



Obesity and Fertility in Women: Can we and should we treat obesity prior to conception?



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Disclosures

- Consultant: Odega, Bayer, Abbvie, Kindex, Fractyl, Millendo, NIH
- Research Funding: Ferring, NIH, Tobacco Settlement Funds PA

Off Label Medications

Sibutramine, Orlistat, Phentermine/Topiramate:
Not indicated for infertility

Obese women should lose weight prior to conception as it will clearly improve their chances for pregnancy and a healthy pregnancy

**The most entrenched
conflict of interest in
medicine is a
disinclination to reverse a
previous opinion**

Cover Quote, The Lancet, April 9-15,
2011

Conclusions

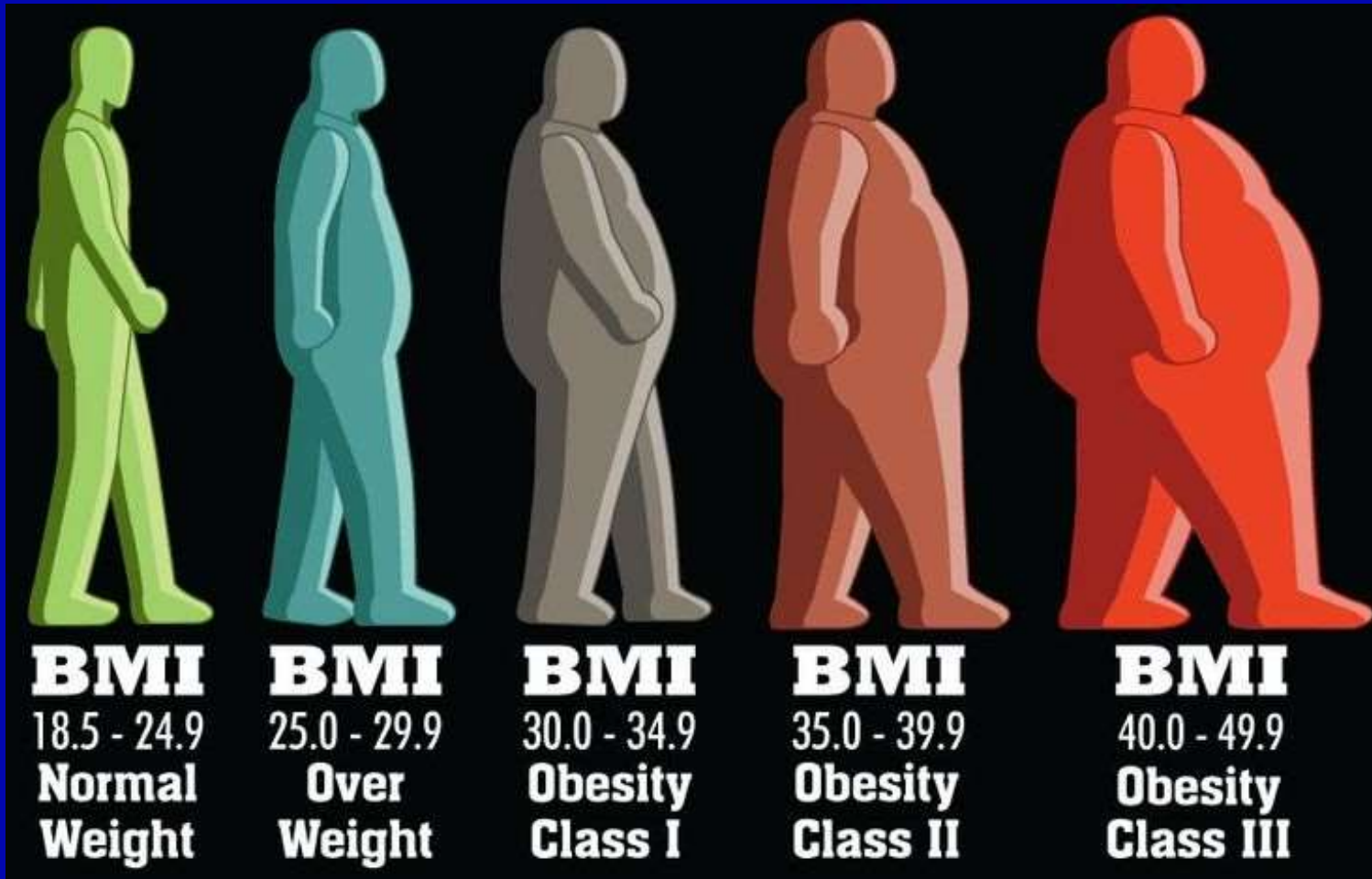
- Obesity is epidemic in western societies
 - ◆ It is associated with reproductive failure (women more than men)
- Obesity alone, however, is only a minor contributor to reproductive failure and pregnancy complications
 - ◆ There is no female cutpoint beyond which it is absolutely “unsafe” to have a pregnancy
- Treatments to restore normal weights are largely ineffective in most obese women and may hold reproductive harms not imagined

Disclaimer

- Tonight's talk is focused solely on reproduction, not long term health.
- The talk is focused on the effects of obesity *per se*, not associated comorbidities
- What weight is ideal for reproduction might not be applicable for long term health.
- Obesity treatments that improve long term health (diabetes, heart disease cancer) might not have the same benefits on improving reproduction

BMI: Body Mass Index

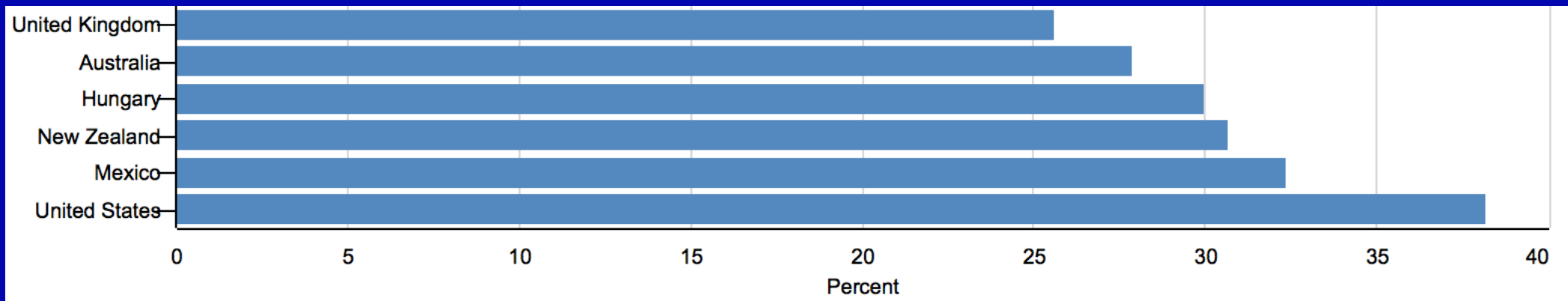
- Weight corrected for height (kg/m^2)



BMI: Not always an accurate measure of fat



New Zealand: Bronze Medal for World Obesity



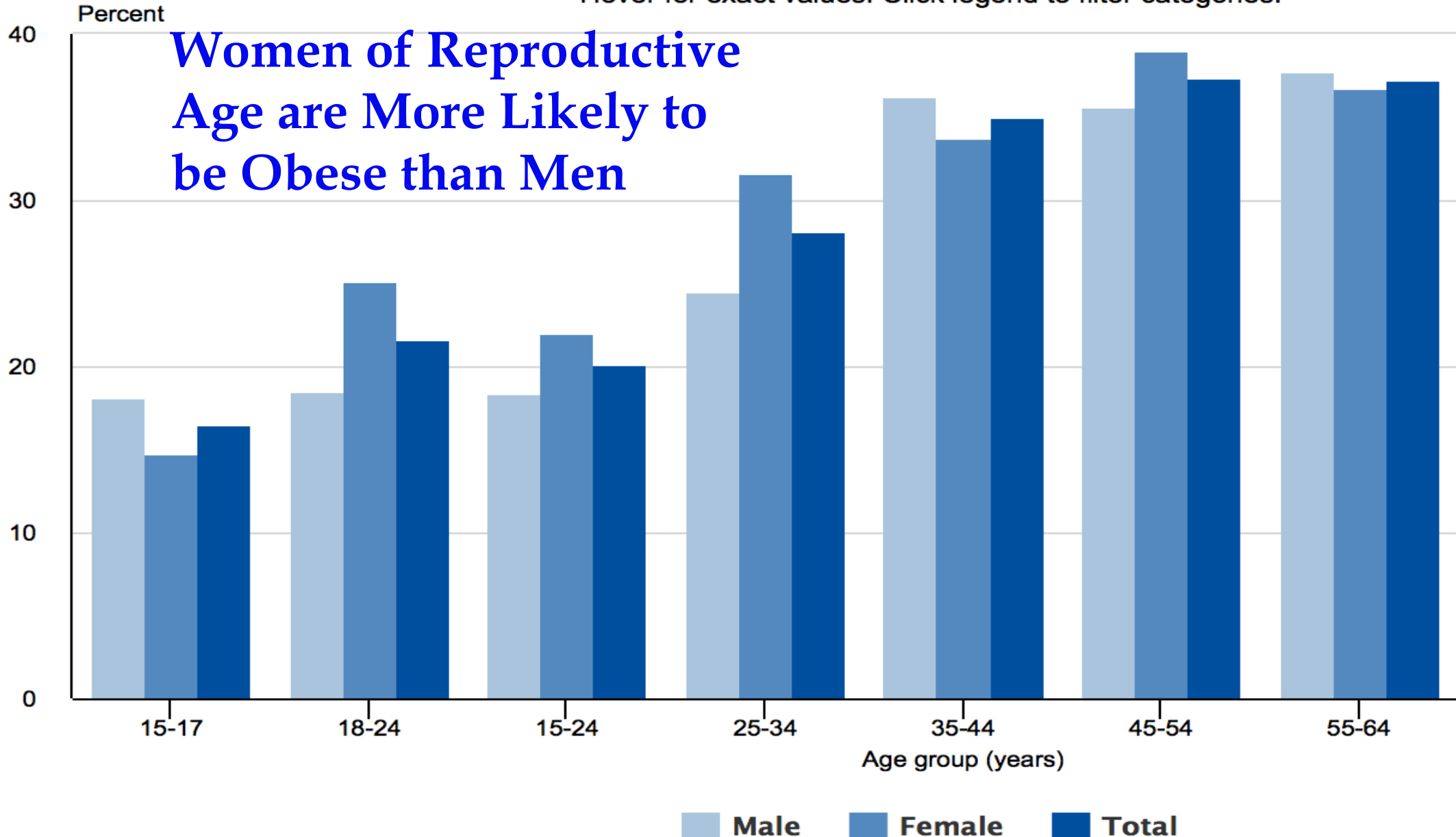
1 in 3 New Zealanders are Obese

Proportion of population, 15 years and over, who are obese

By age group and sex, 2015/16

Hover for exact values. Click legend to filter categories.

Women of Reproductive
Age are More Likely to
be Obese than Men



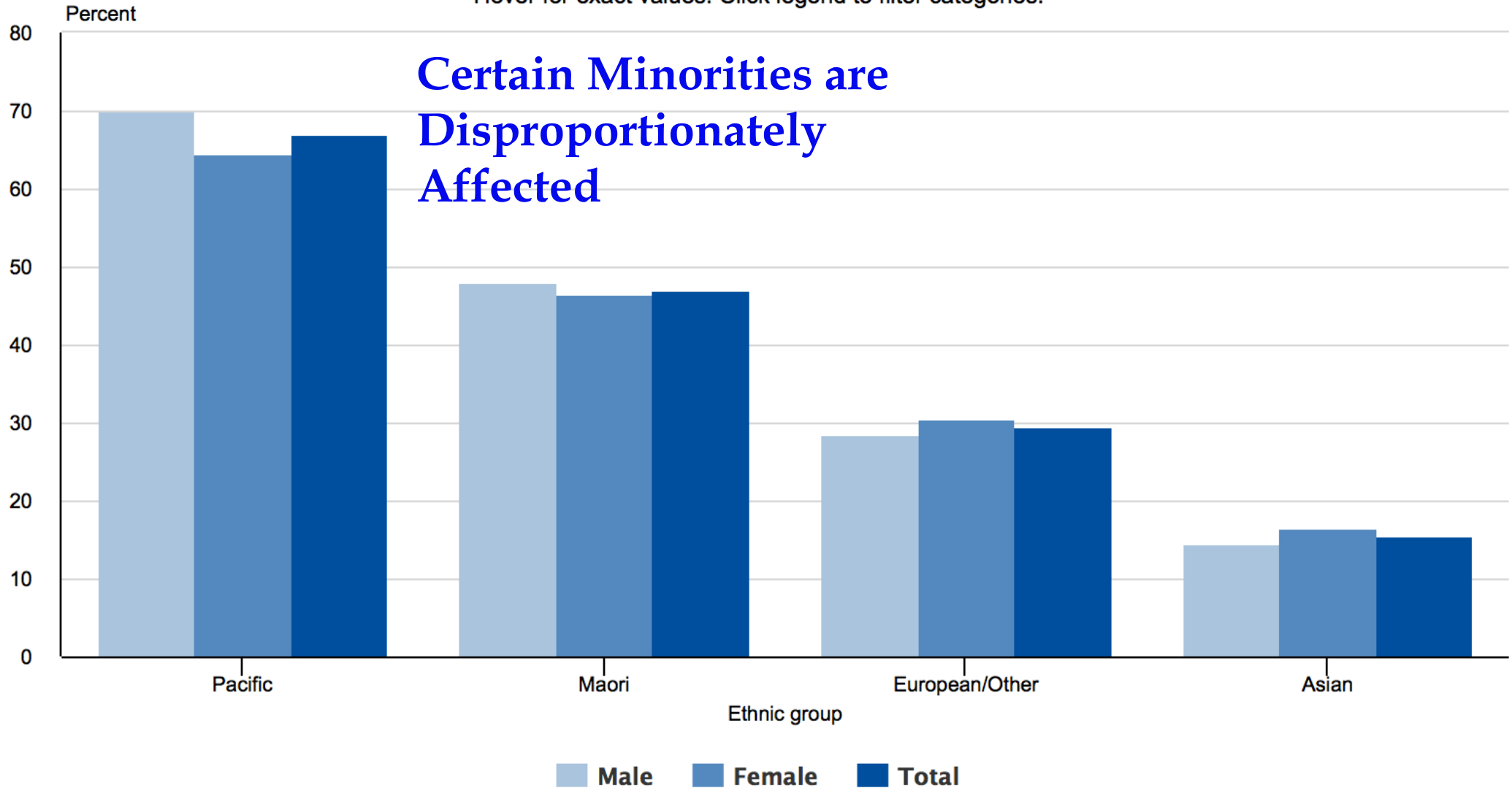
Proportion of population, 15 years and over, who are obese



By ethnic group and sex, 2015/16

Hover for exact values. Click legend to filter categories.

**Certain Minorities are
Disproportionately
Affected**



Epidemiologic Association of Female Obesity with Reproductive Failure

Pre-pregnancy

- Increased time to spontaneous pregnancy
- Increased prevalence of ovulatory dysfunction
 - ◆ Polycystic Ovary Syndrome
- Increased Mood Disorders and Diminished Sexual Function

Pregnancy

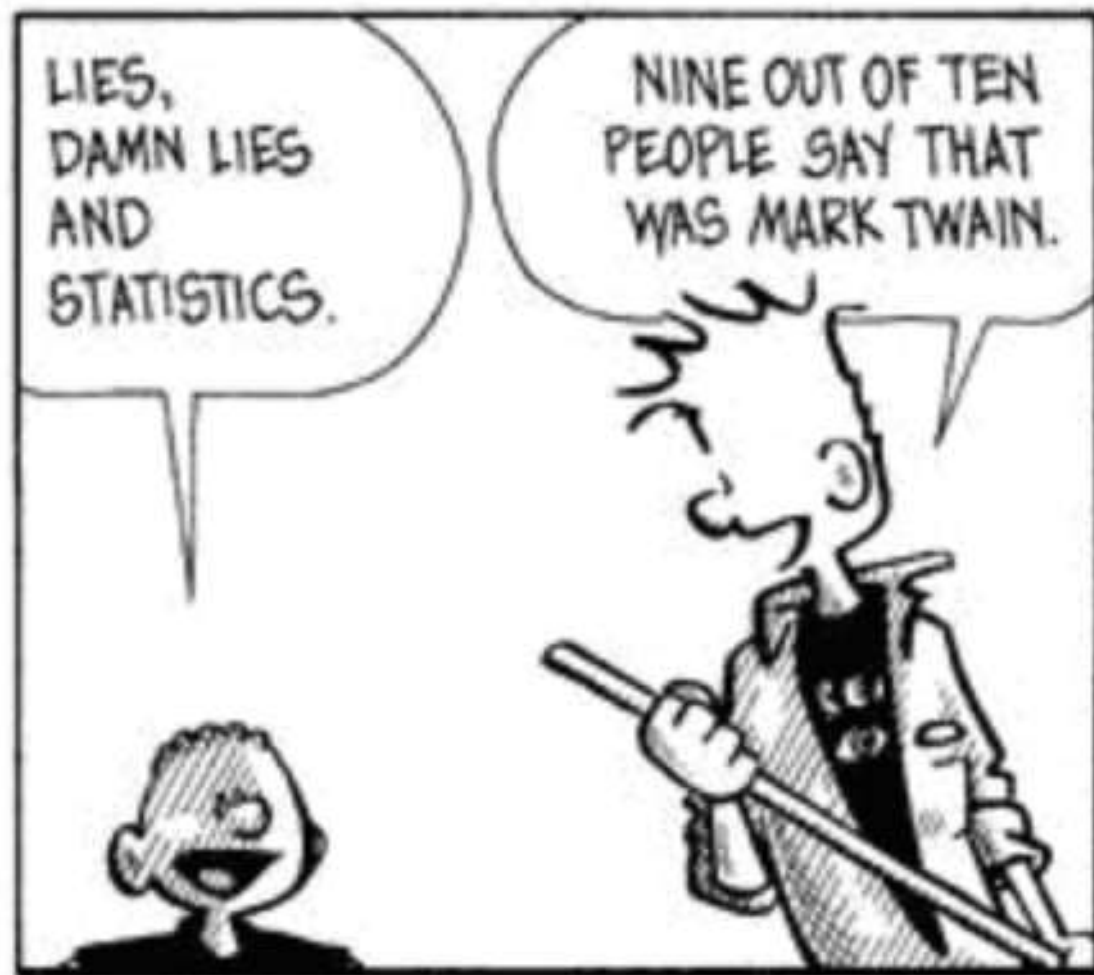
- Increased rate of failure to conceive with treatment
- Increased rates of pregnancy loss (all points of pregnancy)
- Increased rates of major pregnancy morbidities
 - ◆ Preterm delivery (infant)
 - ◆ Hypertensive Disorders (mother)
- Increased risk of operative delivery and associated morbidity

by Jef Mallett



MALLET

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Increased Risk of IVF Failure with Increasing BMI

	Own Oocytes	
BMI Group	Adjusted Odds Ratio	95% Confidence Intervals
18.5-25	1.00	Reference
25-30	1.14	1.07-1.51
30-35	1.31	1.15-1.36
35-40	1.37	1.18-1.51
40-45	1.47	1.14-1.69
45-50	1.76	1.21-2.31

From
SART
Registry
based on
42,699
IVF
cycles

Risks of Death: U.S. National Safety Council 2008 Data

Lifetime risk of death in an automobile accident	1 in 98
Lifetime risk of death in an airplane accident	1 in 7178

