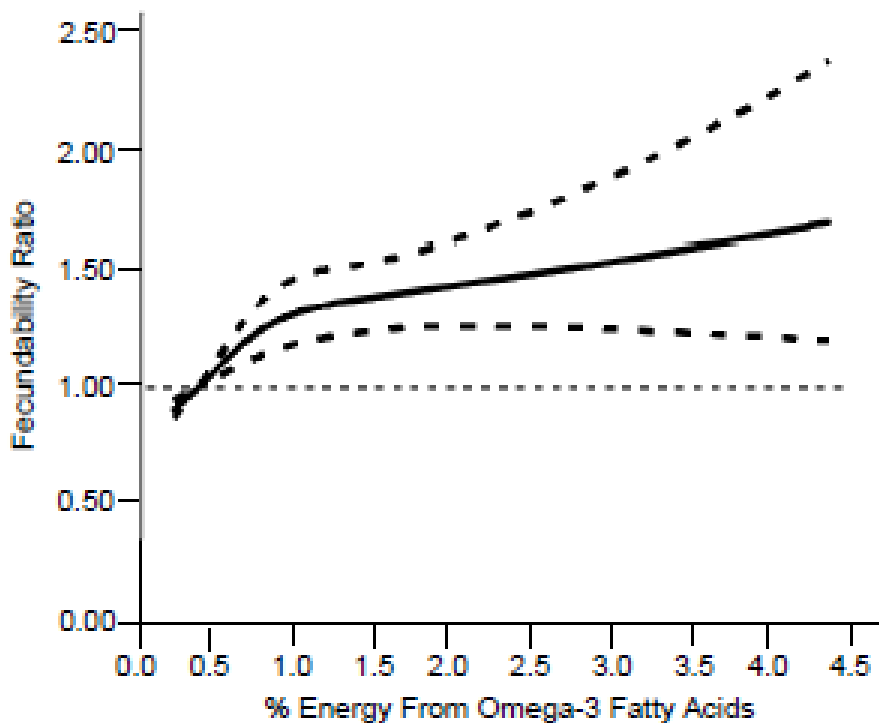


PRESTO

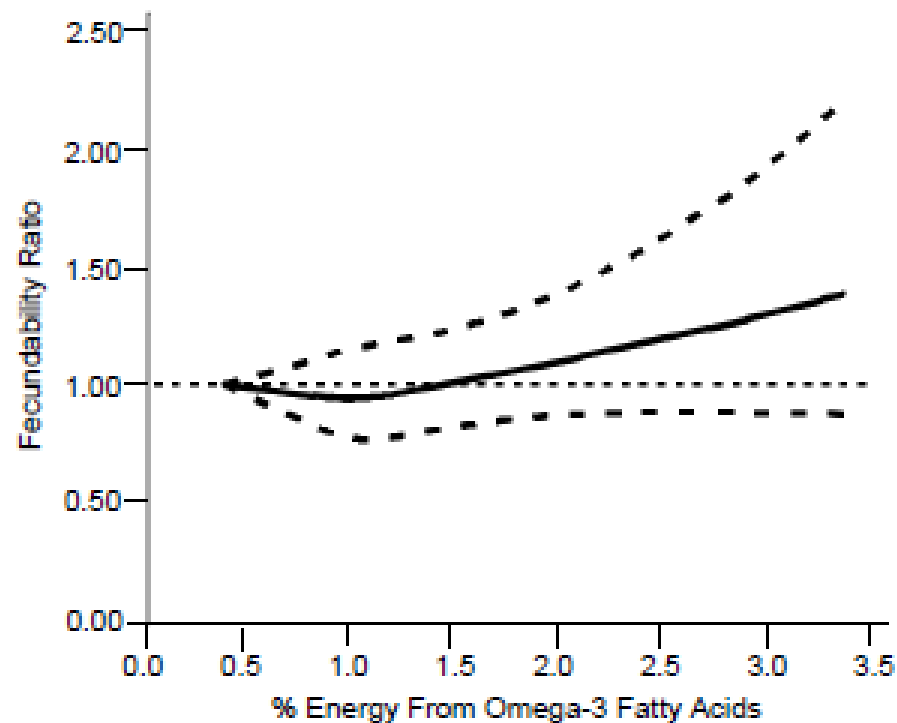


Smart Forældre

# Intake of omega-3 fatty acids and fecundability



PRESTO

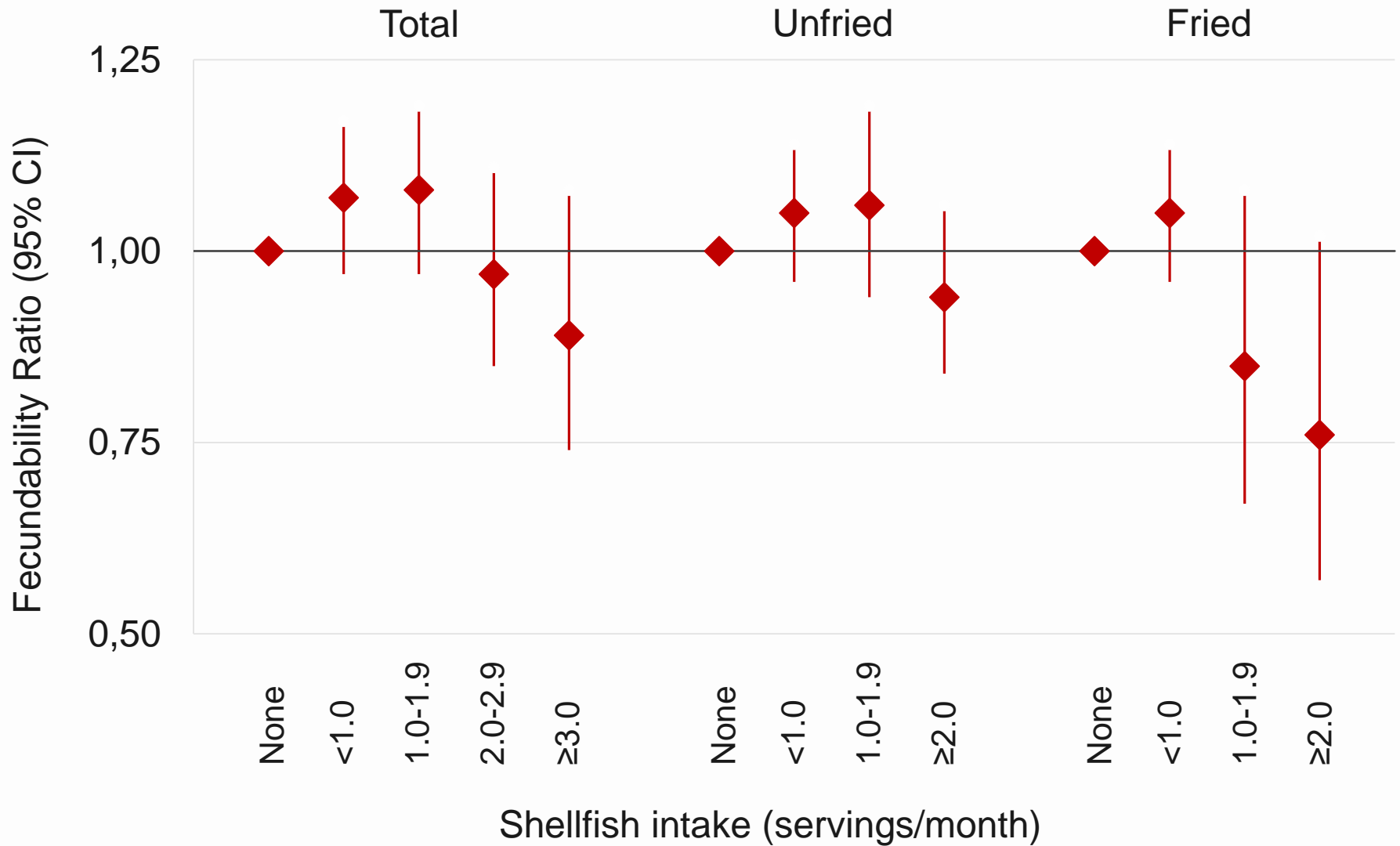


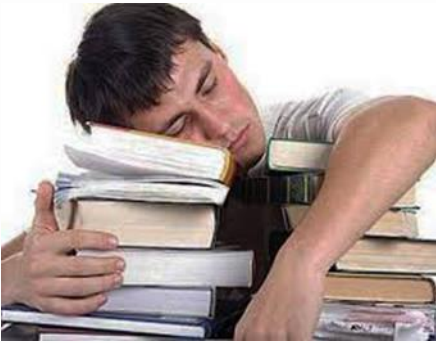
Smart Foraelldre





# Shellfish intake and fecundability



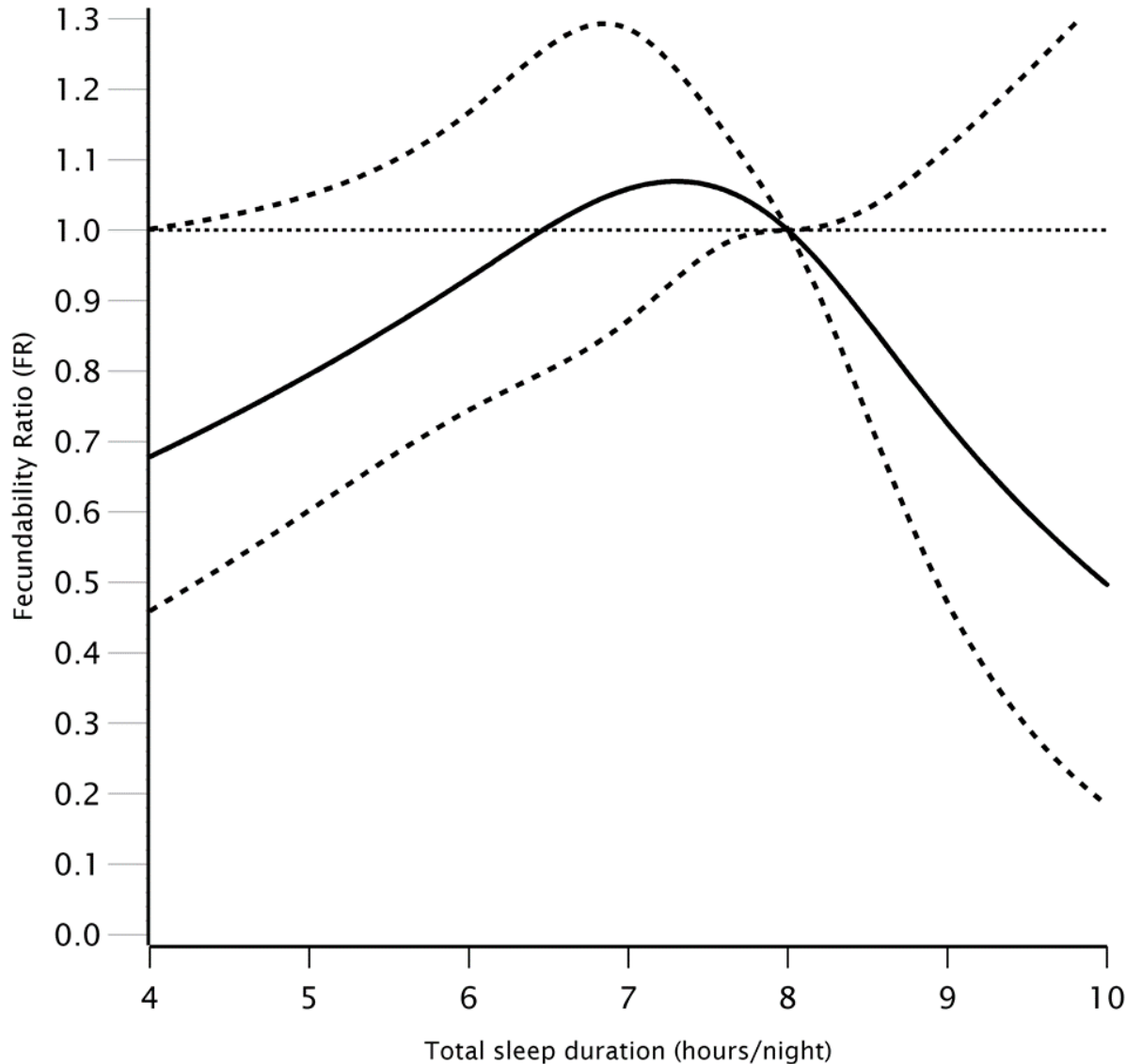


# Male factor analyses



**PRESTO**  
Boston University Pregnancy Study Online

# Male sleep duration and fecundability



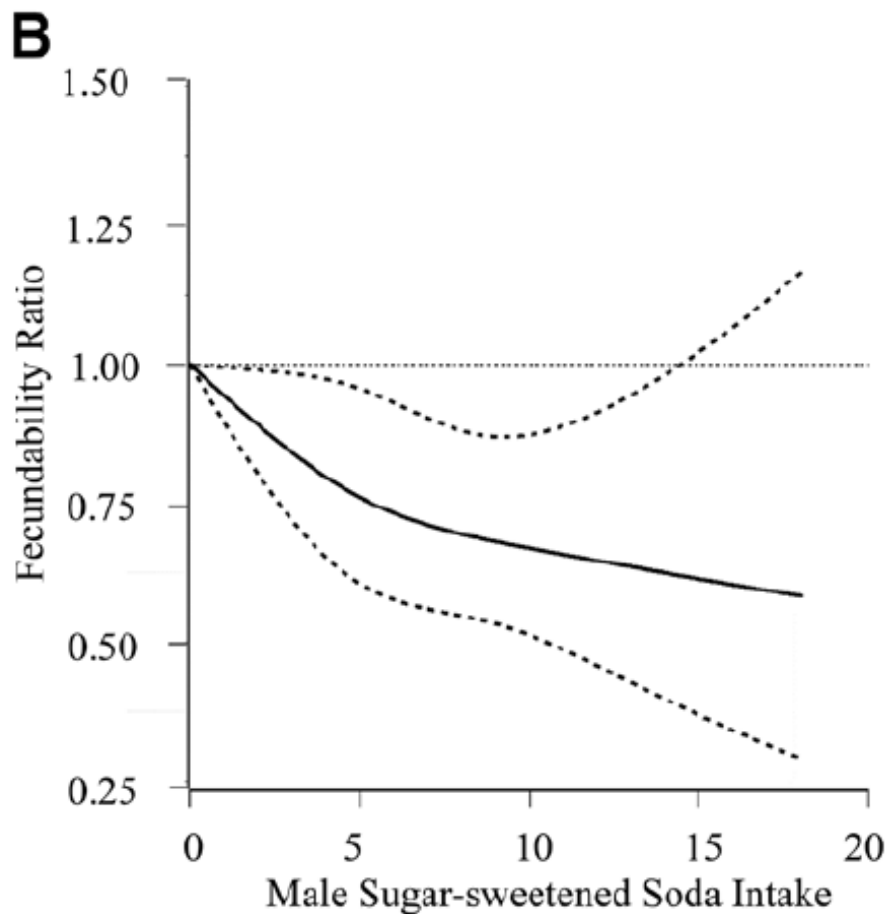
Adjusted for male and female age, male and female BMI, intercourse frequency, and the following factors among males: physician-diagnosed depression, race/ethnicity, education, use of multivitamins or folate supplements, smoking history, employment status, hours of work per week, previously fathered a child, hours of laptop use on one's lap per day, total MET-hours of physical activity per week, caffeine intake, alcohol intake, PSS-10 score, sugar-sweetened soda consumption, and female partner's sleep duration.