**Relative Risk
(RR) of death in
automobile vs
airplane: 72.5
(95% CI 5-1151,
P =.0024)**

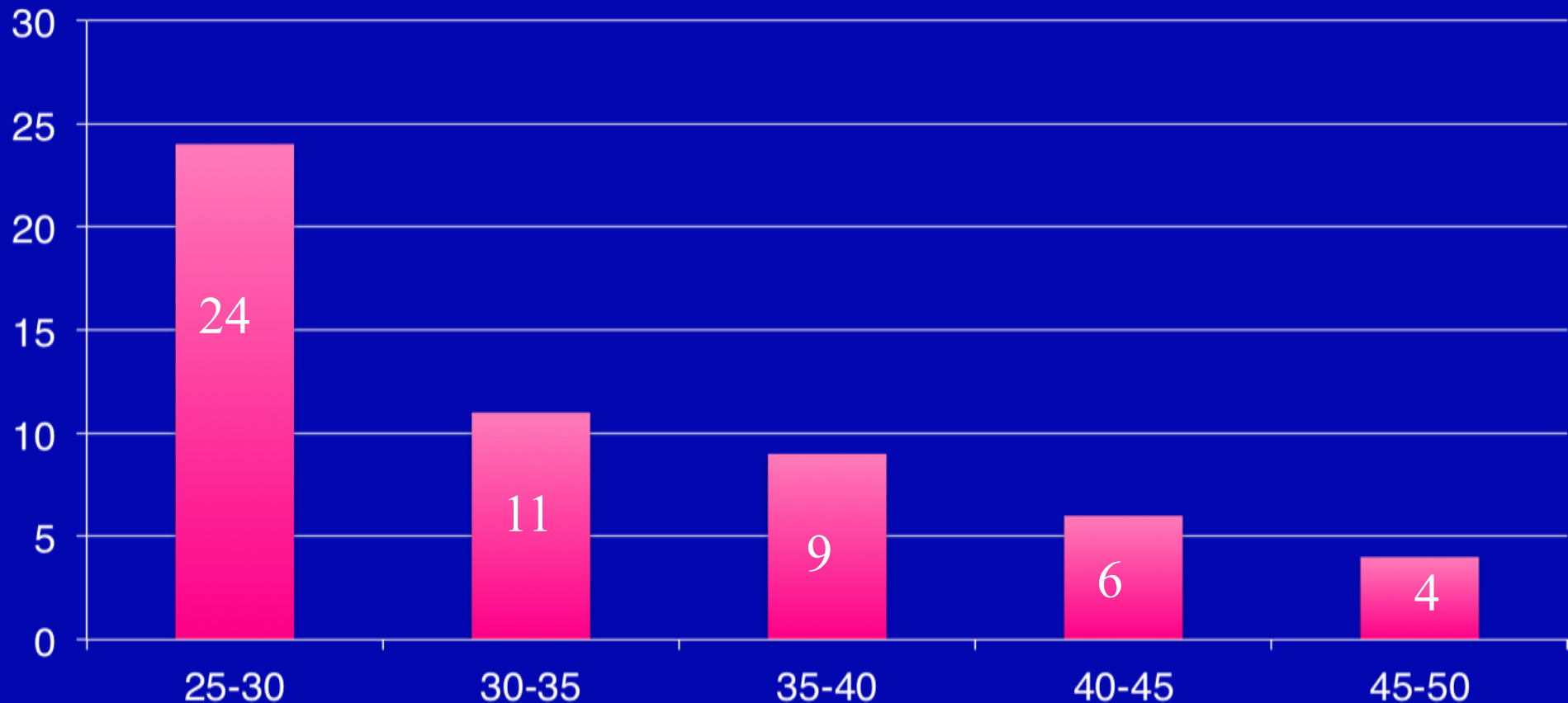
Absolute Chance of IVF Success with Increasing BMI

	Own Oocytes, Age 35-37 years	
BMI Group	Adjusted Odds Ratio	Chance of Live Birth per IVF cycle
18.5-25	1.00	30%
25-30	1.14	26%
30-35	1.31	21%
35-40	1.37	19%
40-45	1.47	16%
45-50	1.76	7%

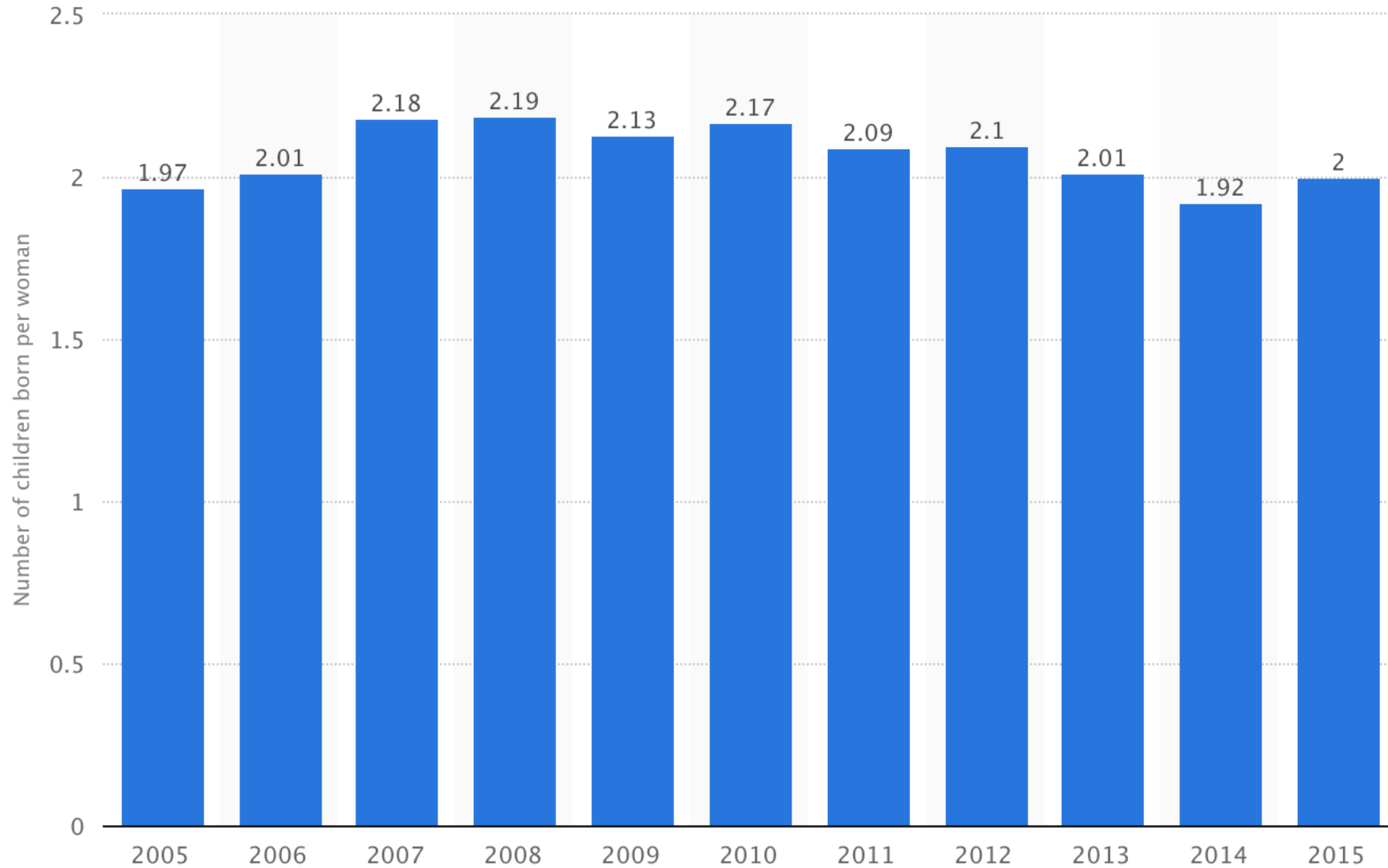
From
SART
Registry
based on
42,699
IVF
cycles
and 2014
SART
success
rates

How many overweight or obese women do I need to treat to experience one weight-related IVF Failure?

NNH: Numbers needed to harm

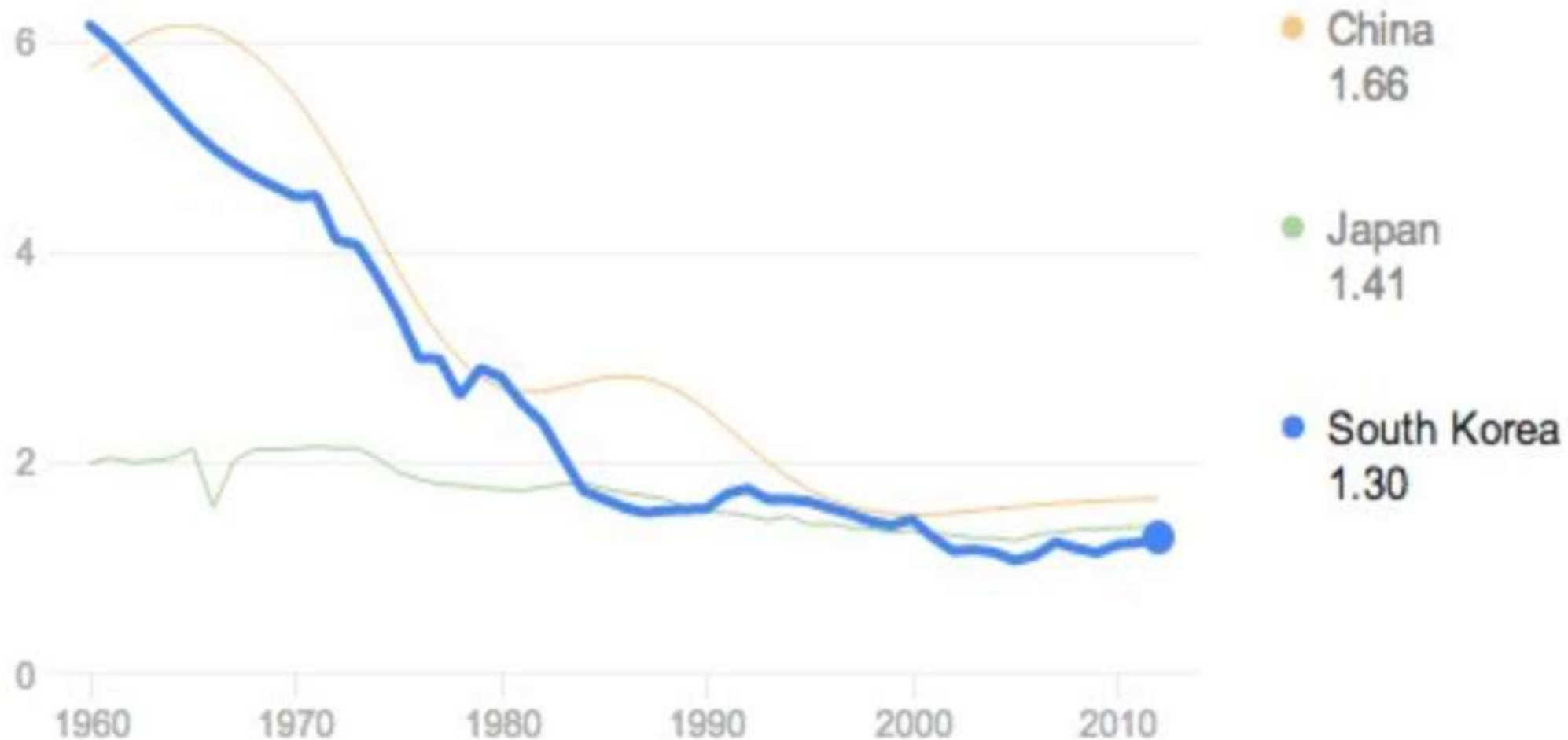


New Zealand: Fertility rate from 2005 to 2015



1.30 births per woman (2012)

South Korea, Fertility rate



Failure to conceive is not a major public health issue in most developed countries

However Doctors may be significantly adding to adverse public health outcomes during pregnancy to mothers and infants, by helping obese women to conceive.

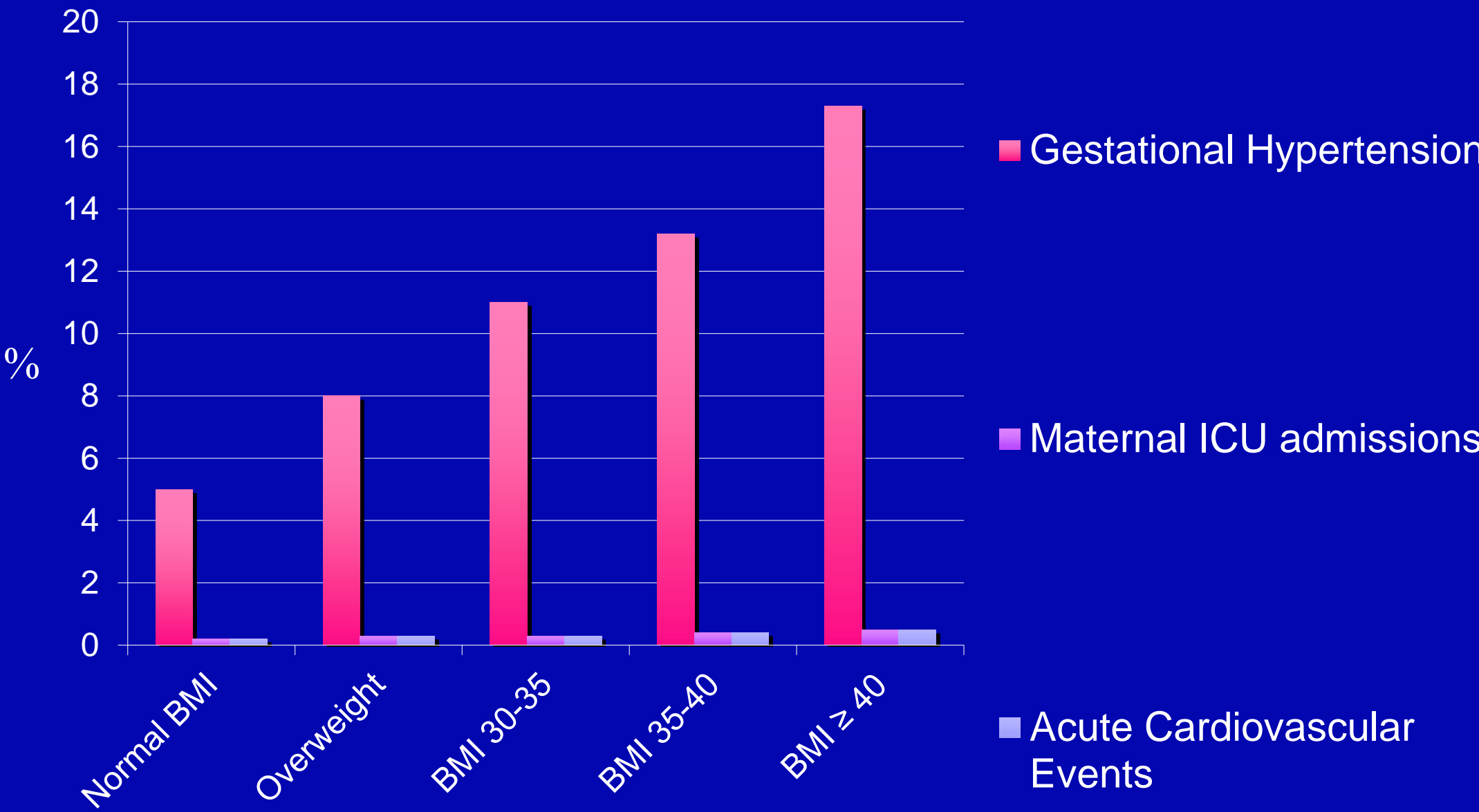
Primum Non Nocere
Hippocratic Oath

First, Do no harm

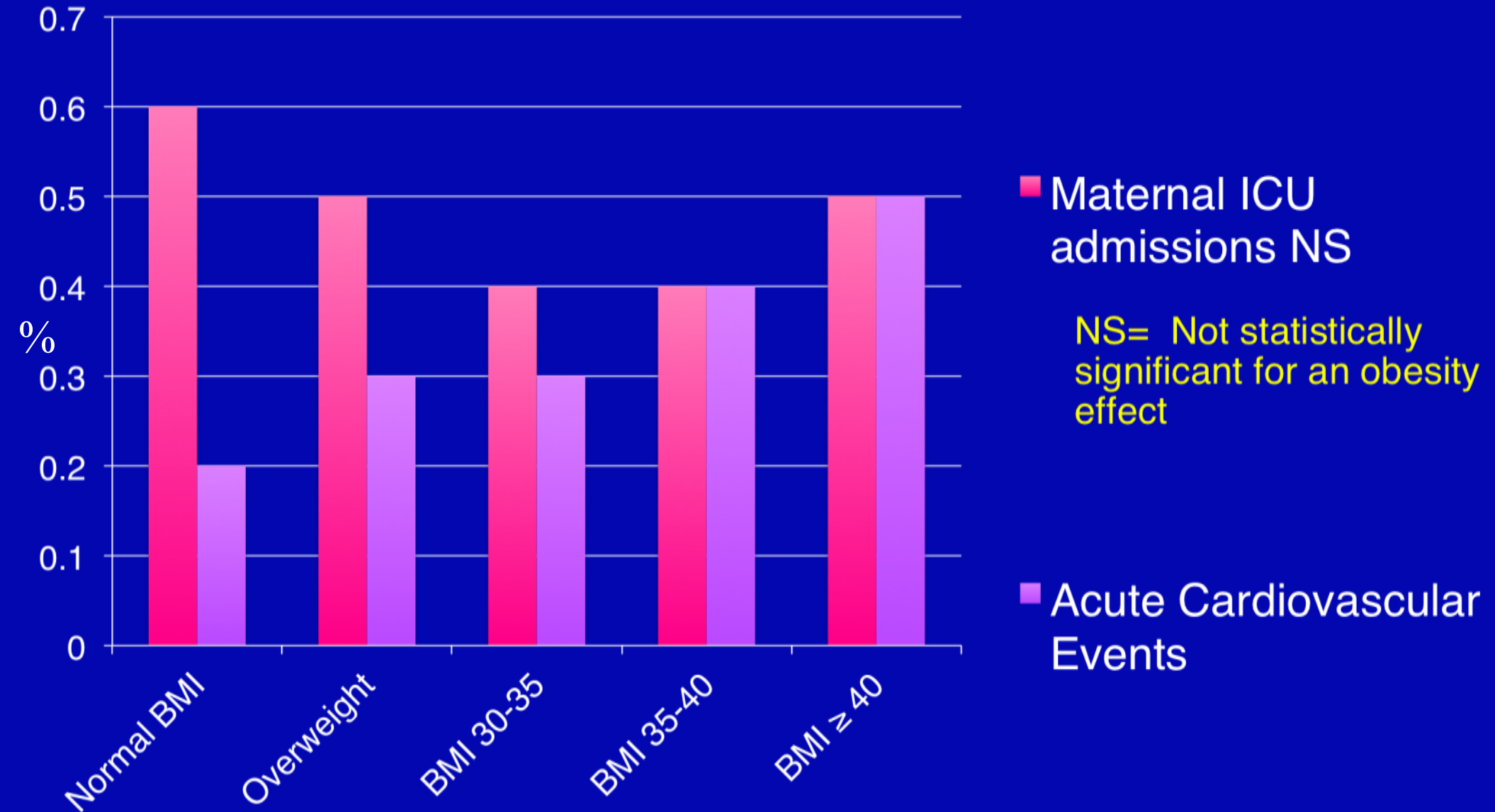
**“Obstetric risks were
variably (and mostly
marginally) increased as
body mass index (BMI)
category and obesity class
increased.”**

N = 148,689 Singleton
Pregnancies, 14 centers,
2002-2008

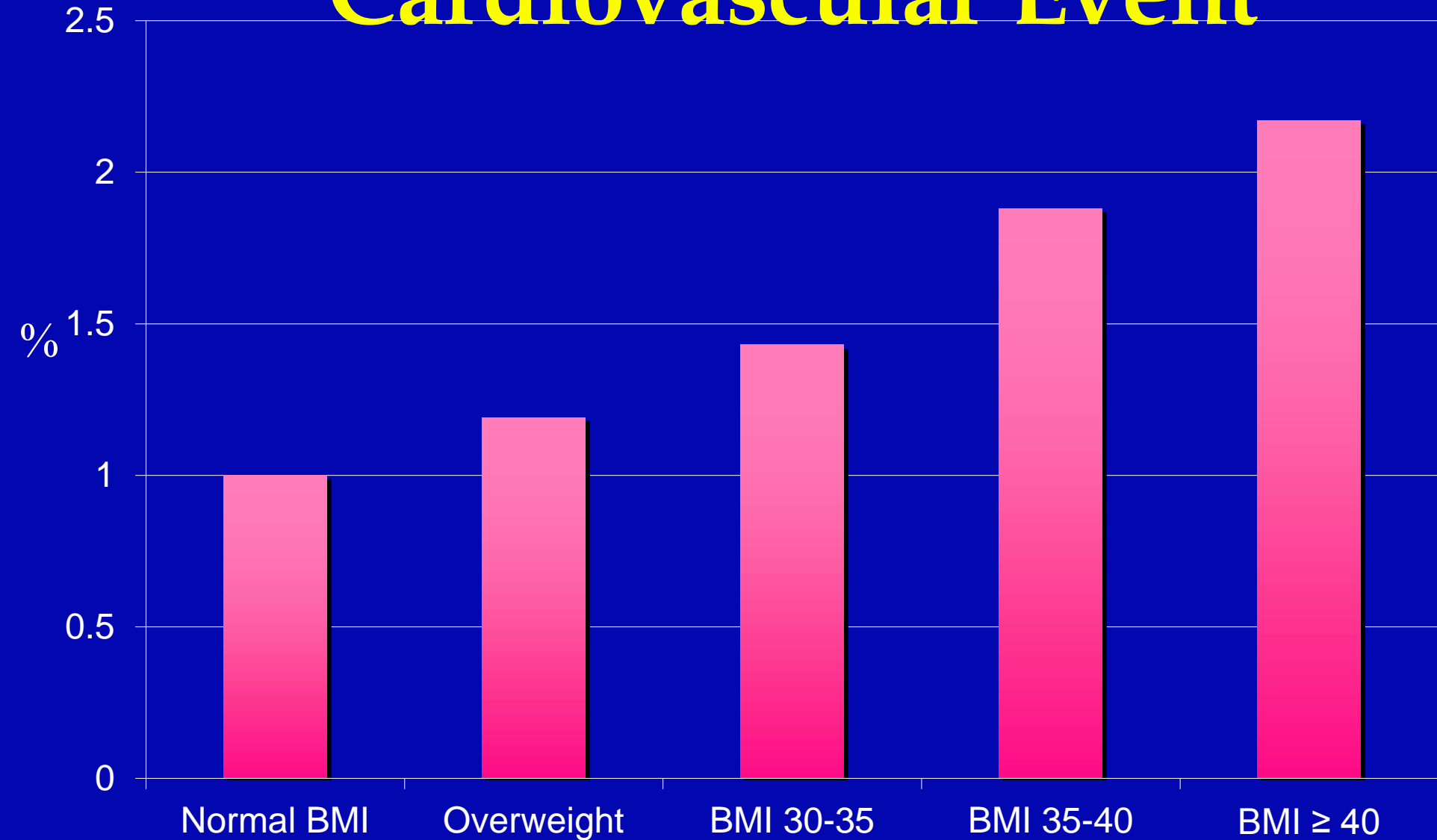
Risk of Maternal Complications by Obesity Class



Risk of Maternal Complications by Obesity Class

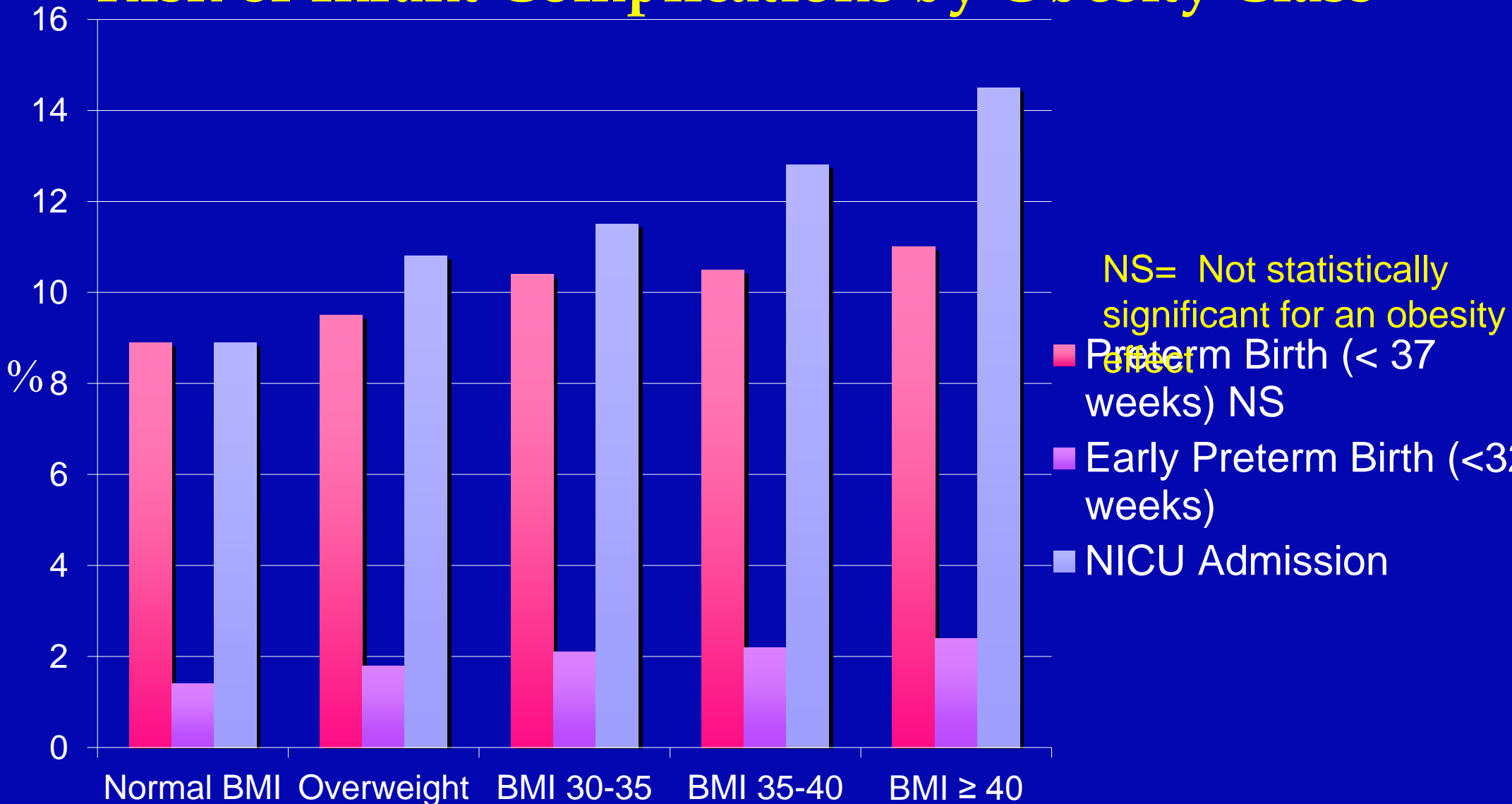


Relative Risk of Acute Cardiovascular Event



Kim SS et al, Obstet Gynecol, 2016

Risk of Infant Complications by Obesity Class



Numbers Needed to Harm in the Most Obese Maternal Group (BMI ≥ 40)

Disorder	Number Needed to Harm (NHM)
Gestational Hypertension	8
Infant NICU Admission	18
Early Preterm Delivery (<32 weeks)	100
Acute Maternal Cardiovascular Event	333

Outcomes	Maternal
----------	----------

Gestational hypertensive disorders	
Gestational diabetes	
Placental previa	
Cesarean delivery	
Prelabor cesarean delivery	
Intrapartum cesarean delivery	
Cesarean delivery after induction	
Cesarean delivery after spontaneous labor	
Operative vaginal delivery	
Induction	
Oxytocin augmentation	
Abruption	
3rd- or 4th-degree laceration	
Hemorrhage	
Blood transfusion	
Maternal fever	
Major puerperal infection	
Infection of genitourinary tract	
Complication of surgical wounds	
Hysterectomy	
Acute cardiovascular events	
Maternal ICU admission	

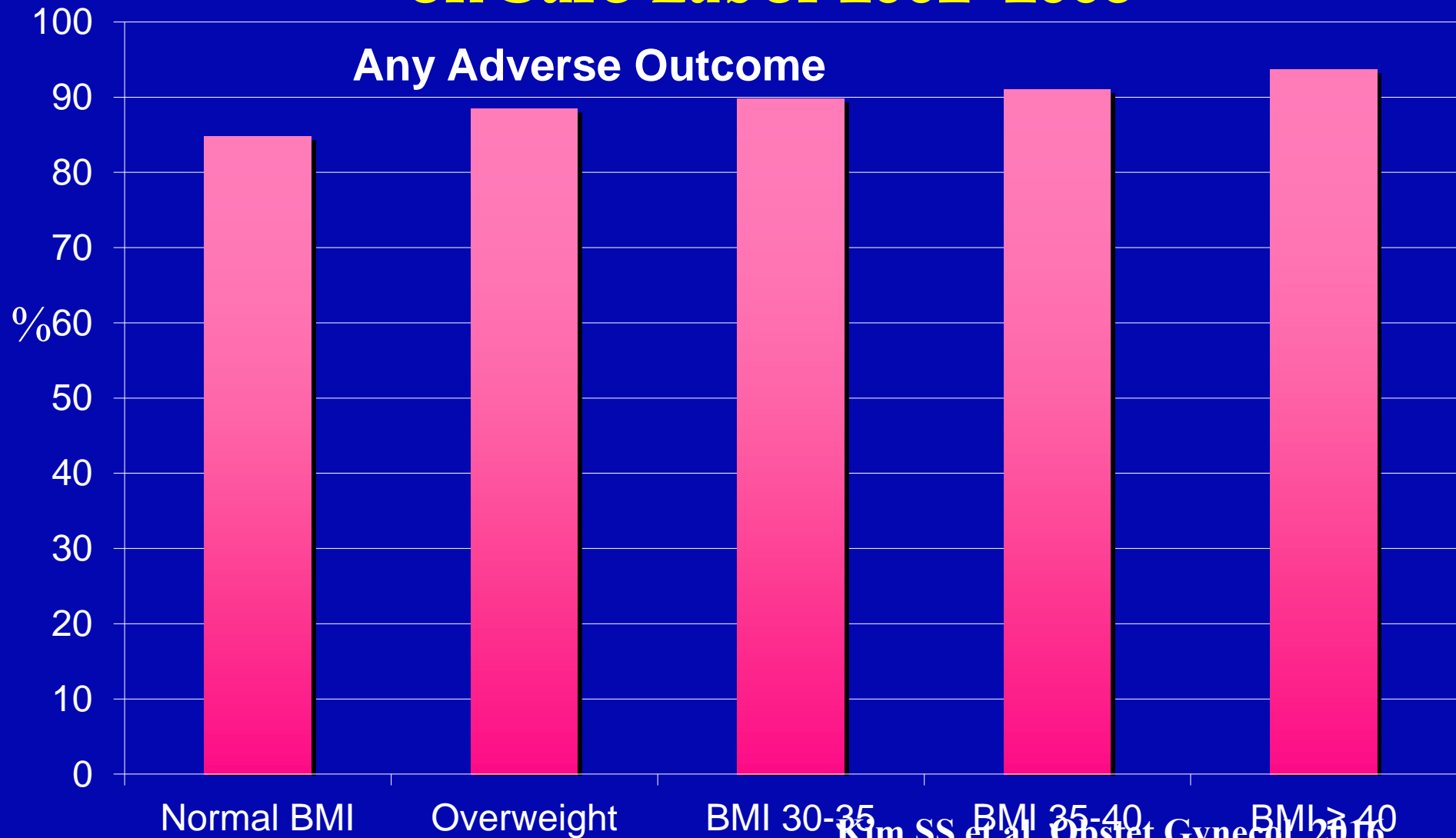
**All the
examined
Outcomes
in Mother
and Infant**

**Kim SS et al,
Obstet Gynecol,
2016**

Outcomes	Infant
----------	--------

Preterm birth at less than 37 wks of gestation	
Early preterm birth at less than 32 wks of gestation	
Late preterm birth at 32 to less than 37 wks of gestation	
Stillbirth	
LGA	
Birth injury	
Congenital anomaly	
Transient tachypnea	
Apnea	
Aspiration	
Asphyxia	
Sepsis	
Seizure	
Intracranial hemorrhage	
NICU admission	
Among preterm births	
Respiratory distress syndrome	
Necrotizing enterocolitis	
PVH-IVH	
Retinopathy of prematurity	

Combined Risk of Obstetric and Neonatal Complications by Prepregnancy Obesity, Consortium on Safe Labor 2002–2008



Kim SS et al, Obstet Gynecol, 2016

Combined Risk of Obstetric and Neonatal Complications by Prepregnancy Obesity, Consortium on Safe Labor 2002–2008

BMI Group	Adjusted Relative Risk	95% CI	Number Needed to Harm
Normal BMI	1.00	--	--
Overweight	1.05	1.05-1.06	27
30-35	1.07	1.07-1.08	20
35-40	1.09	1.08-1.10	16
>40	1.12	1.11-1.13	11

Obesity and Female Reproduction

- Obesity is associated with increased risk for reproductive failure and maternal and infant morbidity
 - ◆ Not every morbidity is increased
 - ◆ Normal weight women have high baseline rates for similar morbidities
- However the risk, when present with obesity, tends to be linear and marginal
 - ◆ Even for the highest weight classes

Obesity Comorbidity/Obesity Management

Does weight loss in overweight or obese women improve fertility treatment outcomes? A systematic review

K. A. Sim, S. R. Partridge and A. Sainsbury

August 2014

Conclusion: “While the overall quality of the studies included in this review was poor.... (only 2 RCTs, not powered for live birth)”

Small Studies Favor Lifestyle Intervention Improving Fertility

Reference, Year	N	Intervention	Outcome
Becker GF et al, Am J Clin Nutr, 2015	26	Hypocaloric/ Low glycemic index diet vs control x 12 weeks	3 live births in diet arm
Sims KA and et al, Clin Obesity 2014	59	Varying Low Calorie Diet/Group intervention vs Usual Care x 12 weeks	Live Birth Rate: 44% in diet vs 14% in Usual Care

Essay

Why Most Published Research Findings Are False

PLoS Med. 2005;2:1371

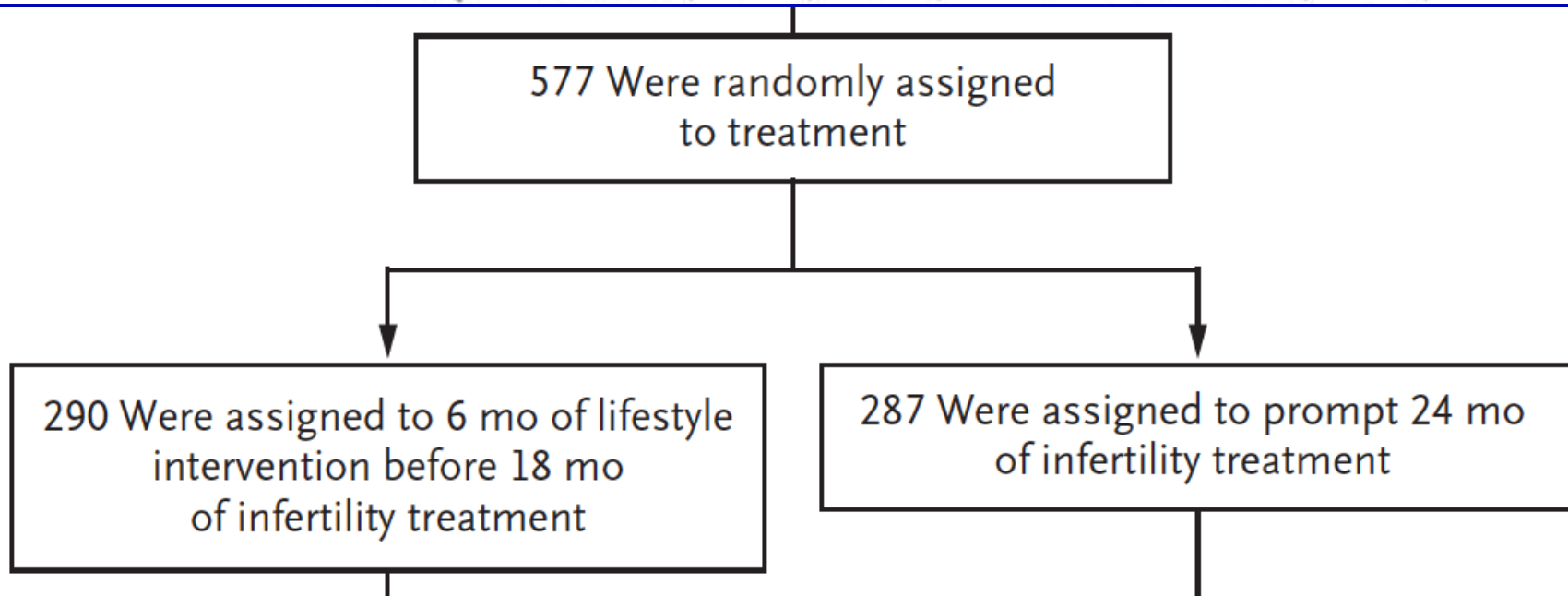
John P. A. Ioannidis

- Study is small
- Greater number and lesser pre-selection of tested relationships
- Greater flexibility in design, definitions, outcomes, and analyses

ORIGINAL ARTICLE

Randomized Trial of a Lifestyle Program in Obese Infertile Women

Meike A.Q. Mutsaerts, M.D., Ph.D., Anne M. van Oers, M.D.,



The Diabetes Prevention Program

A Randomized Clinical Trial
to Prevent Type 2 Diabetes
in Persons at High Risk: Lifestyle
Modification VS Metformin VS Placebo
Control

The DPP Research Group

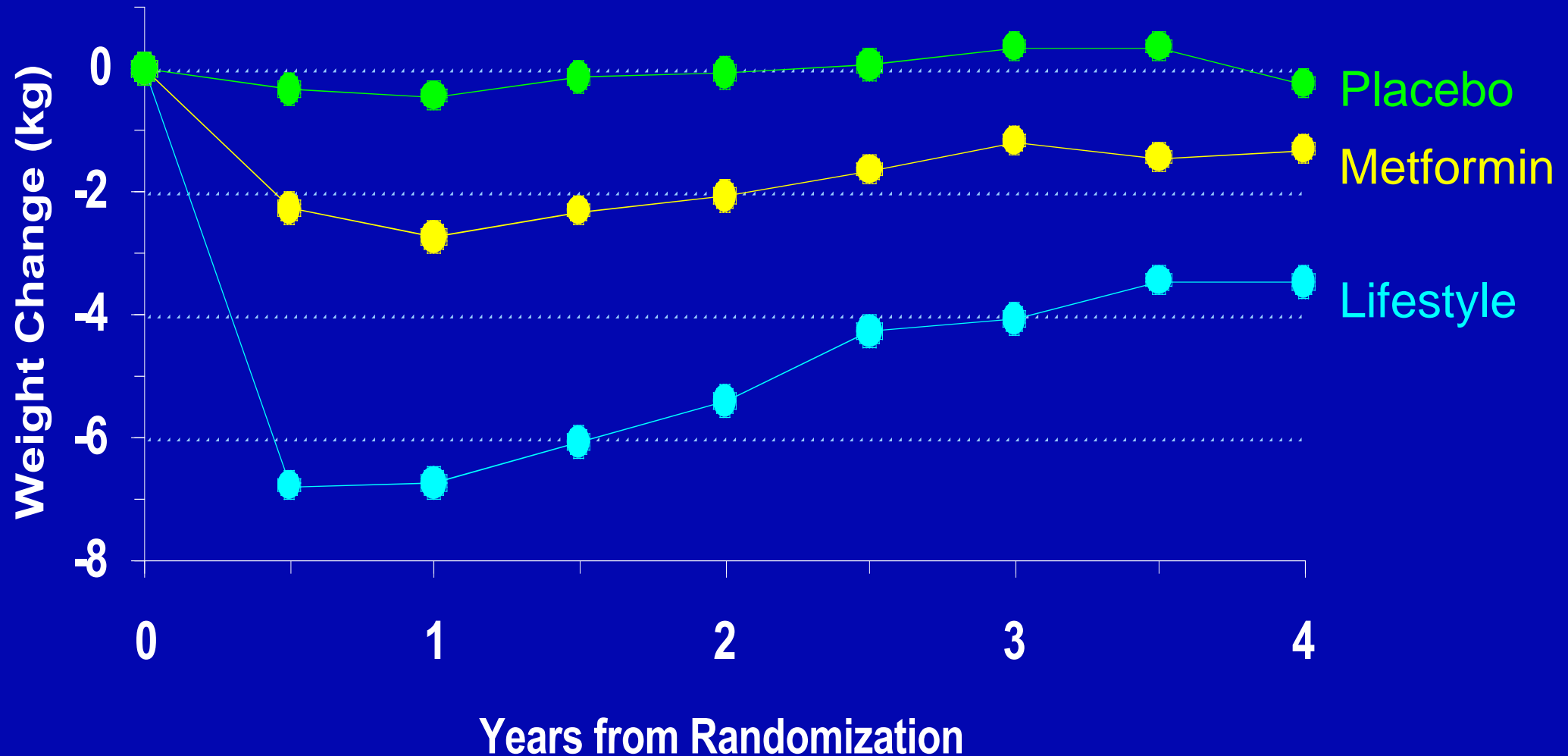


Lifestyle Intervention-Diabetes Prevention Program

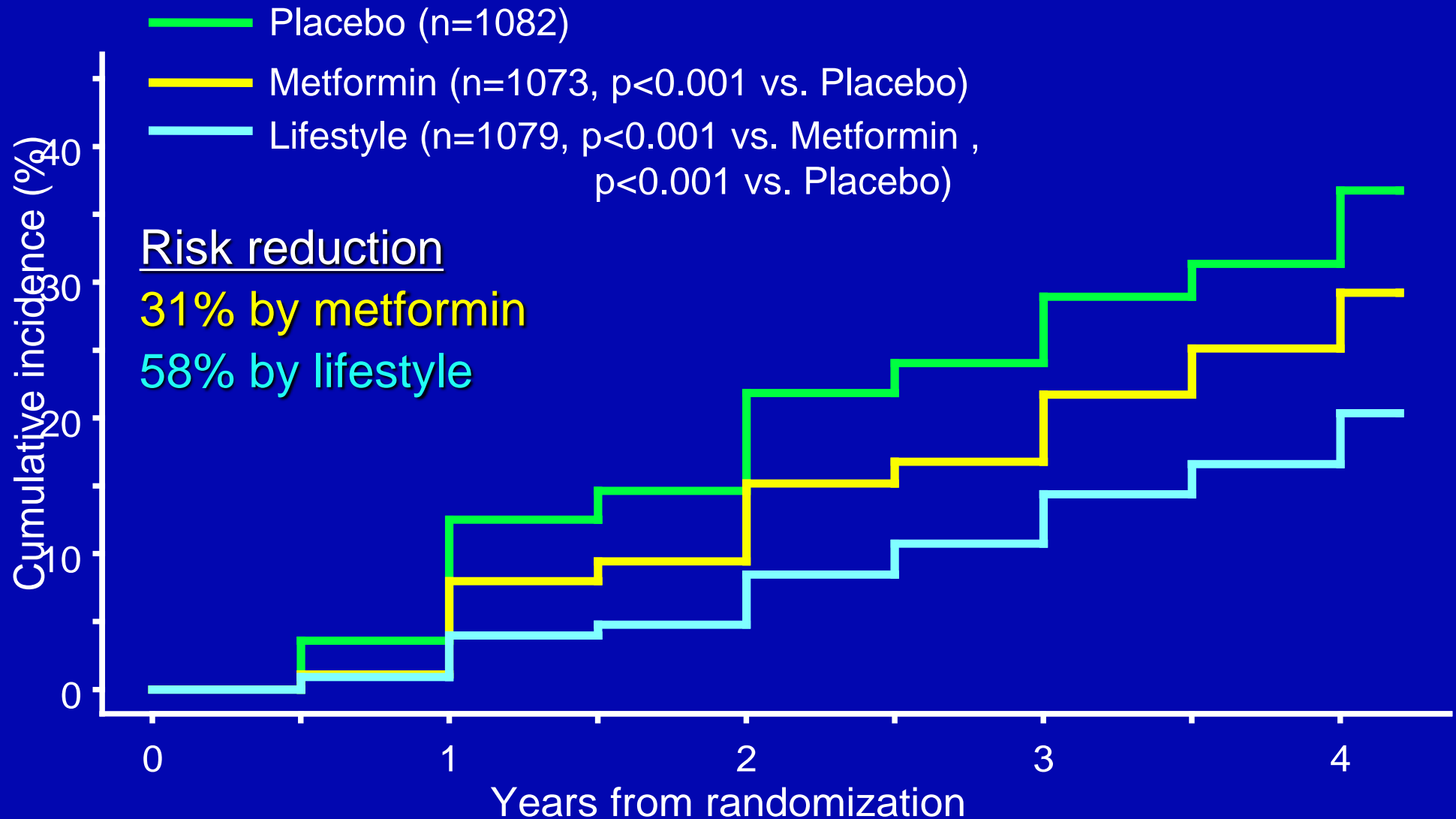
An intensive program with the following specific goals:

- $\geq 7\%$ loss of body weight and maintenance of weight loss
 - Dietary fat goal -- $<25\%$ of calories from fat
 - Calorie intake goal -- 1200-1800 kcal/day
- ≥ 150 minutes per week of physical activity

Mean Weight Change



Incidence of Diabetes



ORIGINAL ARTICLE

Randomized Trial of a Lifestyle Program in Obese Infertile Women

Meike A.Q. Mutsaerts, M.D., Ph.D., Anne M. van Oers, M.D.,

**Mean Starting
Weight ~ 100kg**

577 Were randomly assigned
to treatment

290 Were assigned to 6 mo of lifestyle
intervention before 18 mo
of infertility treatment

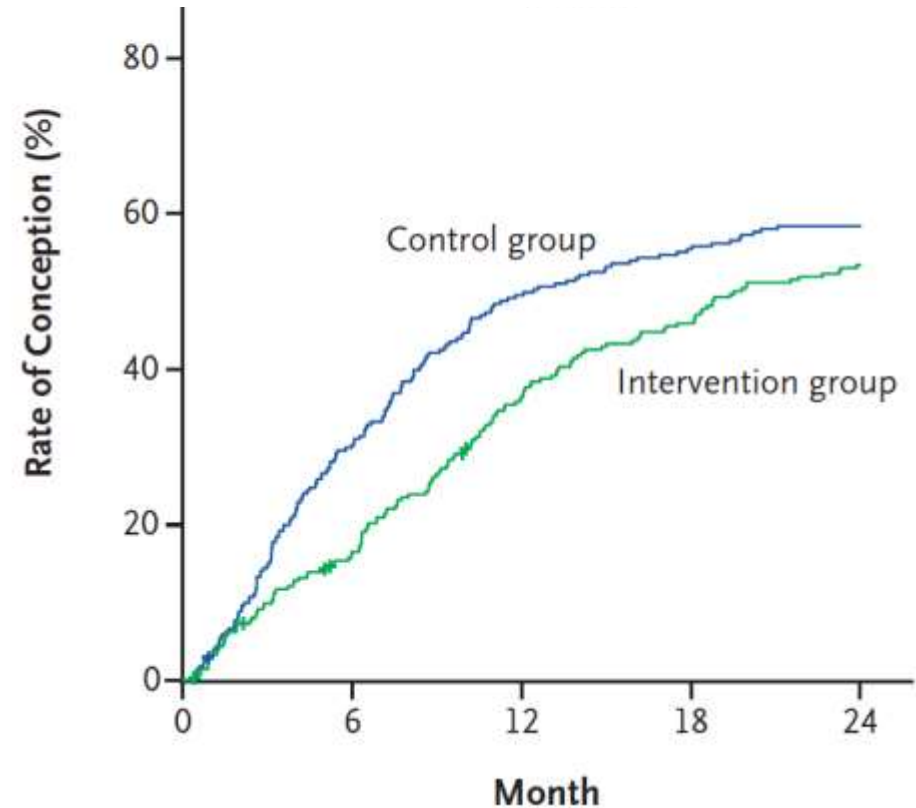
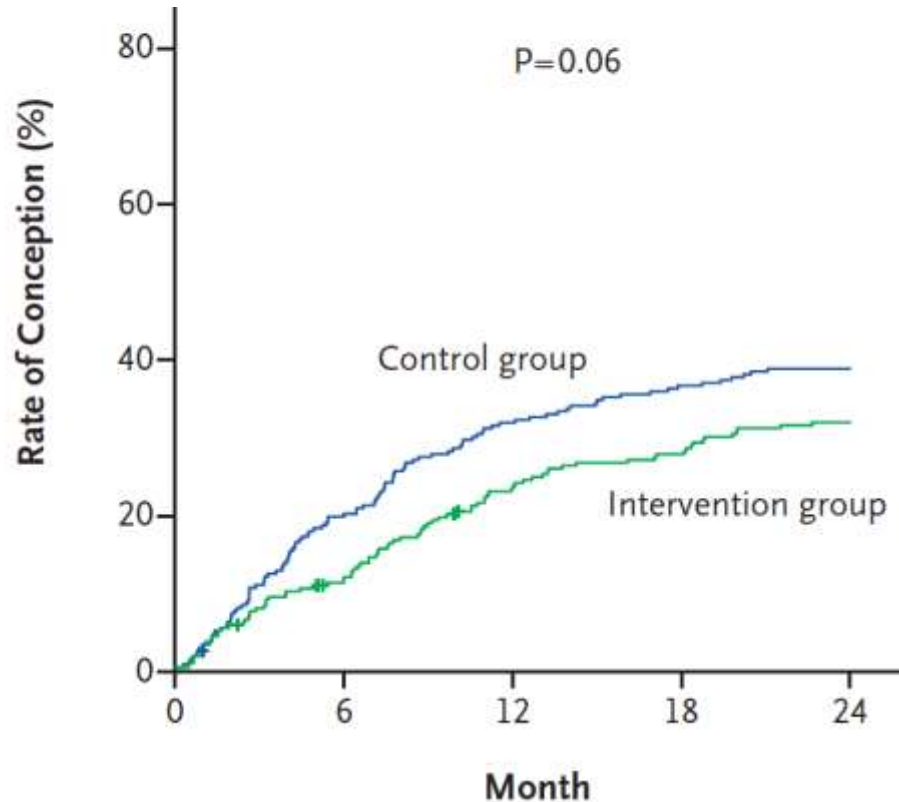
287 Were assigned to prompt 24 mo
of infertility treatment

Lost 4.4 kg

Lost 1.1 kg

CONCLUSIONS

In obese infertile women, a lifestyle intervention preceding infertility treatment, as compared with prompt infertility treatment, did not result in higher rates of a vaginal birth of a healthy singleton at term within 24 months after randomization. (Funded by the Netherlands Organization for Health Research and Development; Netherlands Trial



Mutsaerts et al, NEJM, 2016

No Significant Differences in Pregnancy Complications Between Groups, but..

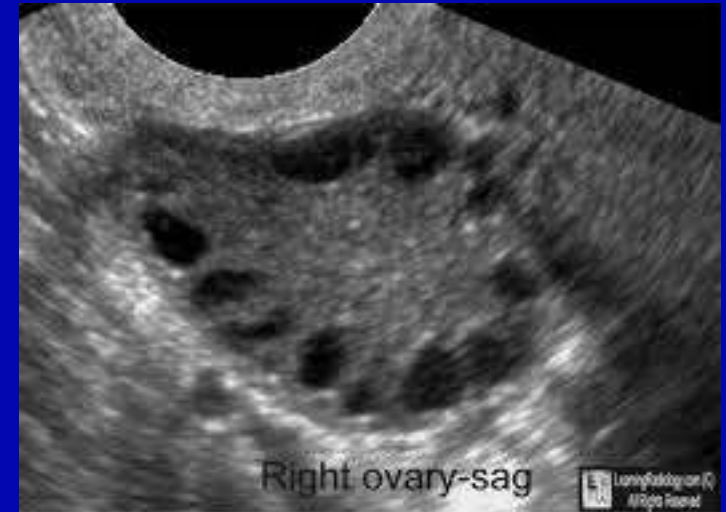
Complication	Intervention	Control	Rate Ratio (95% CI)
Pregnancy Loss	14.6 %	9.5 %	1.54 (0.98- 2.43)

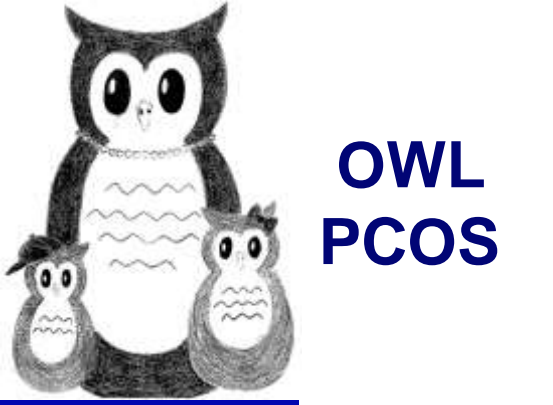
Are there subsets of infertile women who may benefit from weight loss

Is there a dose response relationship, i.e. the more the weight loss the better the fertility response

Polycystic Ovary Syndrome

- A syndrome of excess androgen, chronic anovulation and polycystic ovaries
- The leading female cause of infertility in the U.S.
- Often associated with obesity
 - ◆ Weight loss is thought to improve ovulation and fertility





Clinicaltrials.gov: NCT00704912

**Infertile
Overweight/Obese
Women with PCOS N =**

149

**Lifestyle
Modification**

**Continuous
OCP**

Combined

↓ 16 Weeks ↓

Ovulation Induction with Clomiphene: 4 cycles

Conception: Follow q trimester

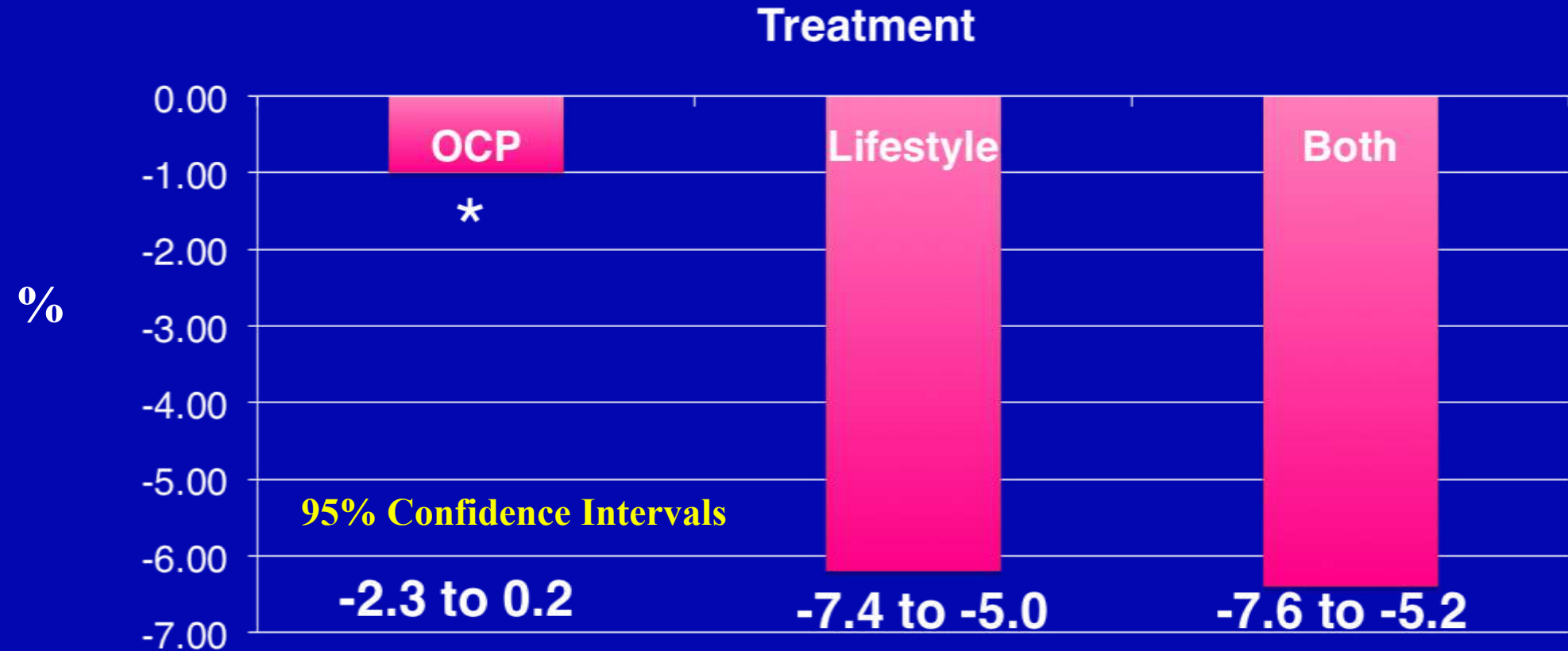
PRIMARY OUTCOME: Live Birth

Legro et
al,
JCEM,
2015

Lifestyle Modification with Weight Loss (7% Target)

- ◆ **Meal Replacements** for all 3 meals with fresh vegetables/fruit supplement (Caloric Restriction)
 - 500kcal/day Deficit
- ◆ Increased Physical Activity (Target: 150 mins/wk)
- ◆ Brief Behavioral Modification Lessons (Monthly)
 - Adapted from the Diabetes Prevention Program
- ◆ **Weight loss medication (BMI \geq 30 only)**
 - Sibutramine 5-15 mg/d
 - After the FDA Sibutramine Advisory in 2010 we used over the counter orlistat (60 mg) TID with meals

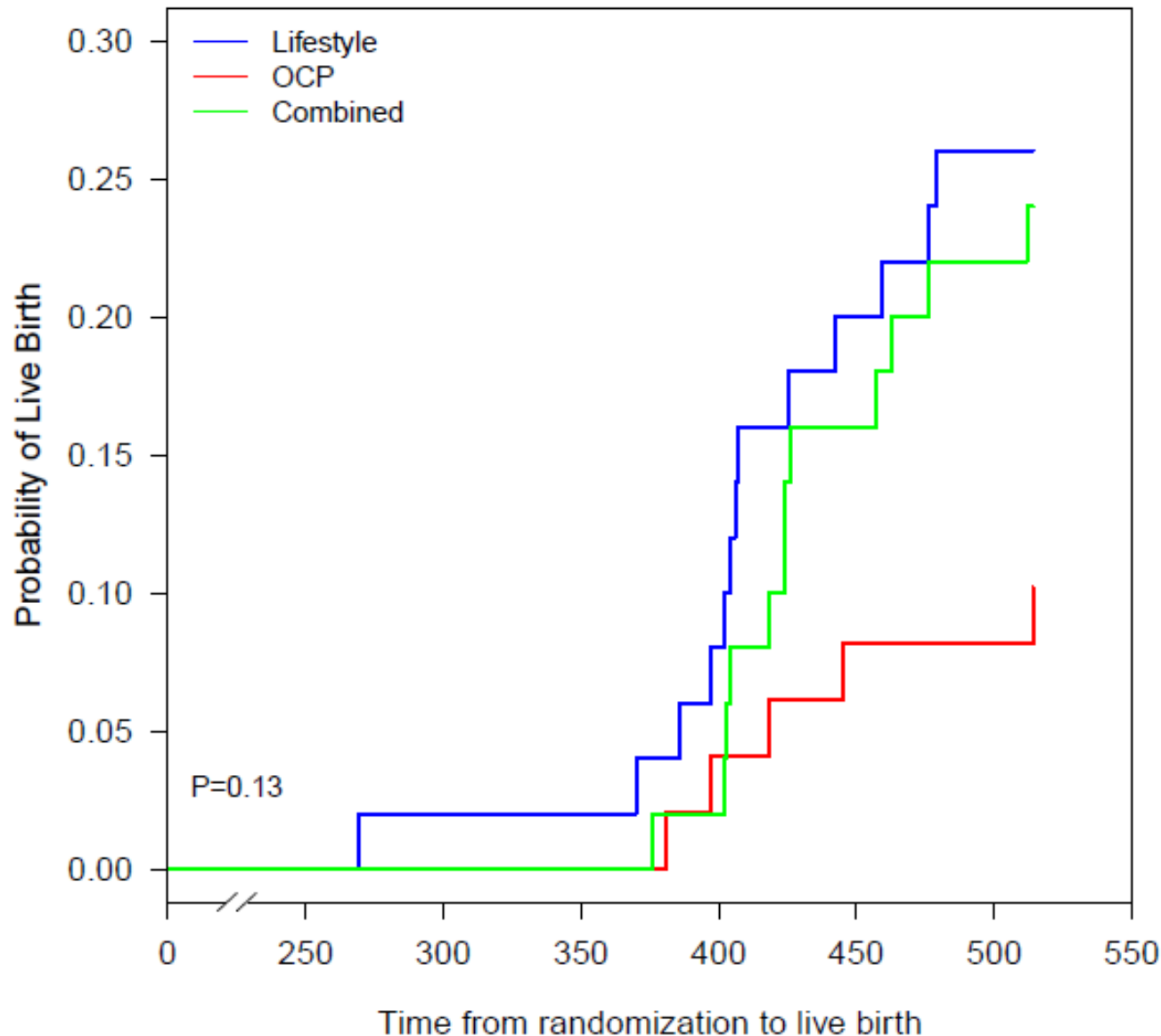
Percent Weight Loss After Preconception Intervention of 16 Weeks



No difference between weight loss with
sibutramine or orlistat

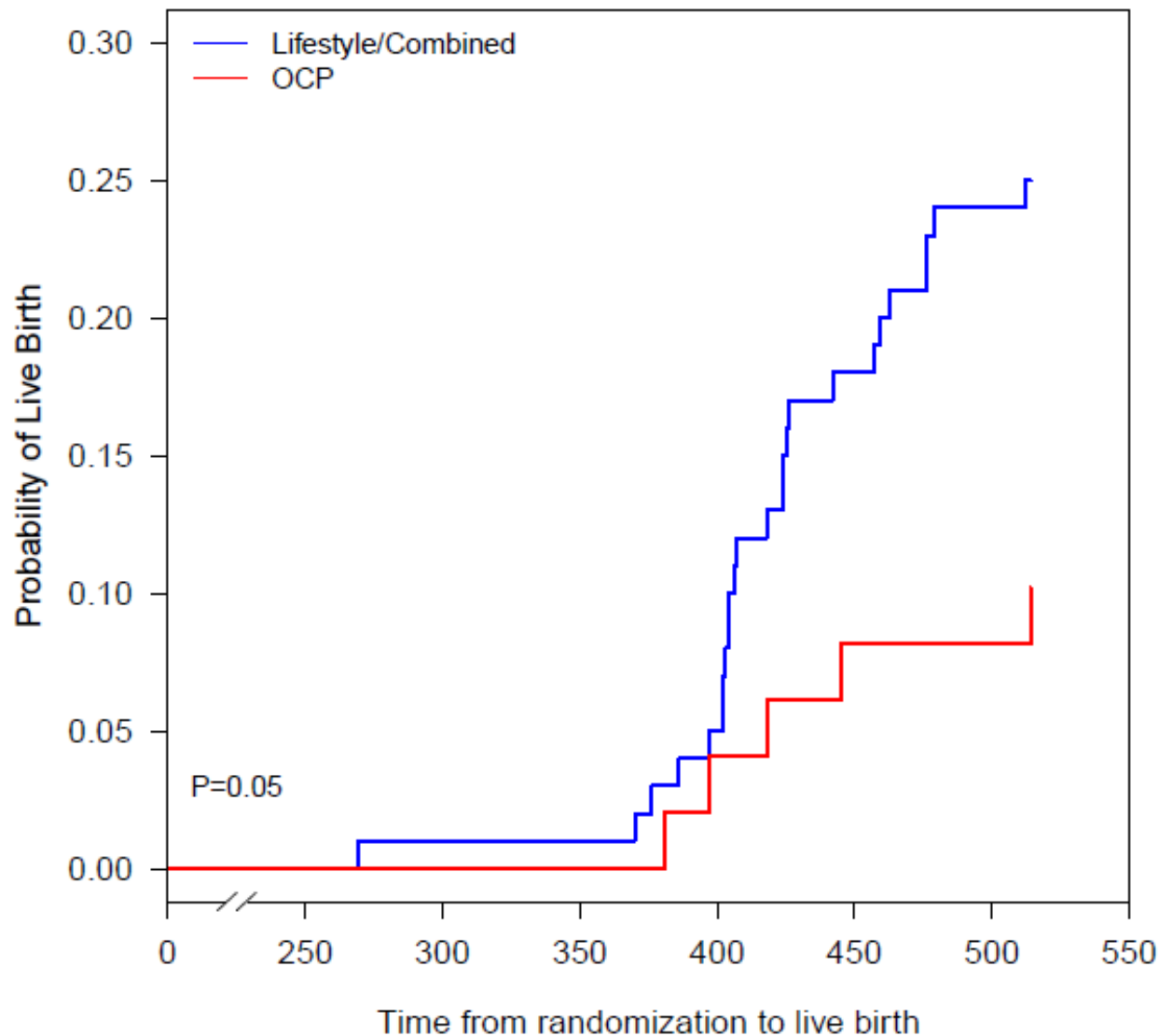
* $P < .0001$

Kaplan Meier Curve: Live Birth Primary Outcome



Legro et al, JCEM, 2015

Post Hoc Analysis: Combination of Lifestyle and Combined into One Treatment Group



Legro et al, JCEM, 2015

Effects of Preconception Weight Loss in Obese Women with PCOS vs Immediate Infertility Treatment

- Women were more likely to ovulate with treatment after weight loss (RR 1.4 95% CI 1.1-3.2)
- Women were more fecund, i.e. more likely to have a baby if they ovulated after weight loss than if they were treated immediately without weight loss (RR 2.5 95% CI 1.4-4.6).