# Intake of Sugar-sweetened Beverages and Fecundability in a North American Preconception Cohort



Elizabeth E. Hatch,<sup>a</sup> Amelia K. Wesselink,<sup>a</sup> Kristen A. Hahn,<sup>a</sup> James J. Michiel,<sup>a</sup>  
Ellen M. Mikkelsen,<sup>b</sup> Henrik Toft Sorensen,<sup>b</sup> Kenneth J. Rothman,<sup>a,c</sup> and Lauren A. Wise<sup>a</sup>



*Epidemiology* • Volume 29, Number 3, May 2018

Adjusted for male & female age, BMI, exercise, education, income, intercourse frequency, doing something to improve conception chances



# Pilot work



**PRESTO**

Boston University Pregnancy Study Online





# Background: PFAS



- Perfluoroalkyl and polyfluoroalkyl substances (PFAS) are persistent synthetic chemicals found in non-stick cookware, clothing, carpets, food packaging, foods (e.g. fish).
- Studies have reported TTP delays in association with:
  - perfluorooctanoate (PFOA)
  - perfluorooctane sulfonate (PFOS)
  - perfluorohexane sulfonate (PFHxS)
  - 2-N-methyl-perfluorooctane sulfonamide acetate (PFOSA)\*
  - perfluorononanoate (PFNA)
- Results varied by study design (pregnancy cohort vs. preconception cohort) and parity (stronger among parous).

*\*U.S. production ceased in 2002*



# Background: PFAS



Retrospective studies	PFOA	PFOS	PFHxS	PFOSA	PFNA	PFDeA	Nullip
Fei, 2009 (DNBC)	↓	↓	NE	NE	NE	NE	↓
Whitworth, 2012 (MoBA)*	↓	↓	NE	NE	NE	NE	↑
Bach, 2015 (DNBC)	↓	null	NE	NE	NE	NE	null
Bach, 2015 (Aarhus Birth Cohort)†	null/↑	null/↑	null	null	null	null	null
Velez, 2015 (MIREC)	↓	null	↓	NE	NE	NE	NE
Prospective studies							
Lum, 2017 (LIFE)	↓	null	NE	↓	↓	null/↑	NE
Jørgensen, 2014 (INUENDO)	null	↓	null	NE	↓	NE	↑PFOA ↓PFNA
Crawford, 2017 (Time to Conceive)	null	null	null	null	null	NE	null
Vestergaard, 2012 (1st Prg Planners)†	null	null	null	null	null	NE	null

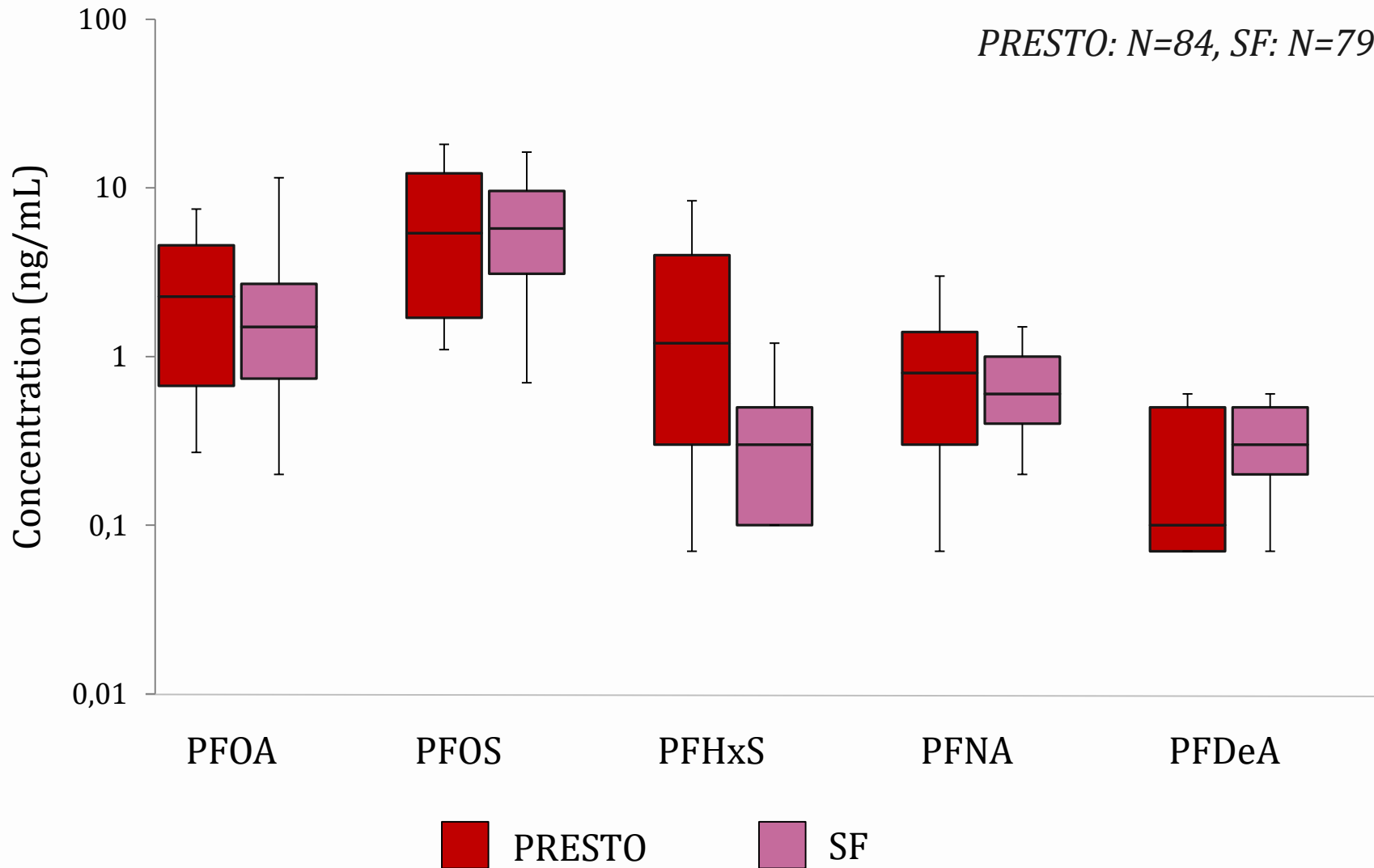
↓ associated with delayed conception; ↑ associated with faster conception; null = little evidence of association; NE = not evaluated;  
 \*Did not measure TTP. †Restricted to nulliparous women only. Norwegian Mother and Child Cohort Study (MoBA); Danish National Birth Cohort (DNBC), Maternal-Infant Research on Environmental Chemicals (MIREC).