Morbid Obesity is Associated with the Highest Risk for Infertility and Adverse Pregnancy Outcomes

Therefore they should benefit the most
from massive weight loss

Effects of Gastric Bypass Surgery on Female Reproductive Function

Richard S. Legro, William C. Dodson, Carol L. Gnatuk, Stephanie J. Estes, Allen R. Kunselman, Juliana W. Meadows, James S. Kesner, Edward F. Krieg, Jr., Ann M. Rogers, Randy S. Haluck, and Robert N. Cooney

Departments of Obstetrics and Gynecology (R.S.L., W.C.D., C.L.G., S.J.E.), Public Health Sciences (A.R.K.), and Surgery (A.M.R., R.S.H.), Pennsylvania State University College of Medicine, Hershey, Pennsylvania 17033; Division of Applied Research and Technology (J.W.M., J.S.K., E.F.K.), National Institute for Occupational Safety and Health, Cincinnati, Ohio 45226; and Department of Surgery (R.N.C.), State University of New York Upstate Medical Center, Syracuse, New York 13210

Followed 29 obese reproductive aged women (off confounding reproductive/metabolic medications) from pre-op (mean weight 132 kg and BMI 49) to 24 months post Roux-en-Y Gastric Bypass

No Change in Ovulation Rate Despite Significant Weight Loss after Surgery

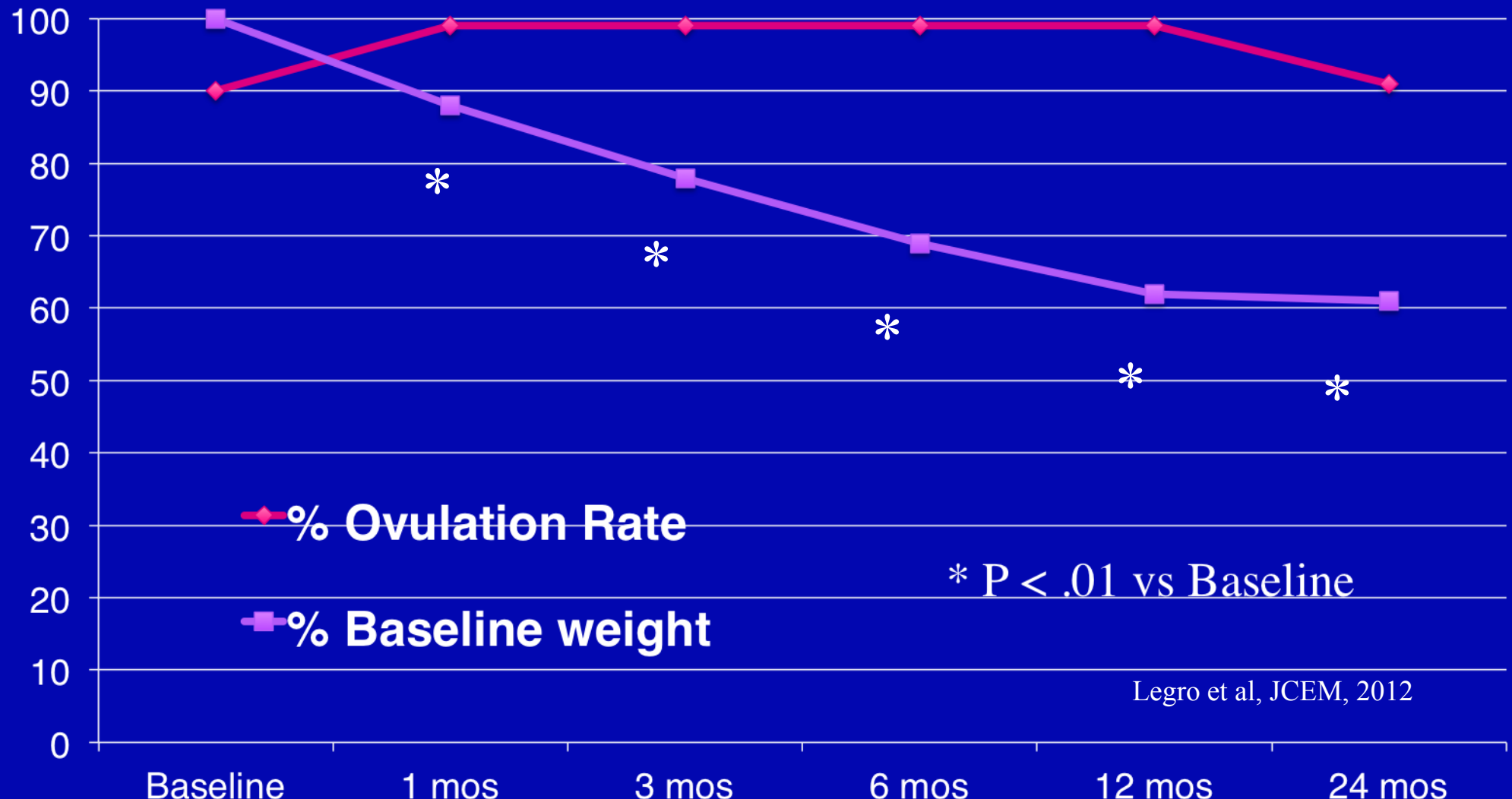
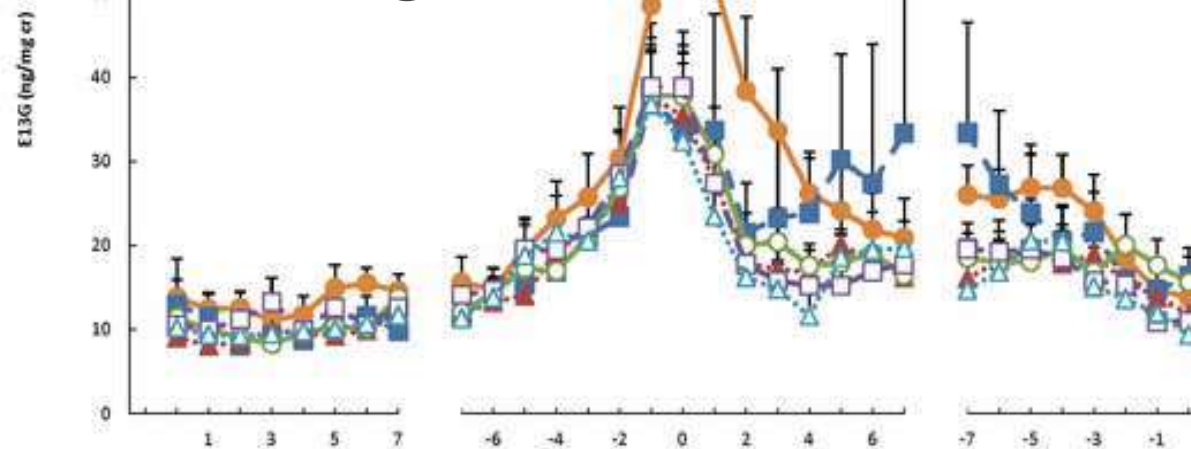
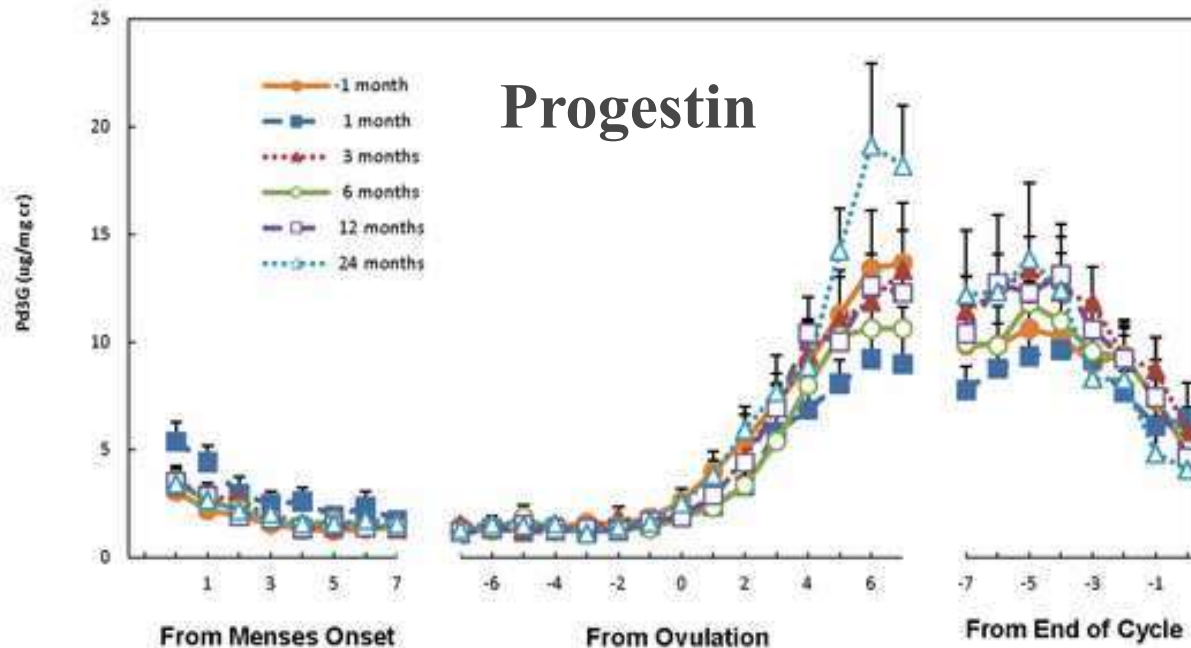


Figure 2. Urinary concentrations (means \pm SE) of E13G and Pd3G plotted relative to onset of menses, ovulation and the end of the cycle for samples collected one month before and 1, 3, 6, 12 and 24 months after women underwent bariatric surgery. Values are corrected for creatinine.

Estrogen



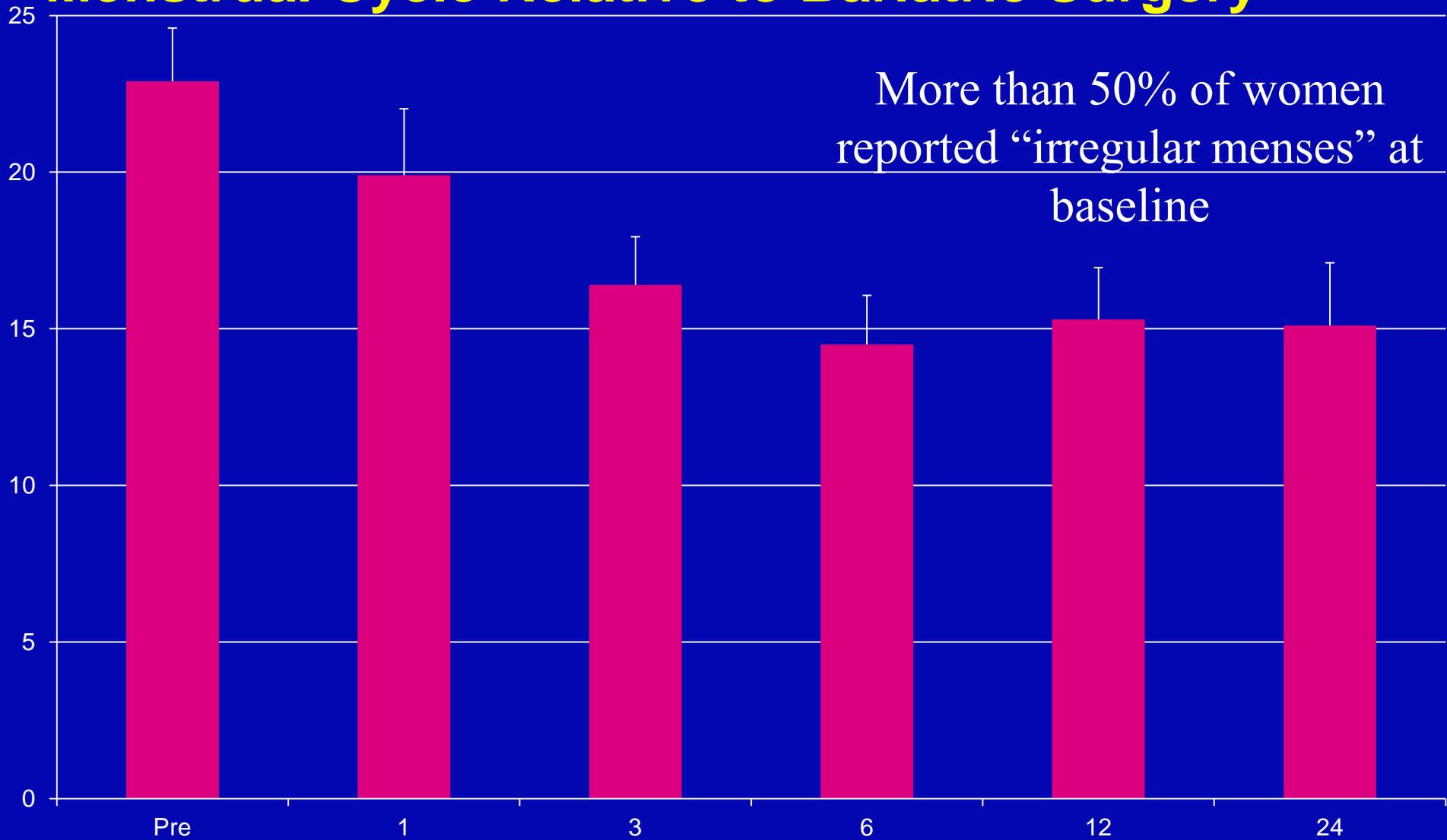
Progestin



Weight Loss
has no Effect
on the
Quality of
Ovulation

Follicular (Estrogen) Phase Length of Menstrual Cycle Relative to Bariatric Surgery

Follicular Phase Length (days)



Months Relative to Surgery

Legro et al, JCEM, 2012

Improved Sexual Function After Bariatric Surgery

	Visit 1 (1mo pre-surgery)	Visit 5 (12mo post-surgery)	
Sexual Function	Mean (SD) [n]	Mean (SD) [n]	P-value*
Female Sexual Function Index Total Score	16.3 (8.7) [14]	24.6 (6.8) [17]	0.007

Legro et al, JCEM 2012

ORIGINAL ARTICLE

2015

Outcomes of Pregnancy after Bariatric Surgery

Kari Johansson, Ph.D., Sven Cnattingius, M.D., Ph.D.,
Ingmar Näslund, M.D., Ph.D., Nathalie Roos, M.D., Ph.D.,
Ylva Trolle Lagerros, M.D., Ph.D., Fredrik Granath, Ph.D.,
Olof Stephansson, M.D., Ph.D., and Martin Neovius, Ph.D.

They identified 627,693 singleton pregnancies in the Swedish Medical Birth Registry, 670 after bariatric surgery: Used a 5 obese control to 1 case analysis

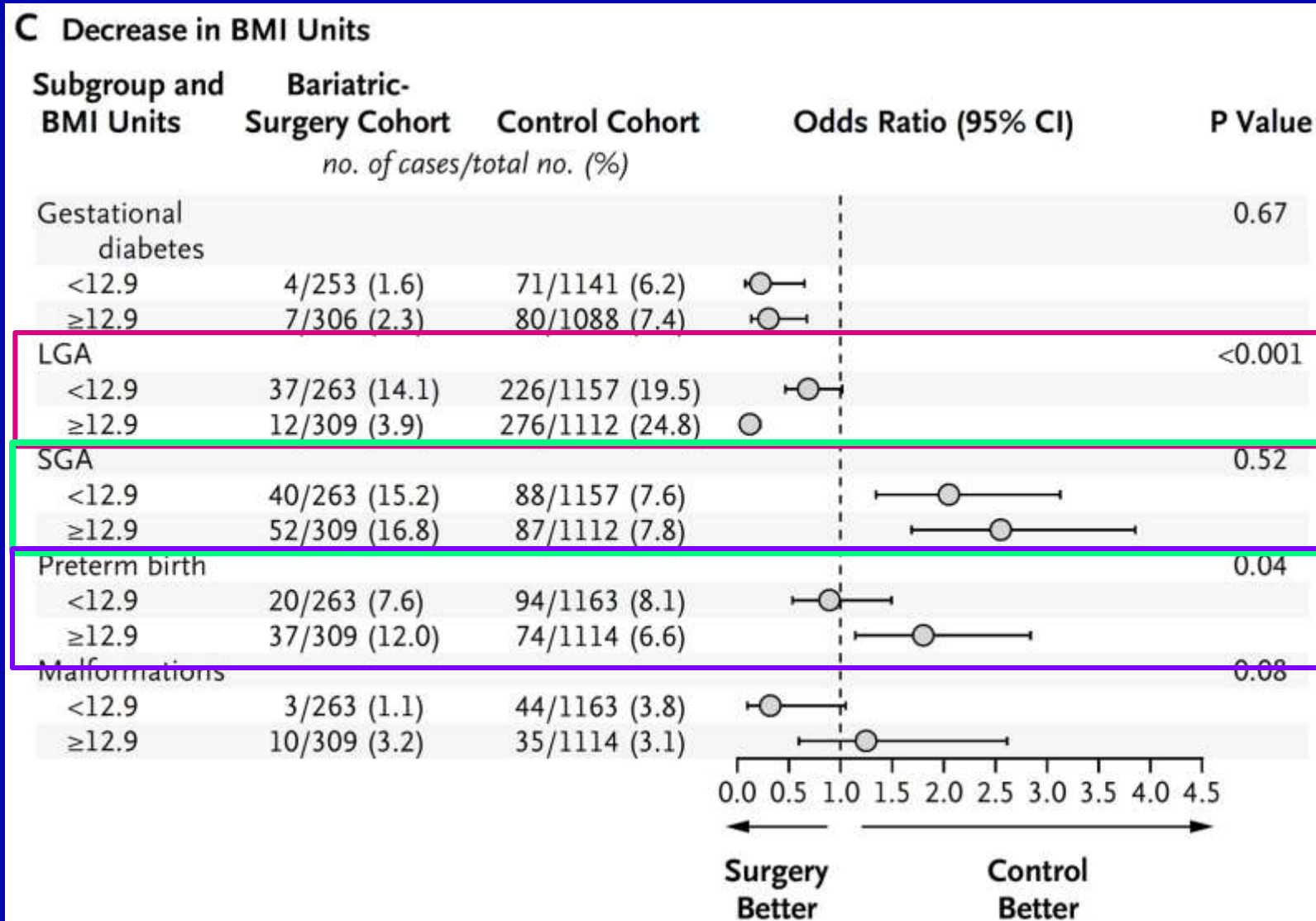
CONCLUSIONS

Bariatric surgery was associated with reduced risks of gestational diabetes and excessive fetal growth, shorter gestation, an increased risk of small-for-gestational-age infants, and possibly increased mortality. (Funded by the Swedish Research Council and others.)

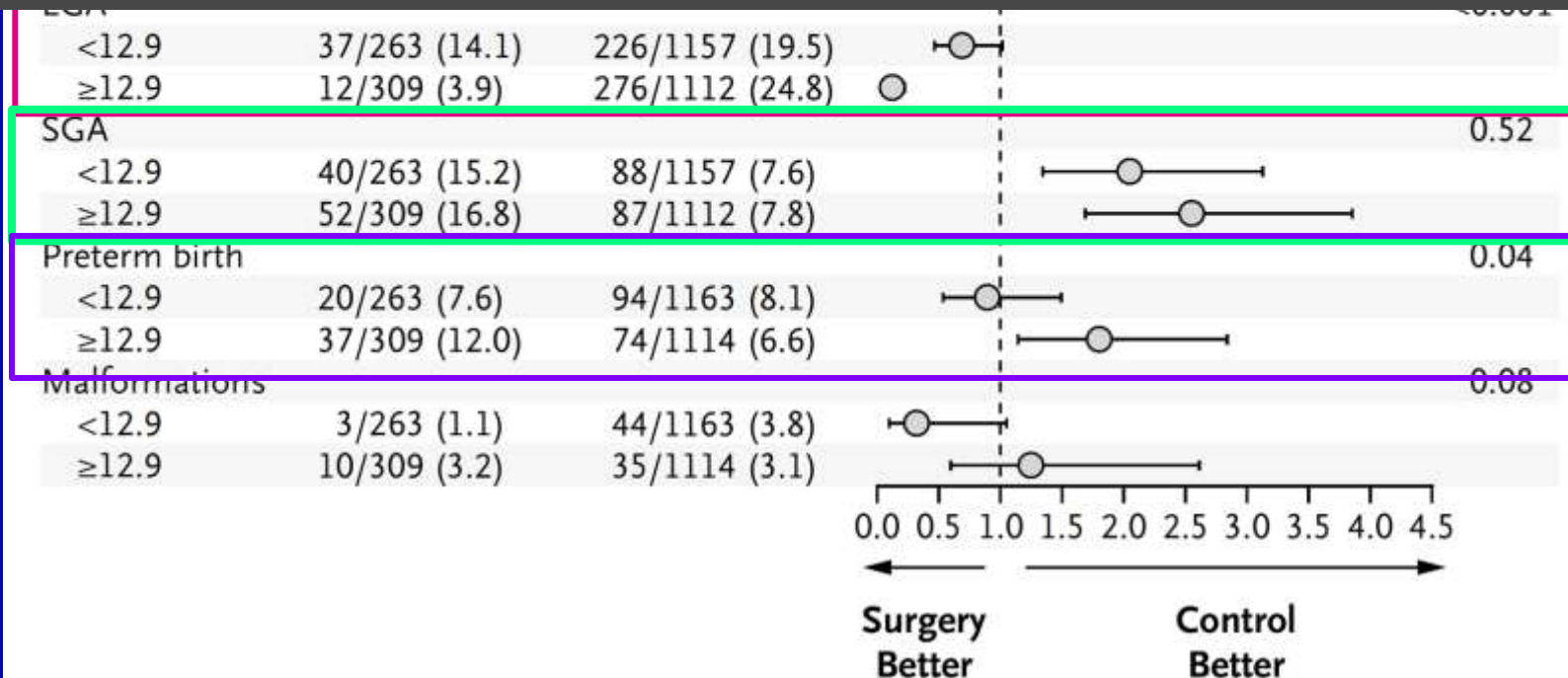
? Increased Risk of Fetal/Neonatal Mortality after Bariatric Surgery

- The risk of stillbirth or neonatal death was 1.7% versus 0.7% (odds ratio, 2.39; 95% CI, 0.98 to 5.85; $P=0.06$).
- There was no significant between-group difference in the frequency of congenital malformations.

Odds ratios for gestational diabetes and adverse perinatal outcomes according to change in BMI in the bariatric surgery cohort versus the control cohort



Women who lost the most weight after bariatric surgery were at greater risk for small babies and preterm birth than obese women without treatment!!



Bariatric Surgery and Reproduction

- The mechanism behind improved fecundity with bariatric surgery may involve improved sexual function, not change in ovulatory function
- There is an increased risk for small babies and preterm labor in obese women who undergo bariatric surgery compared to those who don't
 - ◆ May increase with more weight lost
 - ◆ Concerning trend towards increased infant mortality

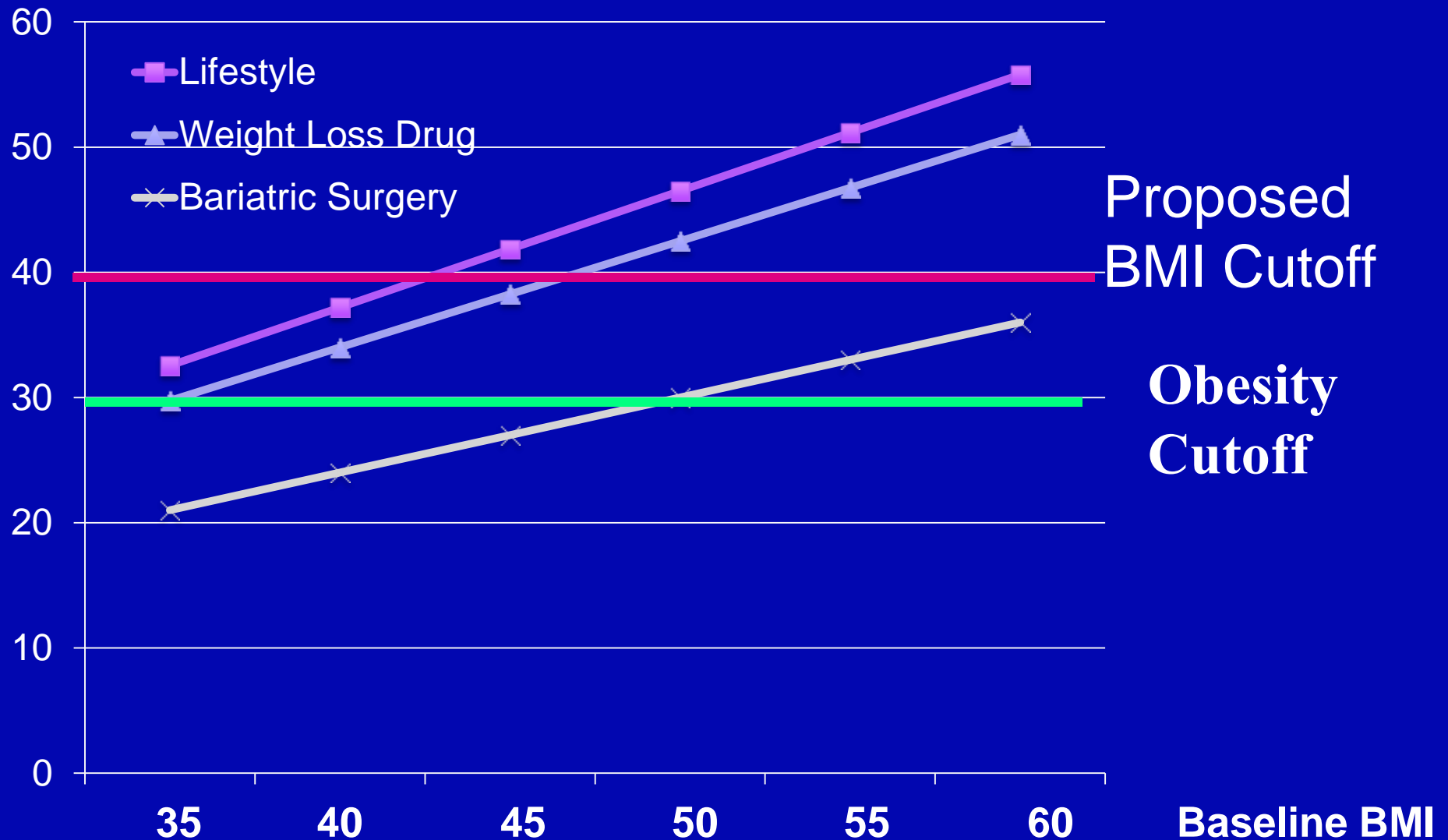
Is there an upper limit of weight beyond which there is no hope of return to a normal weight?

Best Estimates of Weight Loss at 12 mos of Treatment among Compliant Patients

BMI Category	Type of Weight loss	Specific Intervention	Amount of weight loss
30-34.9	Lifestyle	Diabetes Prevention Program	7%
35-35.9	Medication	Phentermine/Topiramate (Qysmia in U.S.)	15%
≥ 40	Bariatric Surgery	Swedish Obesity Study (Roux-en-Y Gastric Bypass)	45%

Best Results of Weight Loss at 12 months of Treatment

BMI
after
12
mos



Proposed
BMI Cutoff

Obesity
Cutoff

Baseline BMI

Factors Associated With Achieving a Body Mass Index of Less Than 30 After Bariatric Surgery

- Patients with a preoperative BMI of less than 40 are more likely to achieve a BMI of less than 30 after bariatric surgery(odds ratio [OR], 12.88; 95% CI, 11.71-14.16) and are more likely to experience comorbidity (diabetes, hypertension, lipid abnormalities) remission.
- Patients with a BMI ≥ 50 have only a 8.5% chance of obtaining a BMI less than 30 after bariatric surgery
- Policies and practice patterns that delay bariatric surgery until the BMI is 50 or greater can result in significantly inferior outcomes.

Varban et al, JAMA Surgery 2017

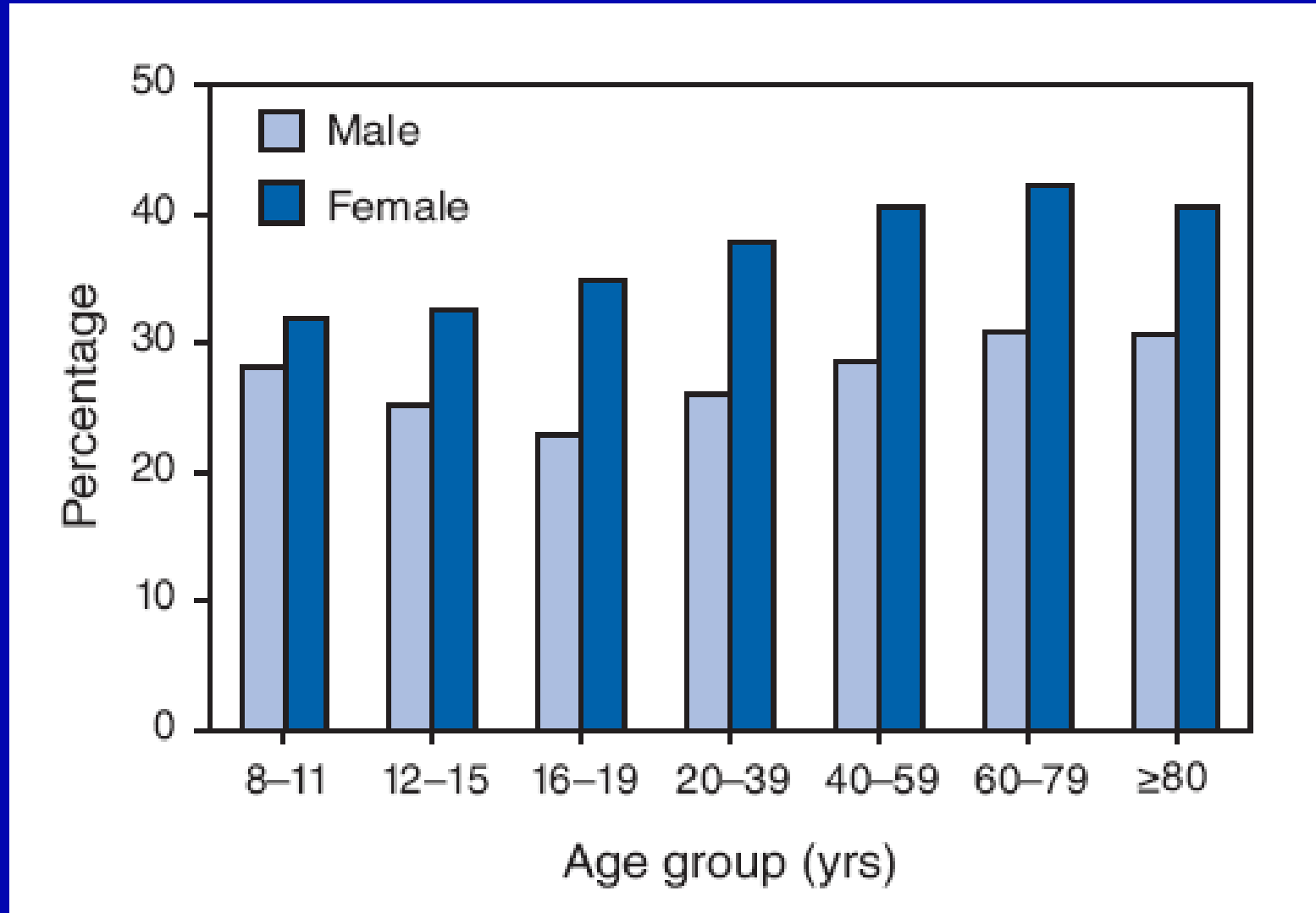
Why is it so difficult for humans
to lose weight?

Why is it more difficult to women to
lose weight than men?

Fat and Female Reproduction

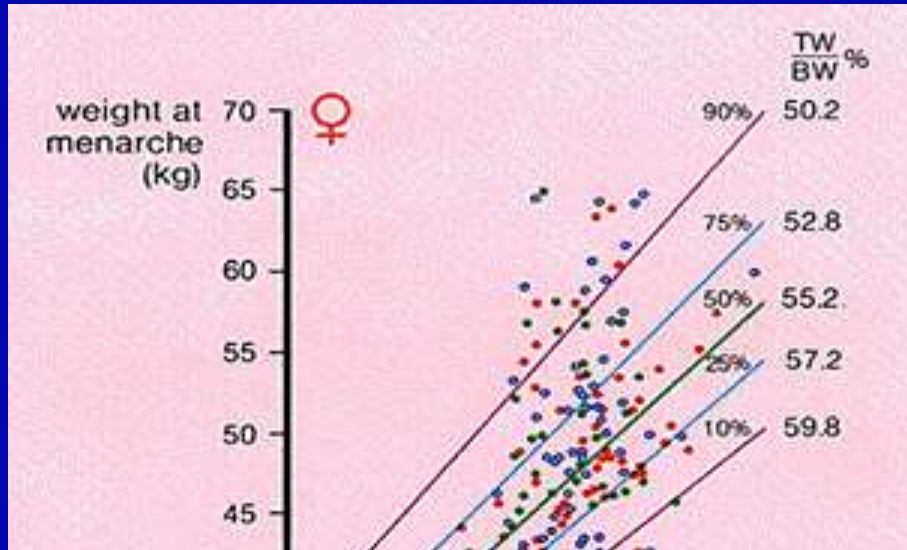
- Fat is essential to female reproductive maturation and for the maintenance of ovulation and ultimately for early pregnancy
- Women have larger percentages of body fat at all life stages than men
- Women lose fat at a slower rate than men when challenged with the same treatment

Body Fat Composition in U.S. Men and Women



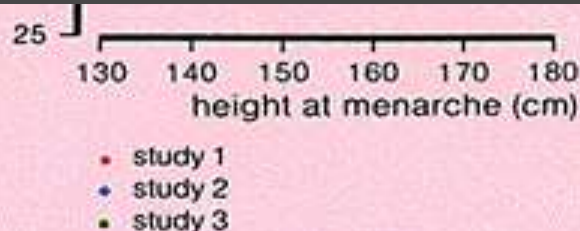
National Health and Nutrition Examination Survey, United States, 1999--2004

Menarche (First Menses) is dependent on a critical fat mass



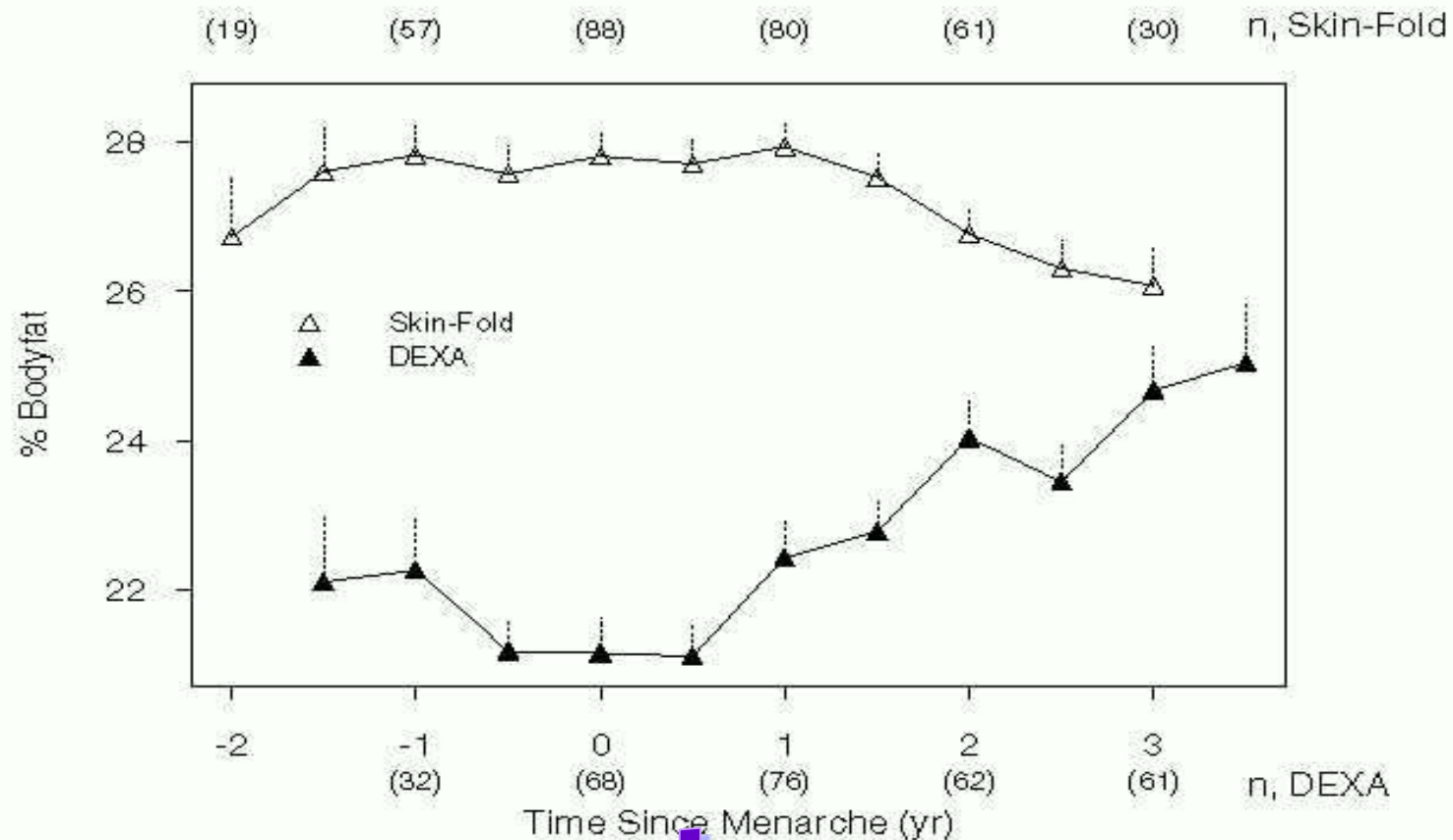
Mean weight
at Menarche
47 kg

The age of menarche has fallen in the developed world over the last 150 years due to improved nutrition and increasing childhood obesity rates