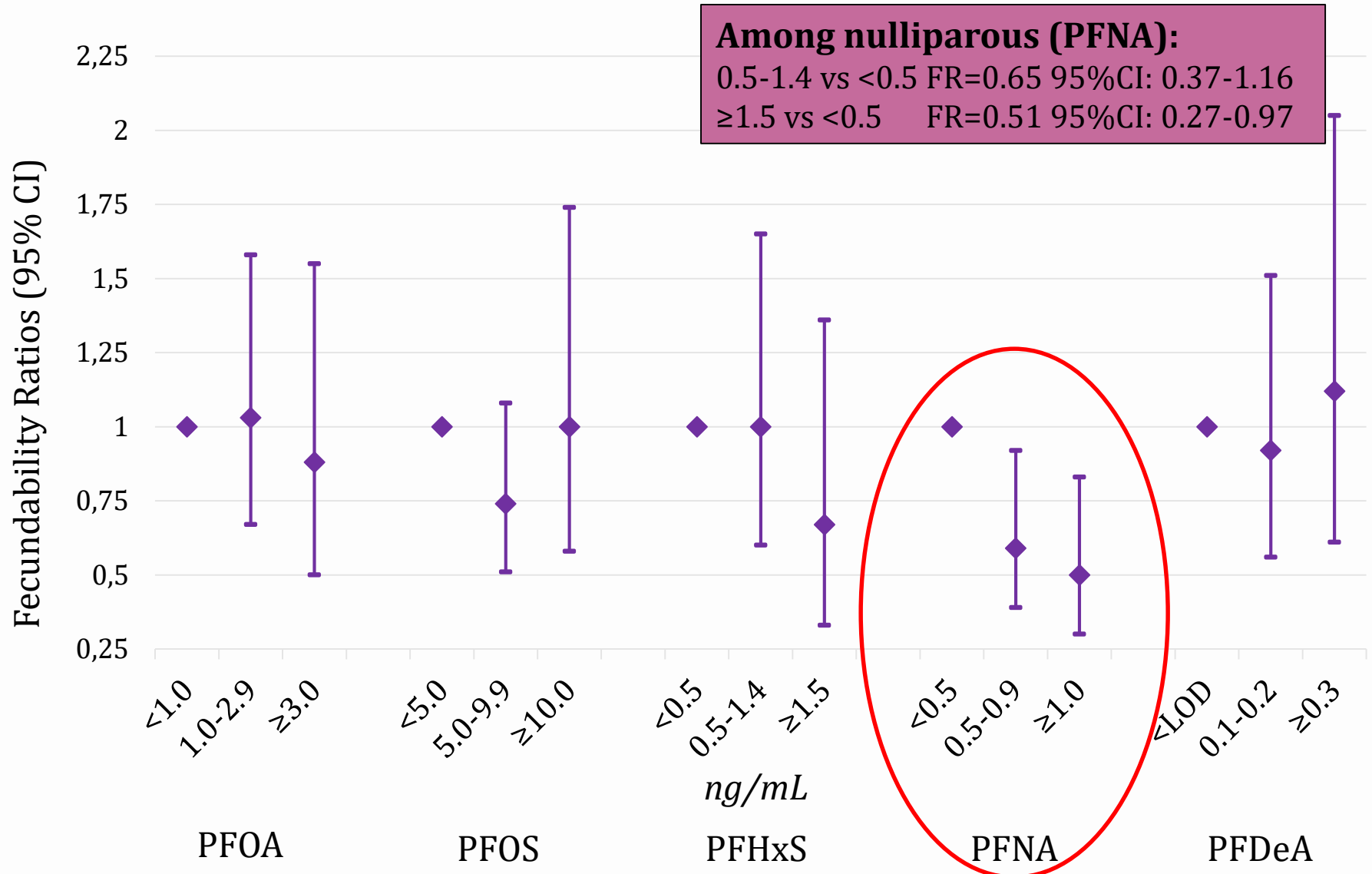
# Serum Levels of PFAS



*PRESTO: N=84, SF: N=79*



# PFAS and Fecundability





# Limitations and Strengths



## Limitations

- Misclassification of exposure
  - Bias likely non-differential
- Outcome misclassification
- Residual/unmeasured confounding
  - By lifestyle? SES?
- Restricted to pregnancy planners
- Differential loss to follow-up?

## Strengths

- Cost-effective methods
- Prospective data collection
- Preconception enrollment
- Confounder data: both partners
- High cohort retention (>82%)
- Access to registry data
- Geographically diverse; full range of fertility spectrum



# Future Directions



- New funding to expand biospecimen collection
- Examine other EDCs and health outcomes (e.g., miscarriage, birth outcomes, child obesity)
- Use novel mixtures analyses
- Include male partners
- Use novel methods to collect biospecimens

# Research Team

## Boston University

Elizabeth E. Hatch (PI-SG/SF)

Kenneth J. Rothman

Kristen A. Hahn

Amelia K. Wesselink

Kathryn McInerney

Craig J. McKinnon

Sydney Willis

Nina Schrager

Yael Nillni

Shruthi Mahalingaiah

Michael McClean

## Aarhus University Hospital

Ellen M. Mikkelsen

Henrik Toft Sørensen

Anders Riis

## Web design/programming

Michael Bairos

## Other consultants

Katherine Tucker (UMass Lowell)

Joe Stanford (U of Utah)

Michael Eisenberg (Stanford)