Frisch RE,
Science, 1974

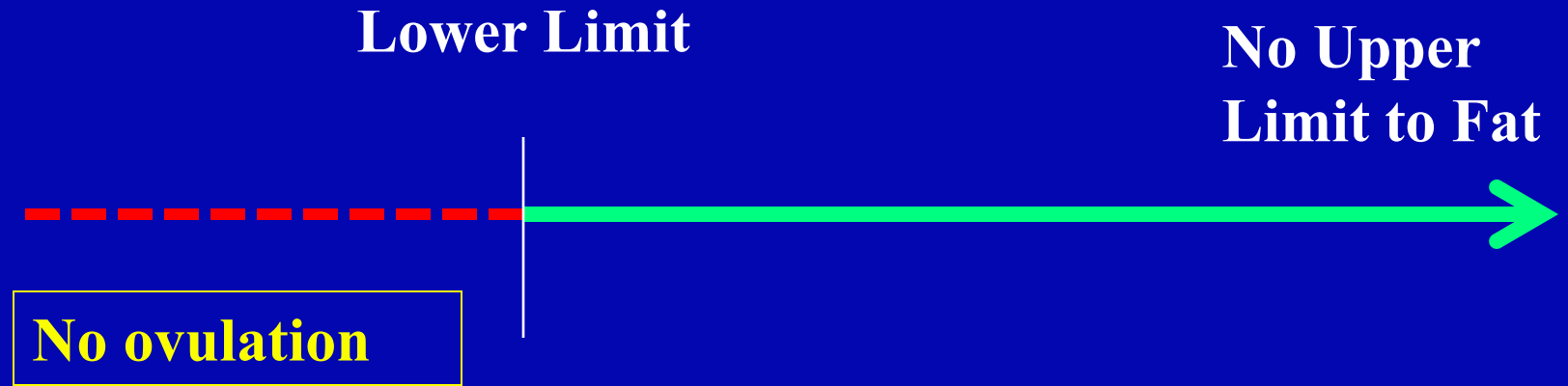
Body Fat % Unchanged During Perimenarche



10 kg of Fat at Menarche

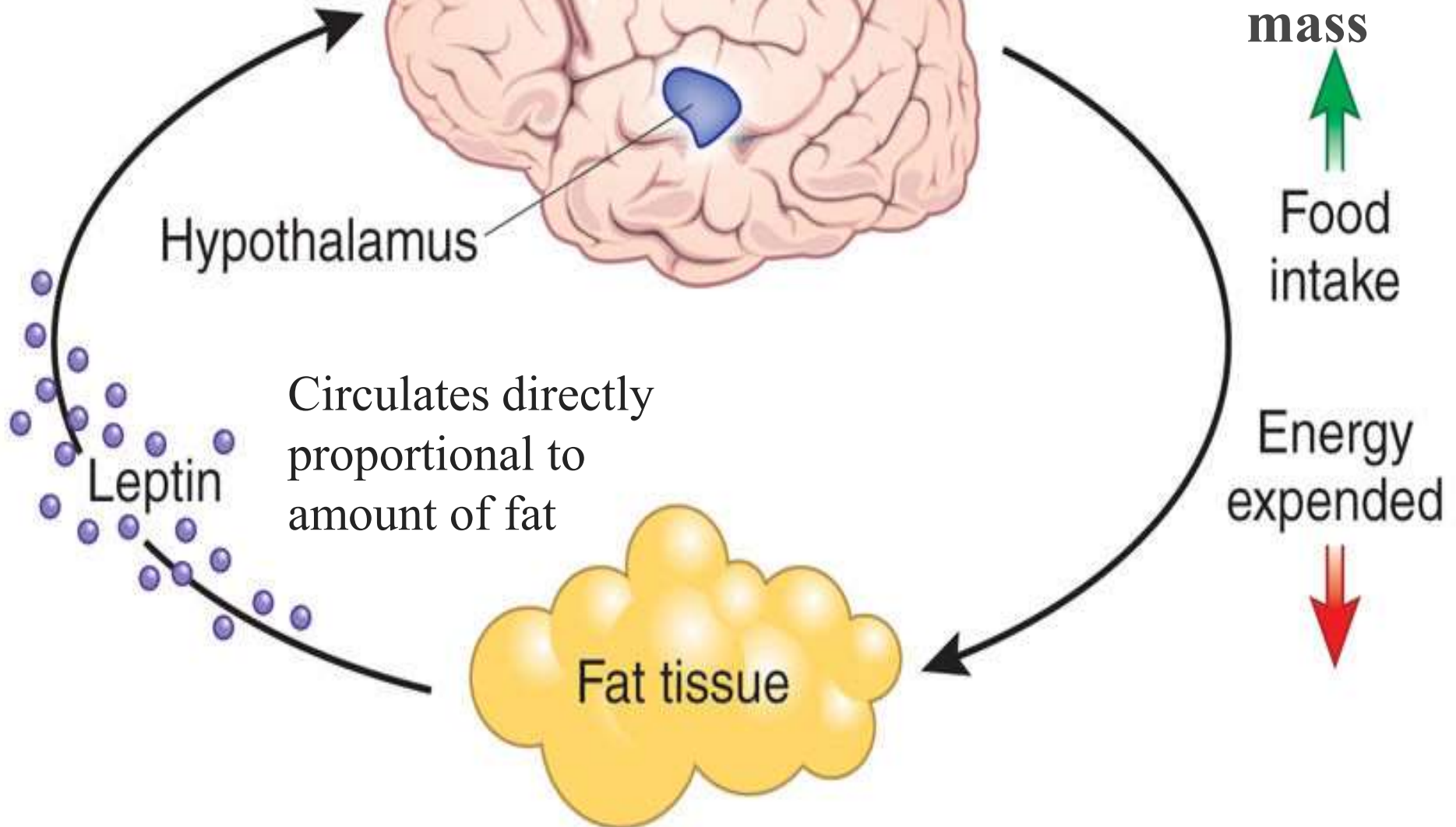
Legro et al, JCEM, 2000

Fat Requirement for Female Reproduction



Anorexia Nervosa
Gymnasts
Marathon Runners

**When Leptin
levels fall due
to decreased fat
mass**



1.



Fat cells empty

2.



No leptin signal

3.



We eat

4.



Fat cells full

5.



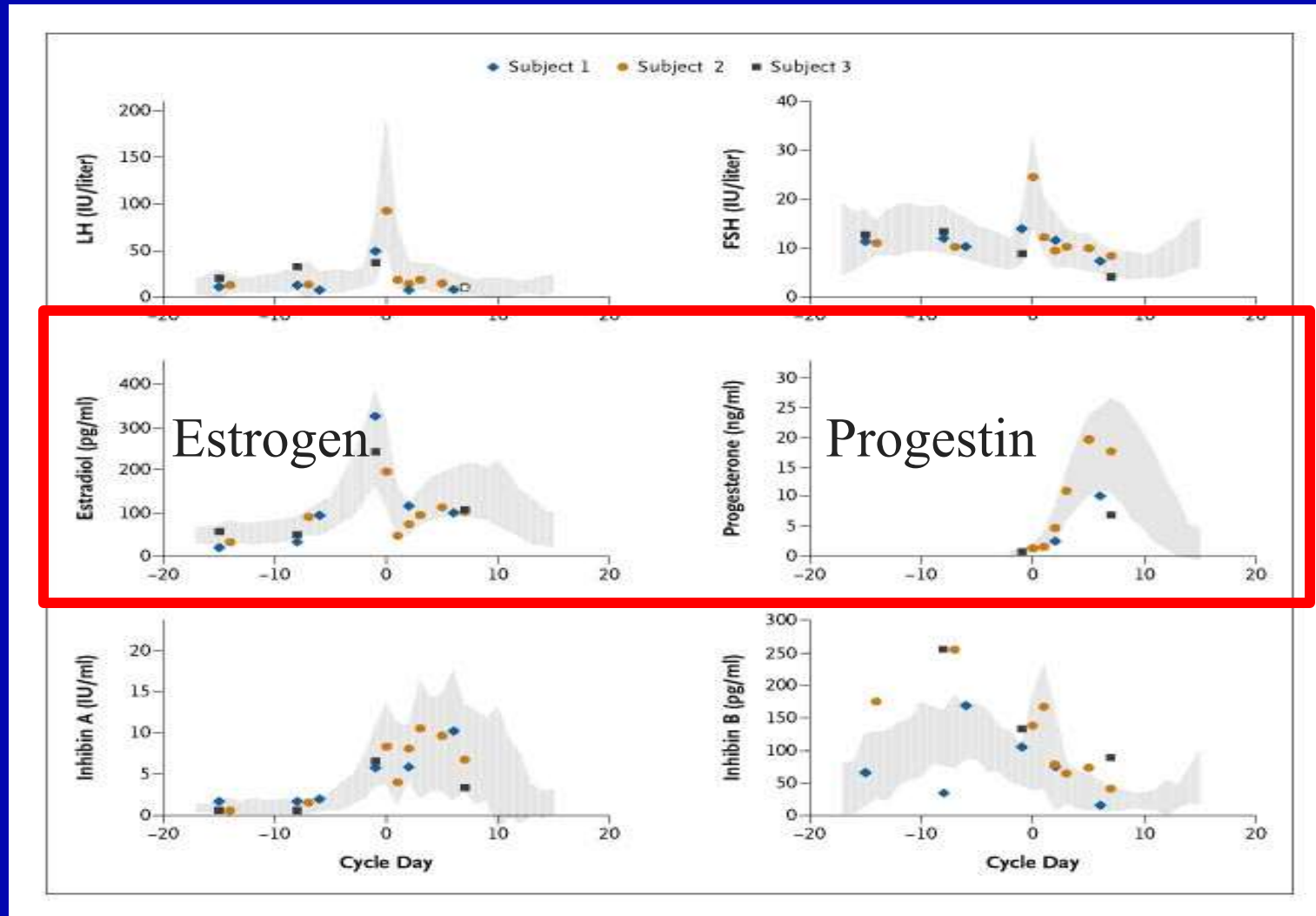
Leptin signal

6.



We stop eating

Restoration of Normal Reproductive Hormone Levels in Thin Women Who Ovulated during Recombinant Leptin Treatment



1.



Fat cells empty

2.



No leptin signal

3.



We eat

4.



Fat cells full

5.



6.



We stop eating

Leptin Resistance

Hypothalamus and Obesity

- The Hypothalamus resets “normal” weight to the highest weight obtained and attempts to maintain that weight (fat mass) at all costs
- Leptin levels are high in obese patients
 - ◆ Giving them recombinant leptin does not result in significant weight loss due to leptin resistance
- There are multiple redundant neural and hormonal pathways to restore weight
 - ◆ There are multiple hormones to stimulate appetite

Gwyneth Paltrow **Jack Black**

SHALLOW
Hal



The
Hypothalamus
is Shallow Hal
when it comes
to Obesity



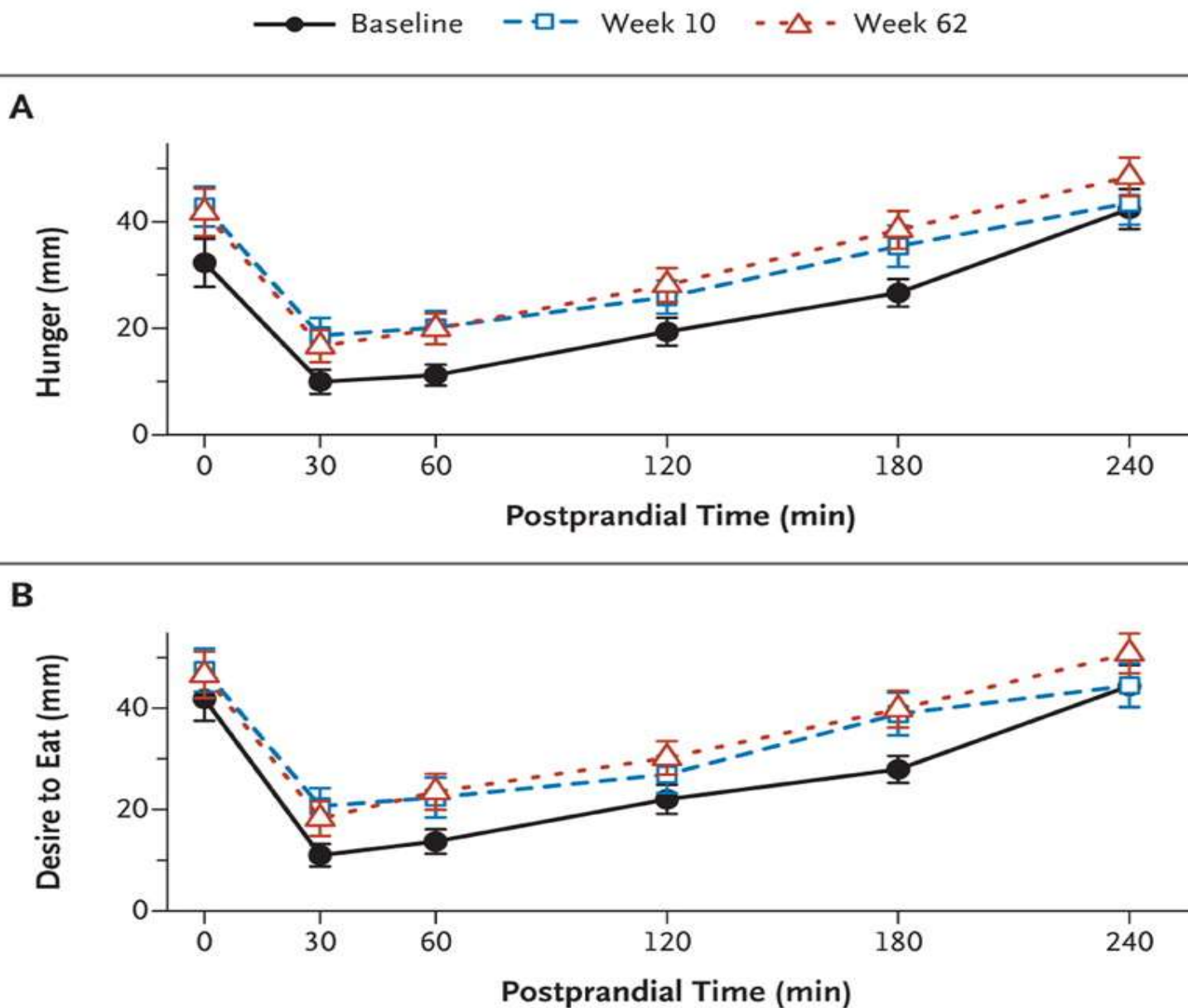
ORIGINAL ARTICLE

Long-Term Persistence of Hormonal Adaptations to Weight Loss

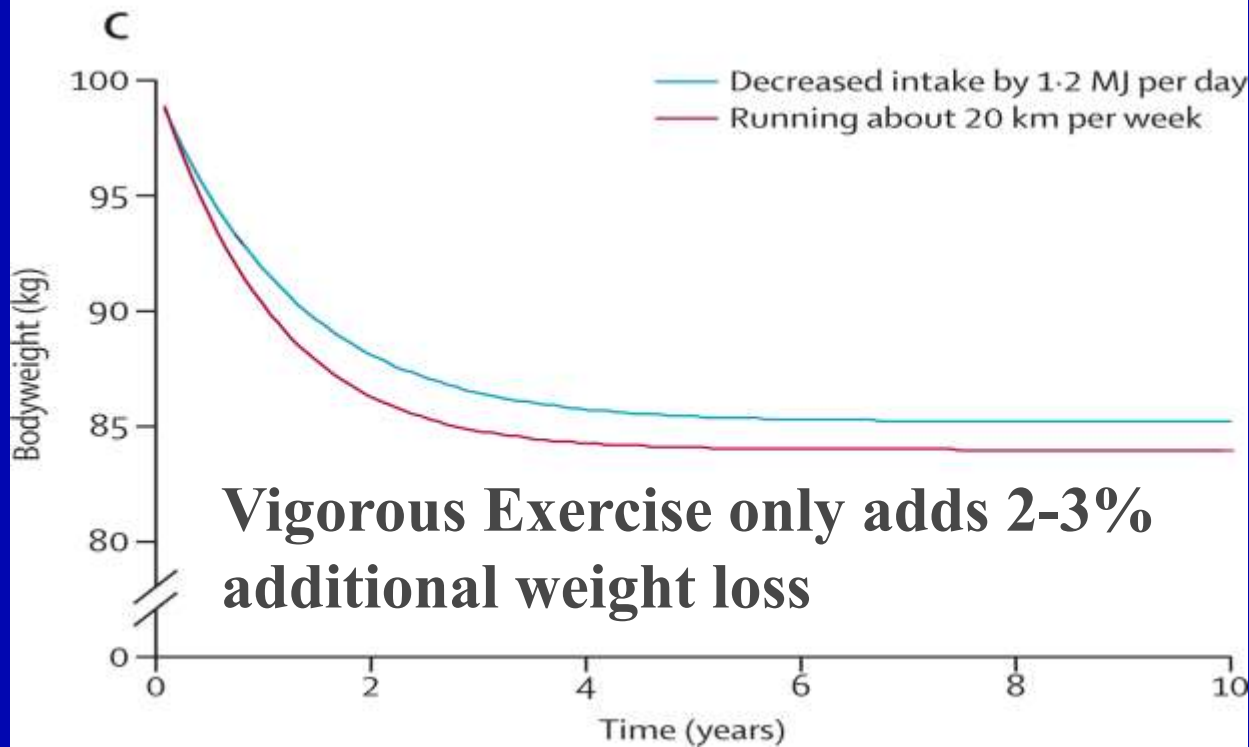
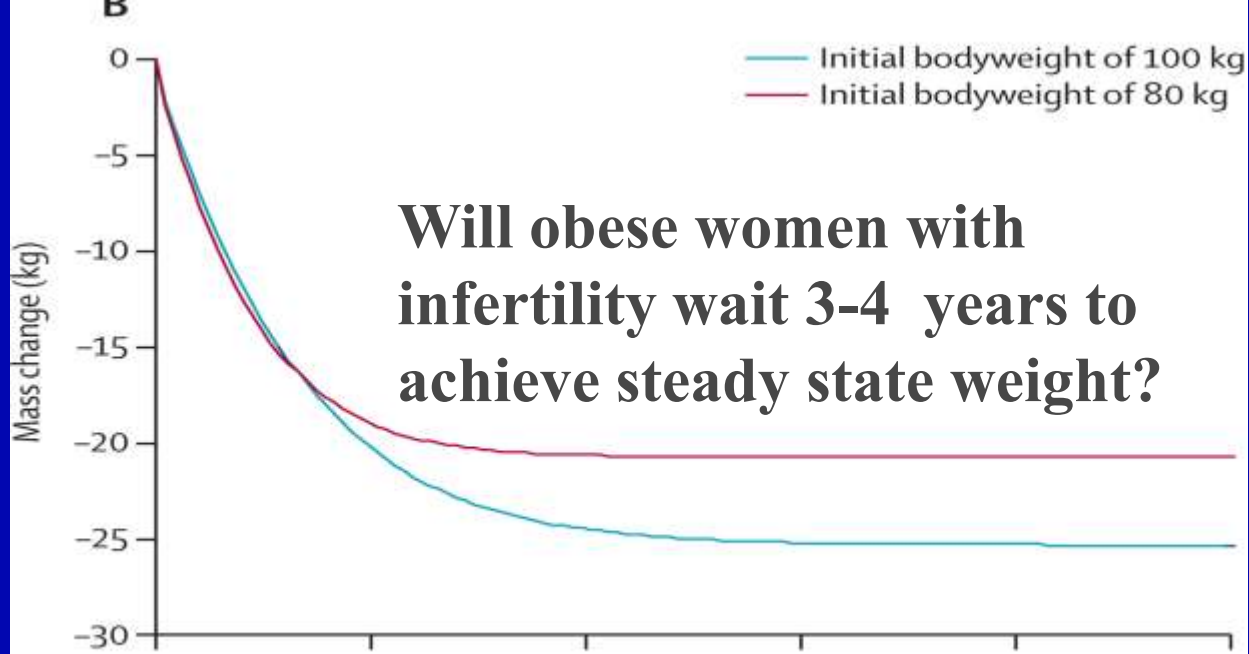
Priya Sumithran, M.B., B.S., Luke A. Prendergast, Ph.D.,
Elizabeth Delbridge, Ph.D., Katrina Purcell, B.Sc., Arthur Shulkes, Sc.D.,
Adamandia Kriketos, Ph.D., and Joseph Proietto, M.B., B.S., Ph.D.

- One year after initial diet-induced weight reduction, levels of the circulating hormones of appetite that encourage weight regain after diet-induced weight loss do not revert to the levels recorded before weight loss.