## Funding sources:

R01-HD060680, R01-HD086742

R21-HD050264, R21-HD072326



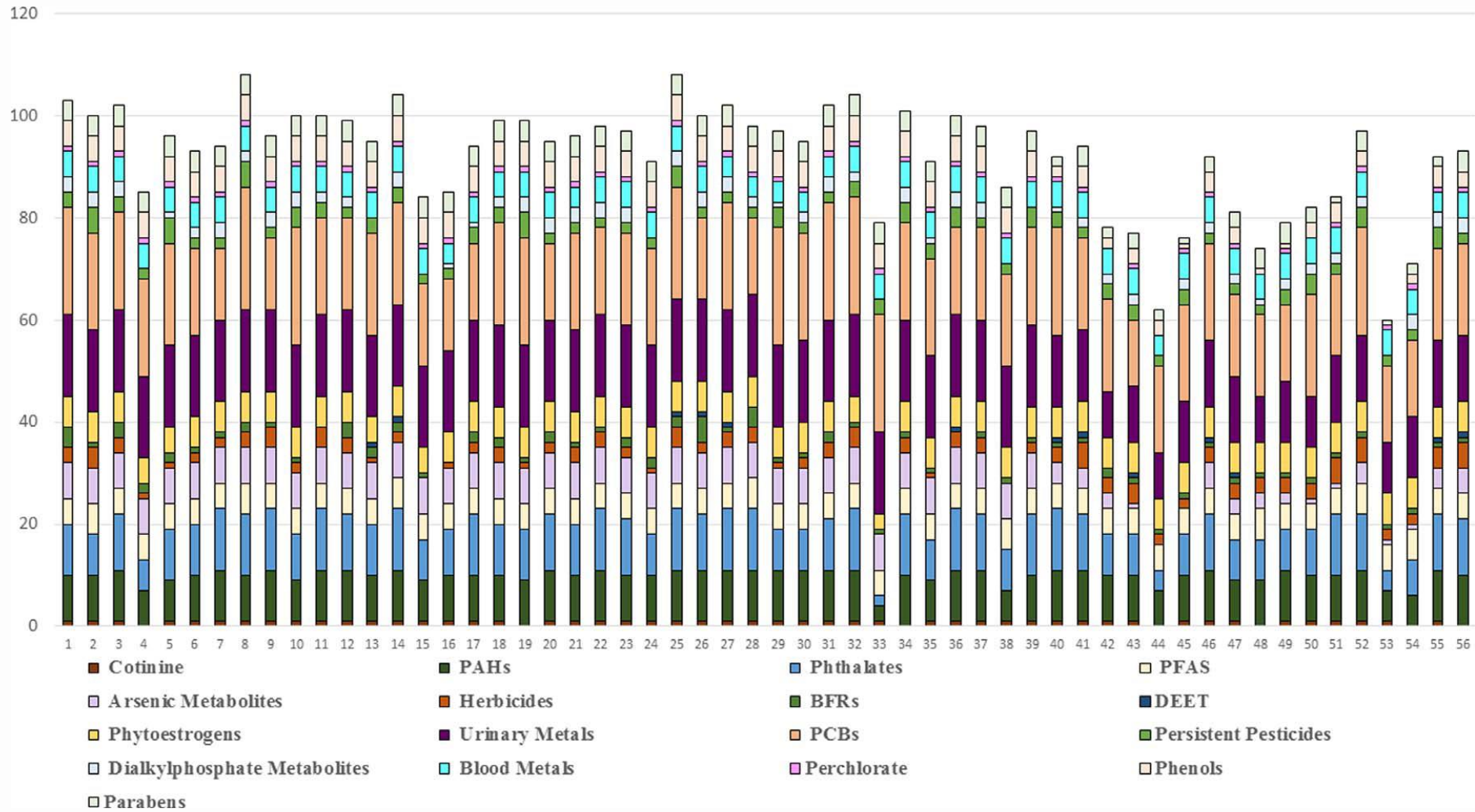


# Evaluation of selection bias (Hatch et al., *Epidemiology* 2016)

	Snart Gravid N=4,801	Danish Medical Birth Registry N=239,791
	Adjusted RR (95% CI)	Adjusted RR (95% CI)
<b>Smoking vs. Low Birth Weight &lt;2500g</b>		
Non-smoker	1.00 (ref)	1.00 (ref)
Current smoker >10 cig/day	2.68 (1.21, 5.91)	2.87 (2.63, 3.12)
<b>Parity vs. Preeclampsia</b>		
Nulliparous	1.69 (1.25, 2.30)	2.27 (2.16, 2.38)
Primiparous	1.00 (ref)	1.00 (ref)
<b>Maternal BMI vs. Macrosomia &gt;4000g</b>		
BMI<20	0.66 (0.51, 0.86)	0.64 (0.62, 0.66)
20-24	1.00 (ref)	1.00 (ref)
25-29	1.33 (1.14, 1.56)	1.28 (1.25, 1.31)
≥30	1.45 (1.21, 1.74)	1.49 (1.45, 1.53)
<b>Maternal BMI vs. Preeclampsia</b>		
BMI<20	0.88 (0.56, 1.37)	0.70 (0.65, 0.75)
20-24	1.00 (ref)	1.00 (ref)
25-29	1.84 (1.37, 2.46)	1.59 (1.51, 1.67)
≥30	3.01 (2.25, 4.04)	2.70 (2.57, 2.83)
<b>Maternal BMI vs. C-section</b>		
BMI<20	0.90 (0.75, 1.09)	0.89 (0.86, 0.91)
20-24	1.00 (ref)	1.00 (ref)
25-29	1.19 (1.03, 1.37)	1.25 (1.23, 1.28)
≥30	1.55 (1.34, 1.80)	1.59 (1.56, 1.63)



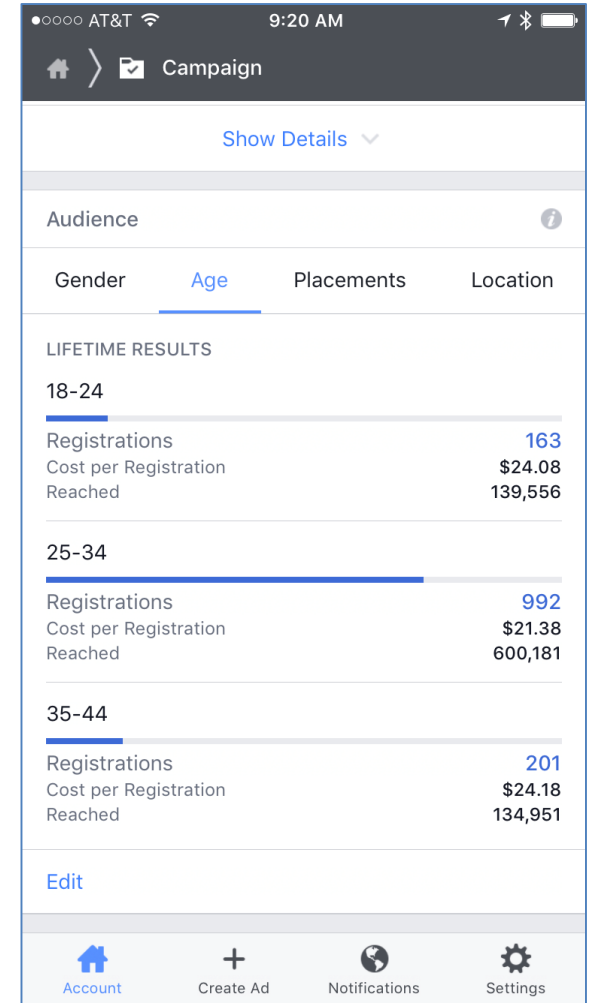
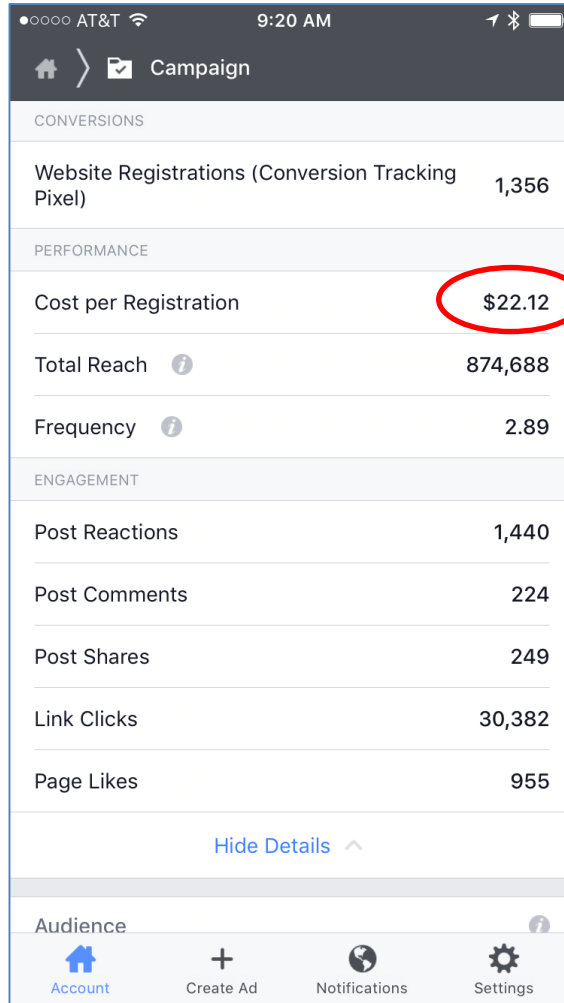
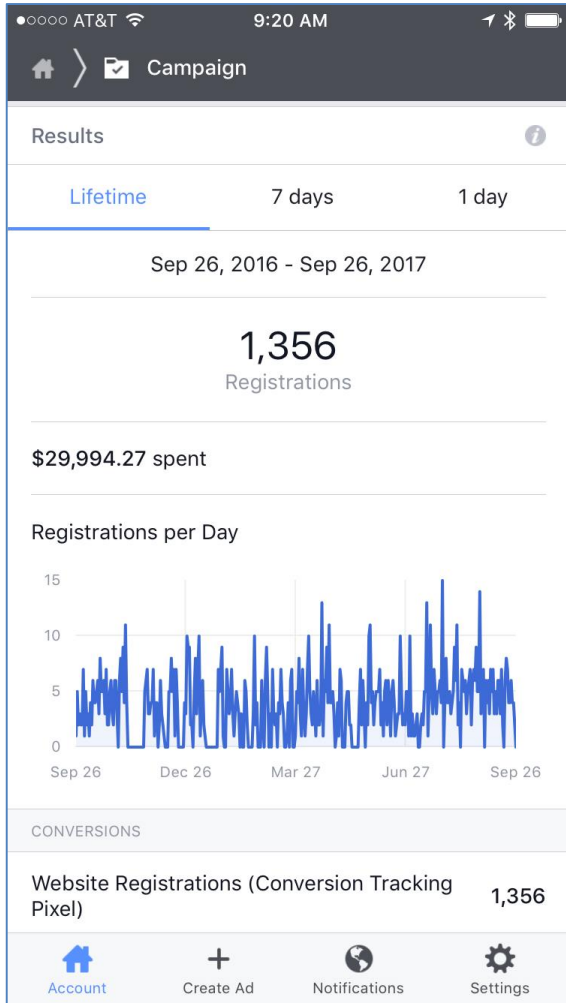
# Total Number of Chemicals Detected in SF



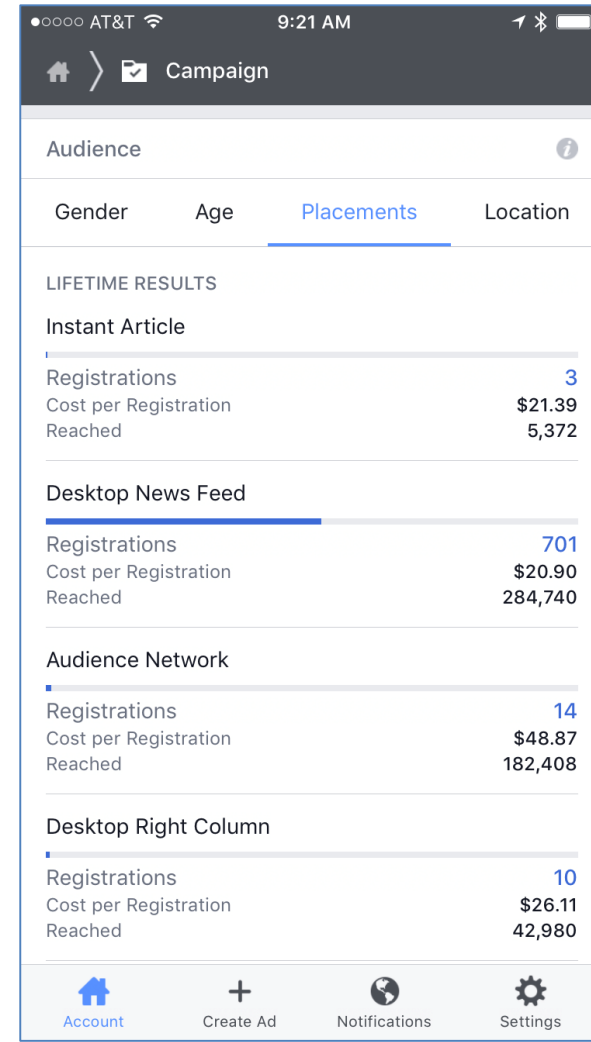
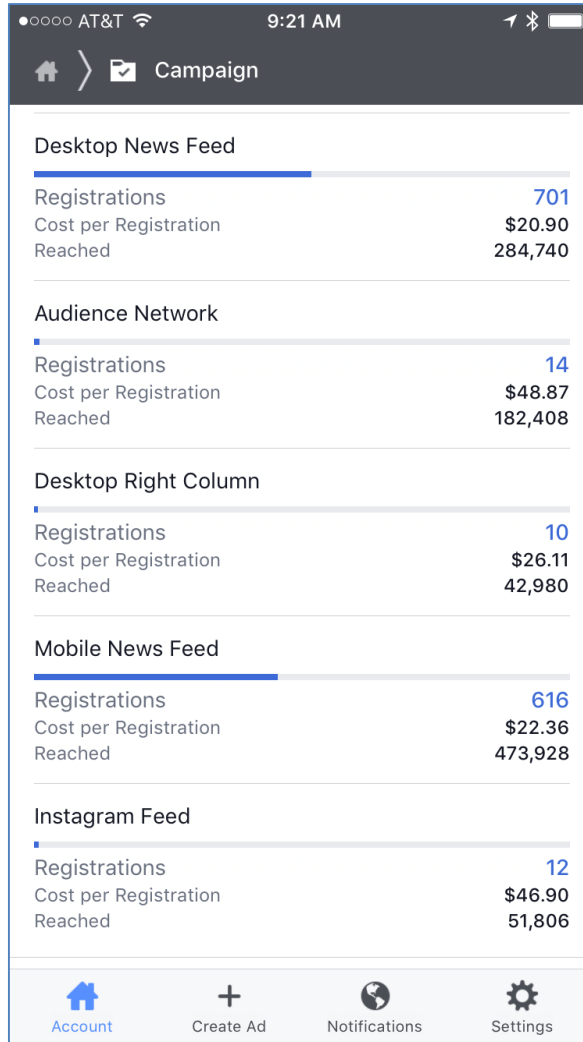
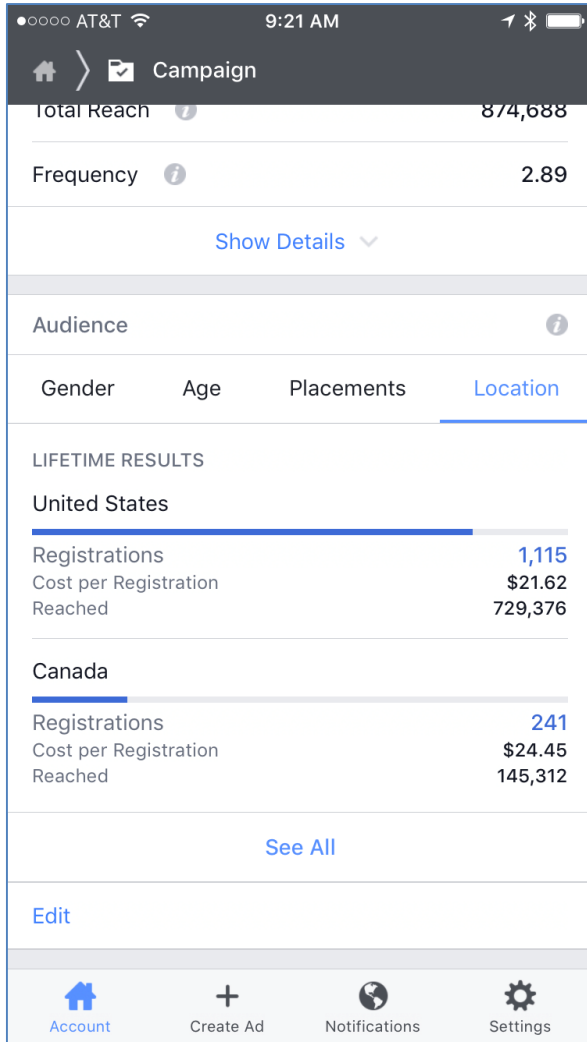
# Why is Facebook so effective for recruitment?

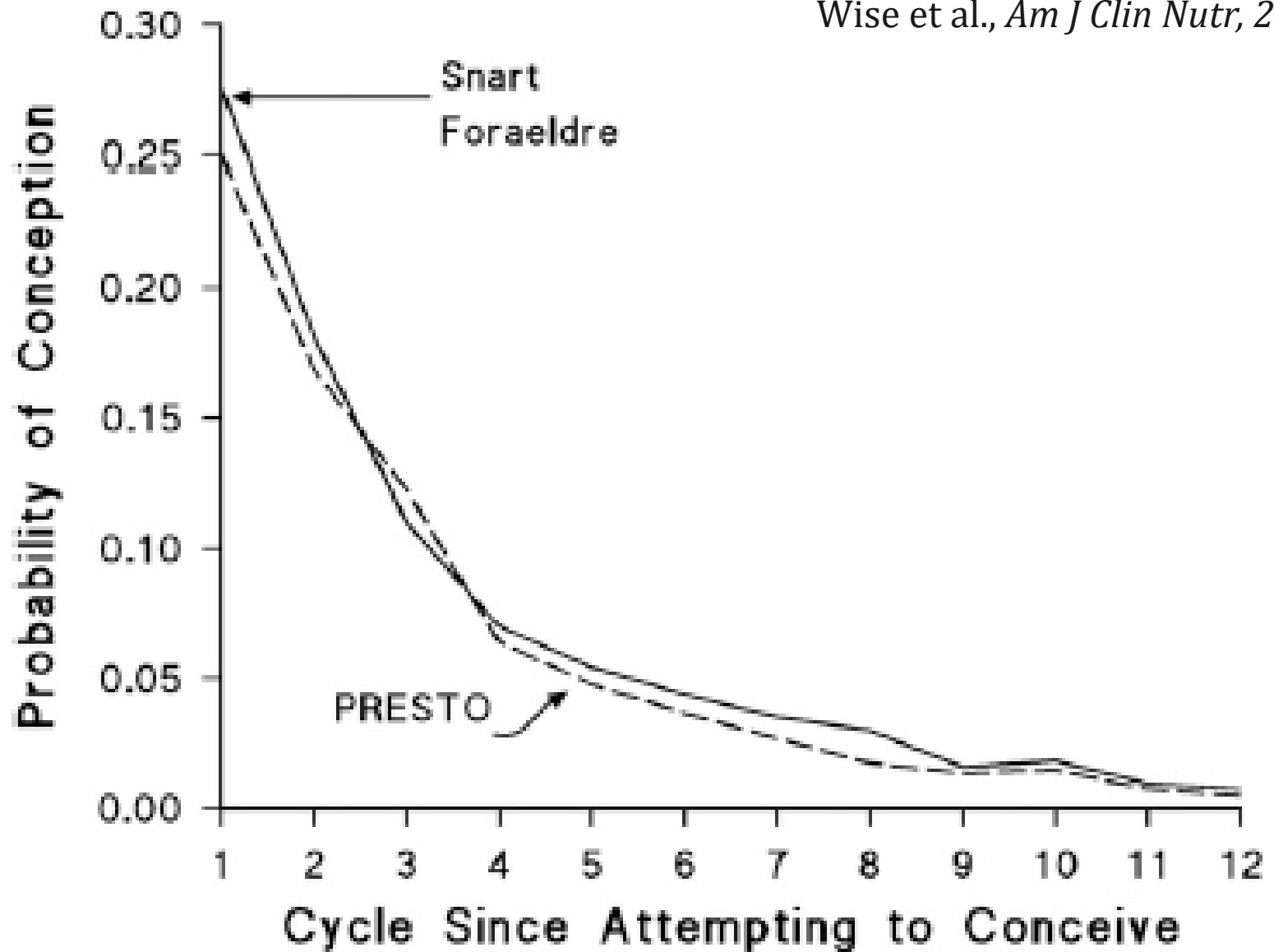
- Can target potential participants based on:
  - Gender
  - Age
  - Language spoken
  - Geographic region (e.g., state/province, zip code)
  - Relationship status
    - Newly engaged
    - Newlywed (e.g., 3, 6, 12 months)
  - Parenting status and age of children
  - Education
  - Specific interests (e.g., church membership)
- Facebook page lends legitimacy to study

# Facebook statistics



# Facebook statistics





**FIGURE 2** Conditional probability of conception per menstrual cycle of attempt time stratified by cohort. PRESTO, Pregnancy Study Online.

# The Effect of Vaccination Against Human Papillomavirus on Fecundability


Kathryn A. McInerney,<sup>a</sup>  Elizabeth E. Hatch,<sup>a</sup> Amelia K. Wesselink,<sup>a</sup> Ellen M. Mikkelsen,<sup>b</sup> Kenneth J. Rothman,<sup>a,c</sup> Rebecca B. Perkins,<sup>d</sup> Lauren A. Wise<sup>a</sup>

Table 2. HPV vaccination and fecundability among pregnancy planners

Exposure	Number of cycles	Number of pregnancies	Crude Fecundability	Unadjusted FR (95% CI)	Adjusted FR (95% CI) <sup>a</sup>
<b>Females</b>					
Unvaccinated	10 332	1402	0.14	1.00 (Reference)	1.00 (Reference)
Vaccinated	4936	751	0.15	1.08 (1.00, 1.17)	0.98 (0.90, 1.08)
Vaccinated <Age 18	1094	154	0.14	1.03 (0.88, 1.20)	1.00 (0.85, 1.17)
Vaccinated ≥Age 18	3842	597	0.16	1.09 (1.00, 1.19)	0.98 (0.89, 1.08)
<b>Males</b>					
Unvaccinated	4177	634	0.15	1.00 (Reference)	1.00 (Reference)
Vaccinated	211	36	0.17	1.03 (0.76, 1.39)	1.07 (0.79, 1.46)
Vaccinated <Age 18	48	8	0.17	0.95 (0.50, 1.80)	1.10 (0.56, 2.19)
Vaccinated ≥Age 18	163	28	0.17	1.06 (0.75, 1.48)	1.06 (0.75, 1.50)

FR, fecundability ratio.

<sup>a</sup>Male and female models are adjusted for age at baseline, education, income, geographic region of residence, race/ethnicity, history of smoking. Models for females are additionally adjusted for abnormal Pap test before age at vaccination and parent's education.

Table 3. HPV vaccination and fecundability stratified by number of sexual partners and history of STI/PID

Exposure	No. of Cycles	No. of Pregs	Crude Fecundability	Unadjusted FR (95% CI)	Adjusted FR (95% CI) <sup>a</sup>
≥10 Sexual Partners					
Females					
Unvaccinated	2958	388	0.13	1.00 (Reference)	1.00 (Reference)
Vaccinated	1304	210	0.16	1.08 (0.90, 1.30)	0.99 (0.79, 1.24)
History of STI/PID					
Females					
Unvaccinated	1436	161	0.11	1.00 (Reference)	1.00 (Reference)
Vaccinated	601	87	0.14	1.27 (1.00, 1.61)	1.35 (0.99, 1.86)
History of STI/PID and No Abnormal Pap Test before Vaccination					
Females					
Unvaccinated	1436	161	0.11	1.00 (Reference)	1.00 (Reference)
Vaccinated	361	56	0.16	1.41 (1.07, 1.85)	1.38 (1.00, 1.90)

FR, fecundability ratio.

<sup>a</sup>Models are adjusted for age at baseline, education, income, geographic region of residence, race/ethnicity, history of smoking. Models for females are additionally adjusted for abnormal Pap test and parent's education.

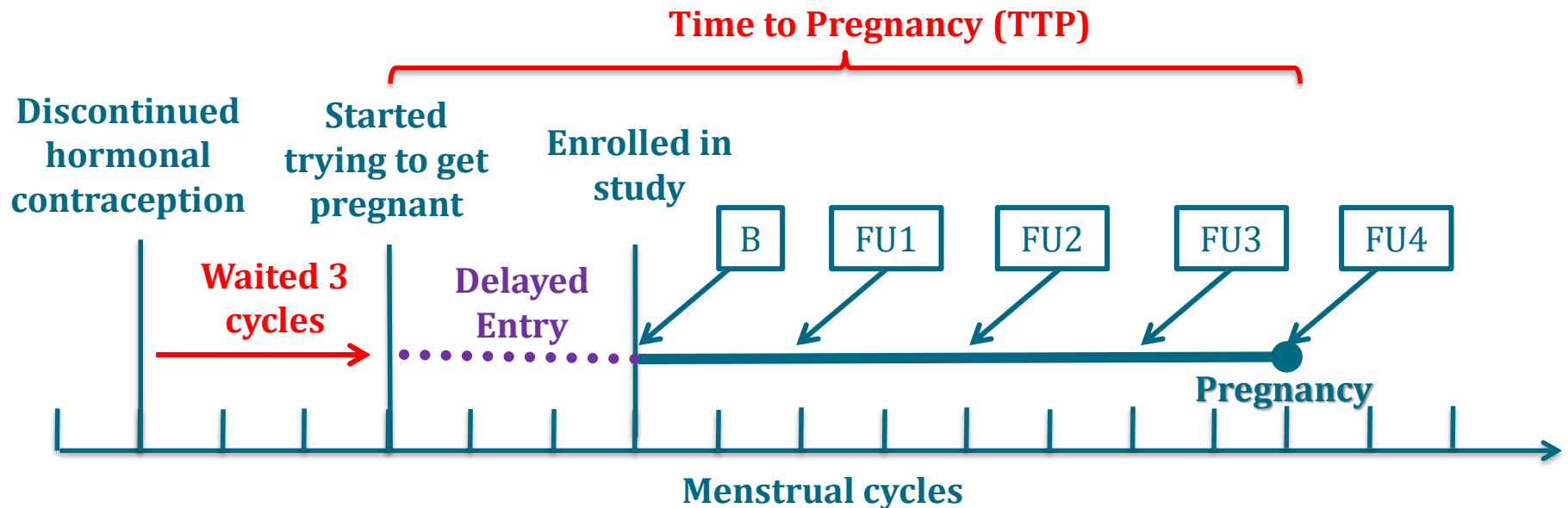


# Calculating Time At Risk

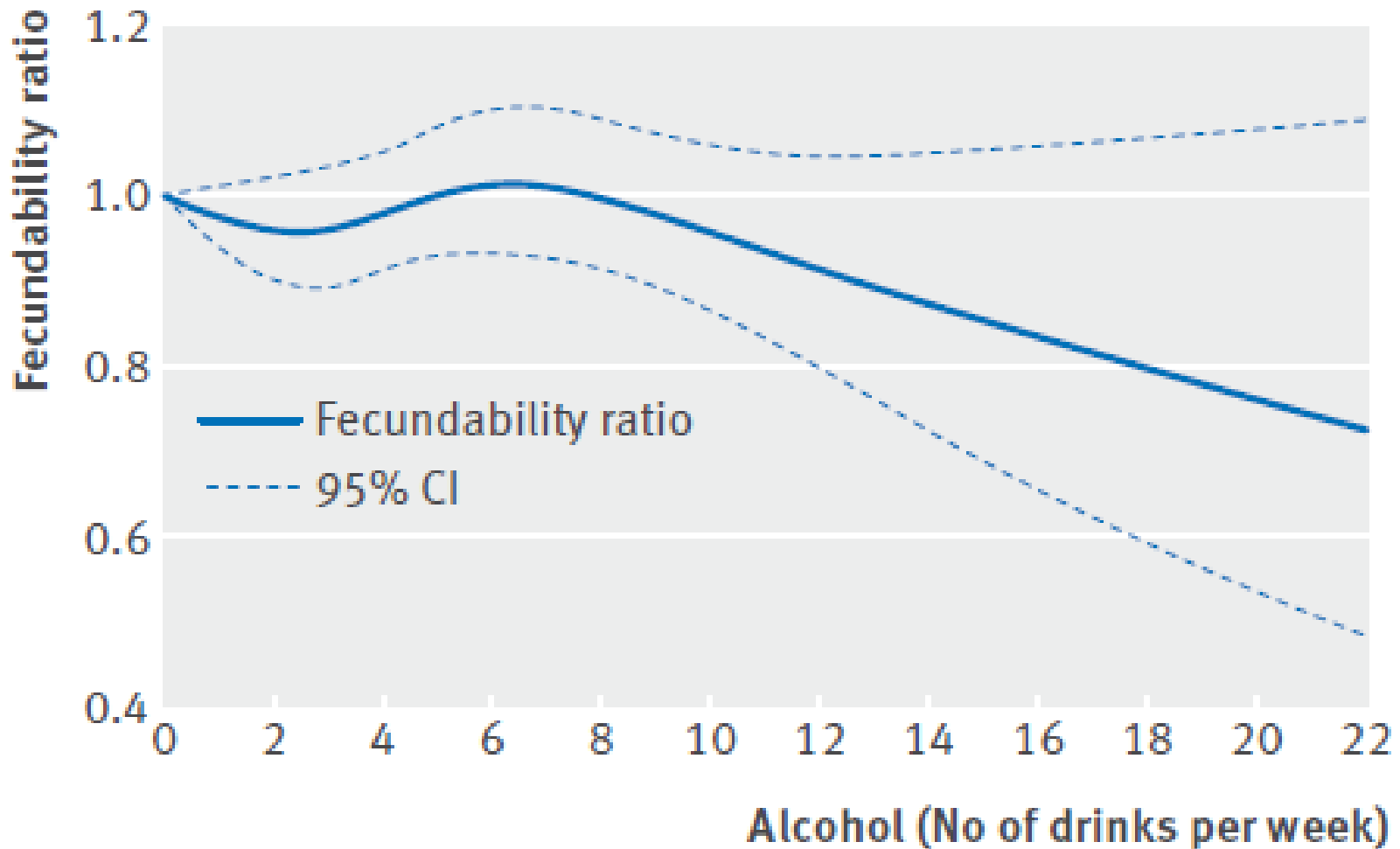


“For how many cycles have you been trying to become pregnant?”

Example: total TTP = 3 cycles (attempt time at study entry) + 8 cycles (observed “at risk” attempt time) = 11 cycles



# Female alcohol intake and fecundability



# Total fish intake and fecundability

PRESTO