**Hunger and
Desire to Eat
are
maintained
after weight
loss for a
prolonged
period (one
year) even
with weight
maintenance
after the
weight loss
intervention**



**Will obese women with
infertility wait 3-4 years to
achieve steady state weight?**



**Effect of
Energy
Deficit
(500kcal/day)
and Vigorous
Exercise
on
Bodyweight**

Hall KD, Lancet 2011

Weight Loss during 30 days of starvation among Men and Women

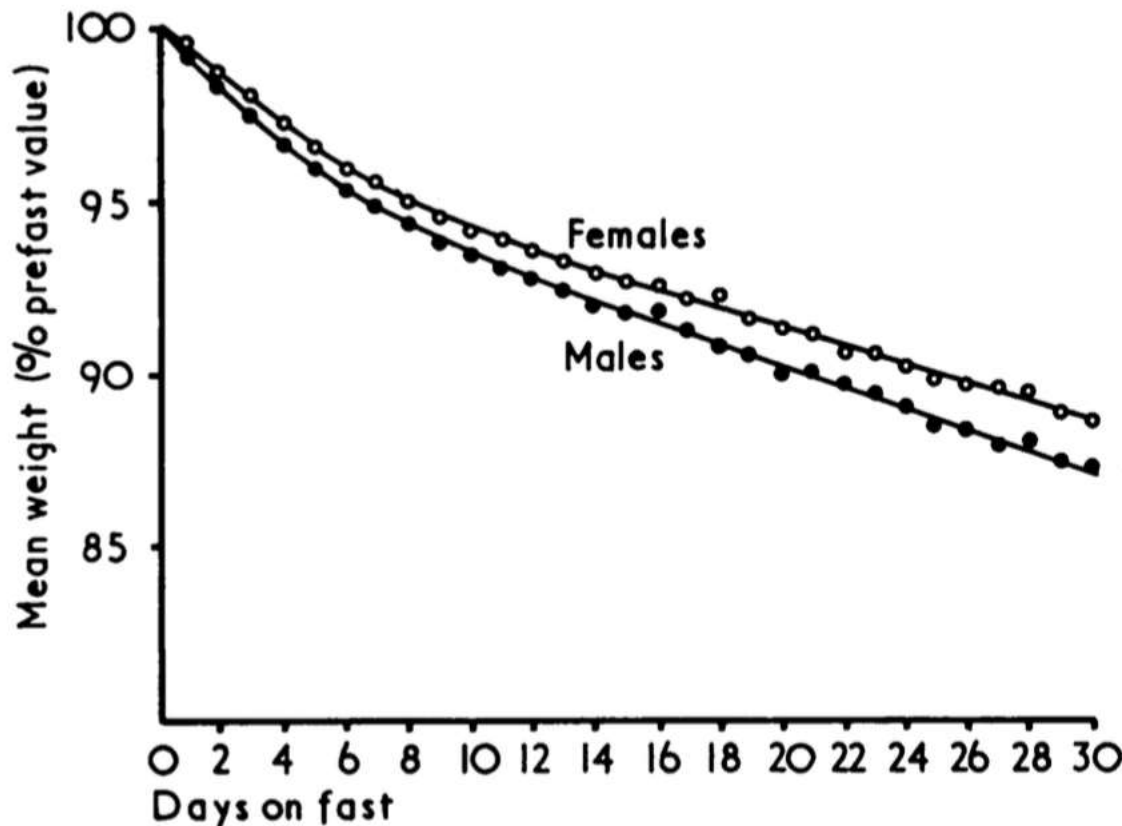


FIG. 2—Mean daily weight of patients during starvation exposed as percentage of weight before fasting.

**“The
therapeutic
regimen
consisted
simply of no
food”**

Runcie and Hilditch,
BMJ, 1974

Excessive weight loss through severe calorie restriction rarely results in long term weight maintenance and may have added reproductive toxicity in women.

Effect of a very-low-calorie diet on in vitro fertilization outcomes

A low-calorie diet in a group of overweight or obese patients for a short period before and during IVF results in variable tolerance to the dietary regime and an unsatisfactory IVF outcome. (Fertil Steril® 2006;86:227–9. ©2006 by American Society for Reproductive Medicine.)

- ~500kcal/d diet
- Lost 2.2-8.8% of body weight in a 4-6 week period
- Poor oocyte number, quality, and fertilization
- Intervention stopped after 10 patients

Victoria Tsagareli, M.D.^a

Manny Noakes, Ph.D.^b

Robert J. Norman, M.D.^a

^a *The University of Adelaide, Research Centre for Reproductive Health, Faculty of Health Sciences, Department of Obstetrics and Gynaecology, Adelaide, Australia; and* ^b *CSIRO Health Sciences and Nutrition, Adelaide, Australia*

Limitations of Weight Loss in Obese Women with Infertility

- Dose?
 - ◆ Is there an ideal rate of weight loss or activity increase
- Duration?
 - ◆ How long should the intervention be instituted
- Timing?
 - ◆ Is the intervention before or during infertility treatment or both?
- Patient Compliance?
 - ◆ Will patients elect to participate
 - ◆ Will they be able to follow our recommendations
 - ◆ How can we as clinicians ensure compliance

Conclusions

- Obesity is epidemic in western societies
 - ◆ It is associated with reproductive failure (women more than men)
- Obesity alone, however, is only a minor contributor to reproductive failure and pregnancy complications
 - ◆ There is no female cutpoint beyond which it is absolutely “unsafe” to have a pregnancy
- Treatments to restore normal weights are largely ineffective in most obese women and may hold reproductive harms not imagined

- Obese women should be told that weight loss prior to conception *MAY* result in minor improvements in pregnancy and pregnancy complication rates.
- Delay in infertility therapy to lose weight *MAY* result in a decreased chance for pregnancy.
- There may be an upper limit of baseline weight which *MAY NOT* benefit (even modestly) from weight loss.

**WE HAVE MET
THE ENEMY
AND HE IS US.**

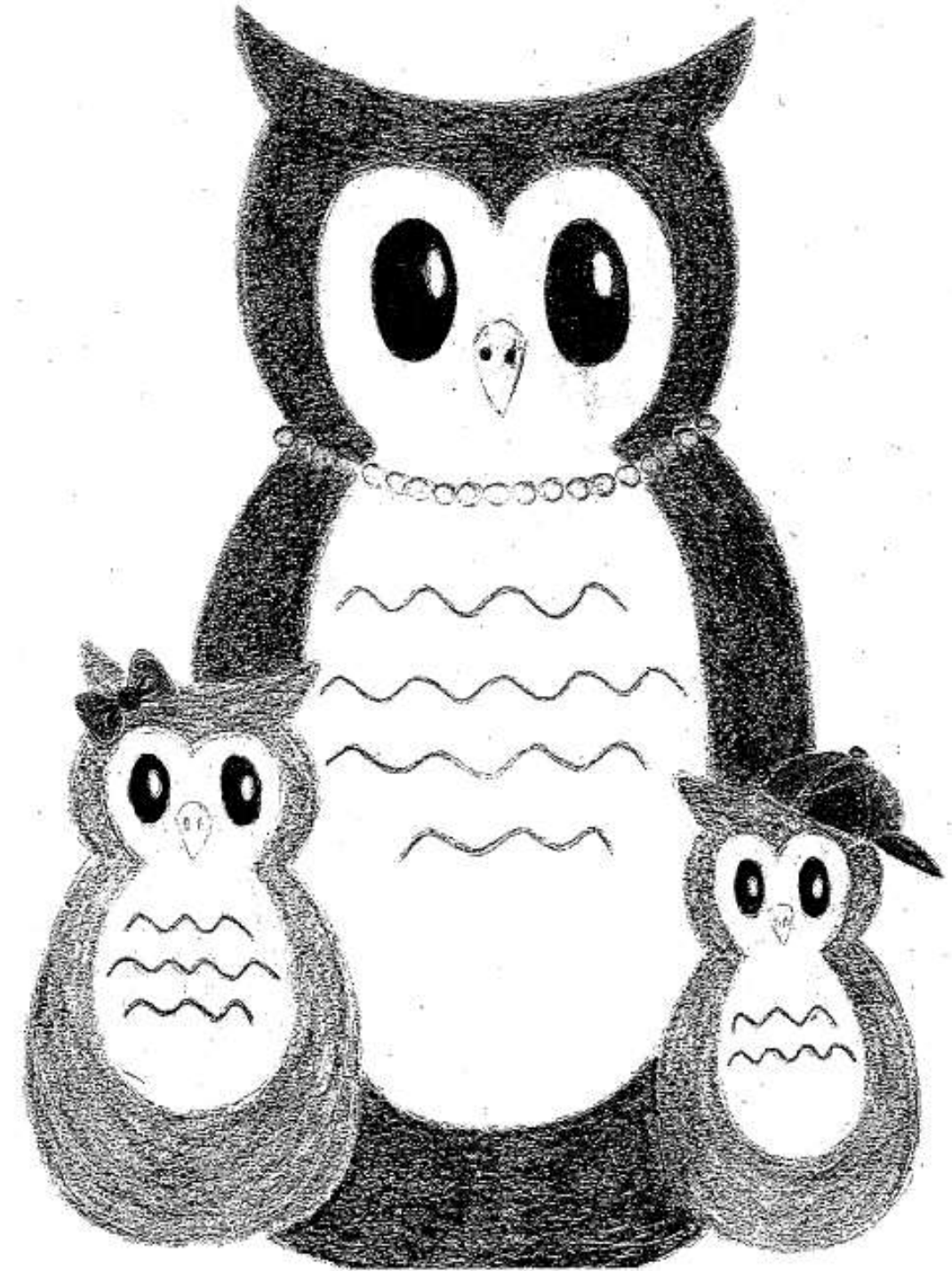


OWL-PCOS: OCP vs Weight Loss for Pregnancy in Polycystic Ovary Syndrome (R01HD056510)



Steering Committee of the PPCOS II Trial





**Thank you
Patient
Participants!**

Sexually Dimorphic Reproductive Effects in Men and Women

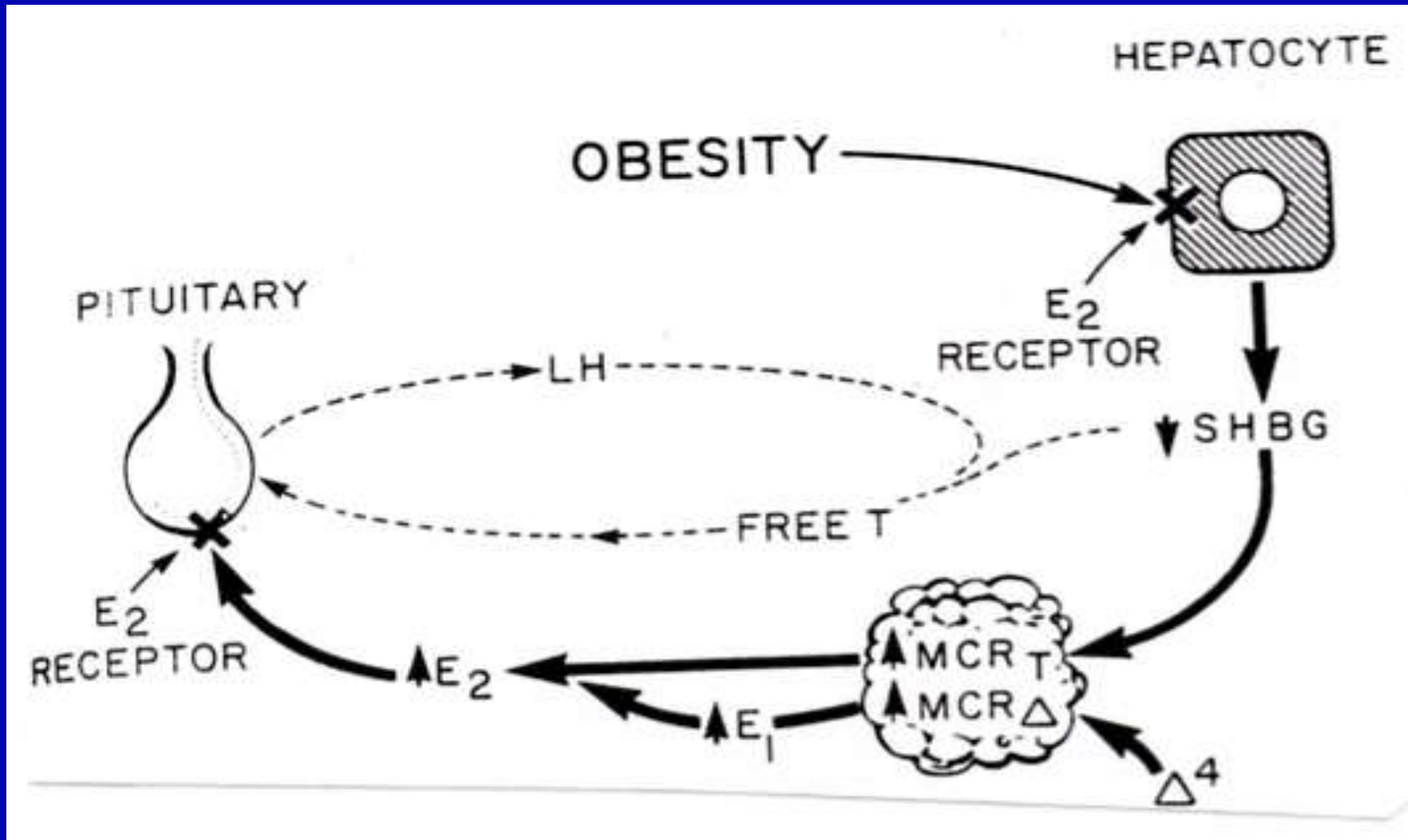
Women

- Early Puberty
- Excess ovarian function with higher androgen levels
- Breast Shrinkage

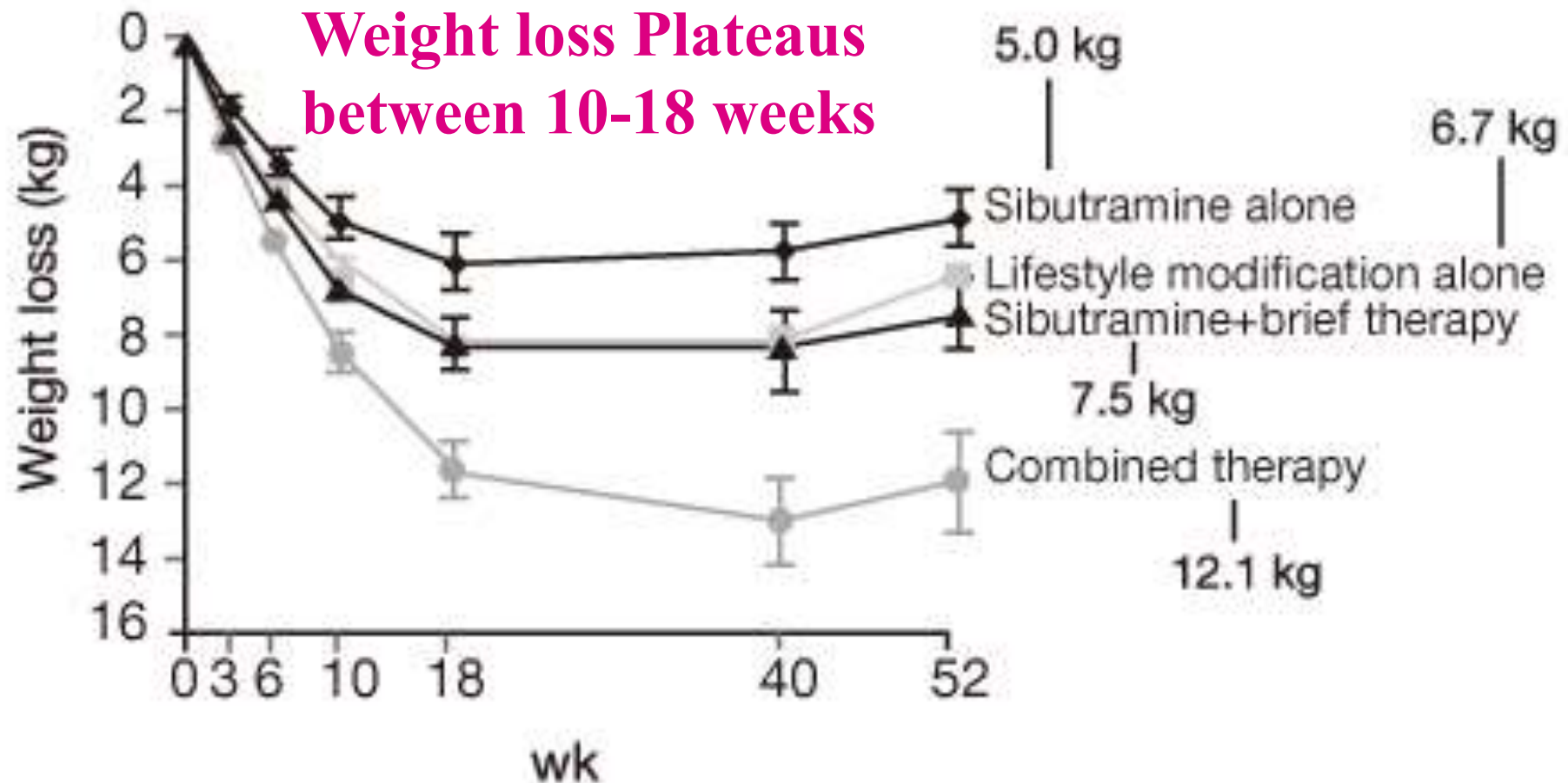
Men

- Delayed puberty
- Decreased testicular function with higher estrogen levels
- Breast Development

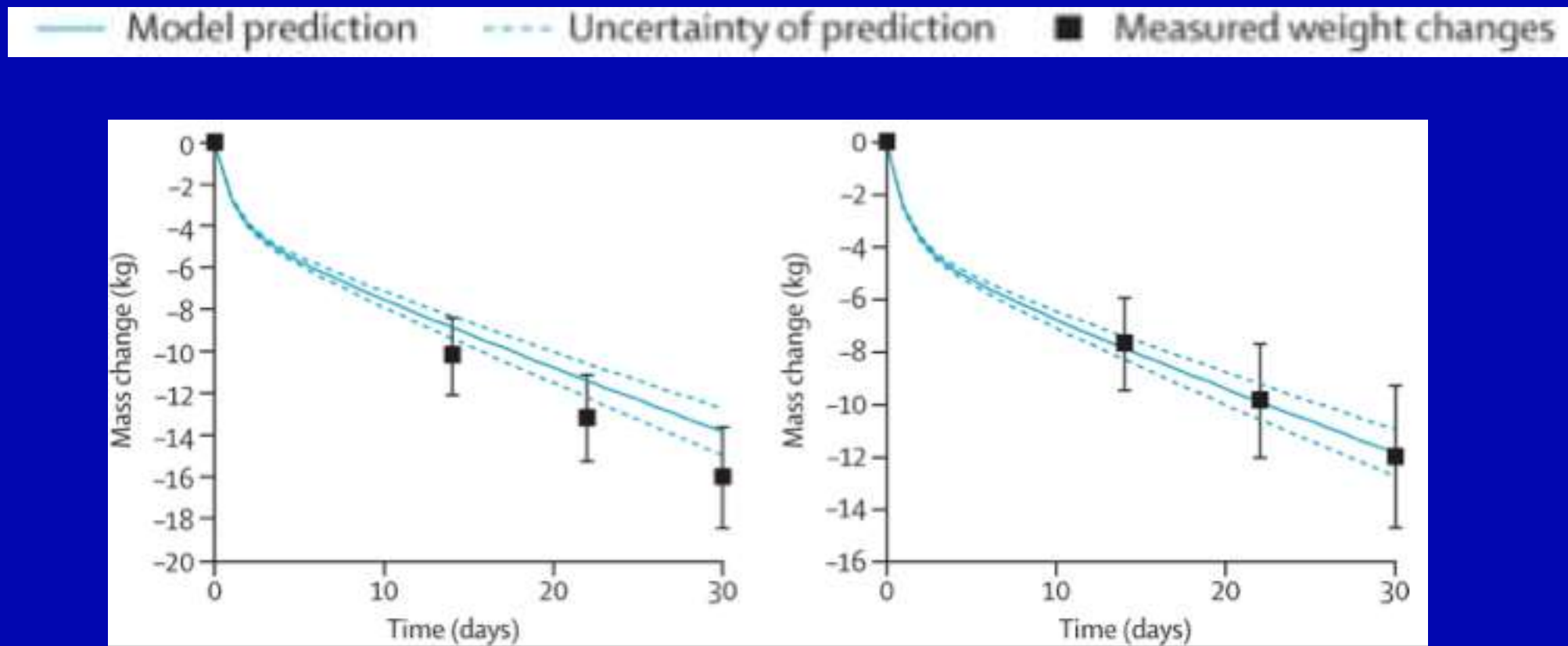
Mechanisms of Hypogonadism in Obese Males or Hypergonadism in Women



Combination Therapy (Lifestyle/Medication/Behavior) Achieves Best Weight Loss



Average weight change during a 30d fast in Obese Men (N =18) or Women (N = 58)



Adapted from Runcie and Hilditch BMJ, 1974

Summary:Lifestyle Lessons Learned 1

- ◆Most patients will not even attempt a lifestyle intervention if it is offered to them
- ◆Many who do will drop out
 - 50% drop out rates in 3-6 month studies
- ◆Severely obese patients may be poor candidates for such programs which focus on activity
 - Focus on diet, given difficulty with weight bearing exercise

Summary:Lifestyle Lessons Learned 2

- ◆ Modest Effects, long time required, much less weight loss than we promise
 - Counterregulatory effects diminish caloric restriction effects
 - Thinner people require fewer calories
- ◆ There will be hurdles to implementing these programs in our current U.S. medical system

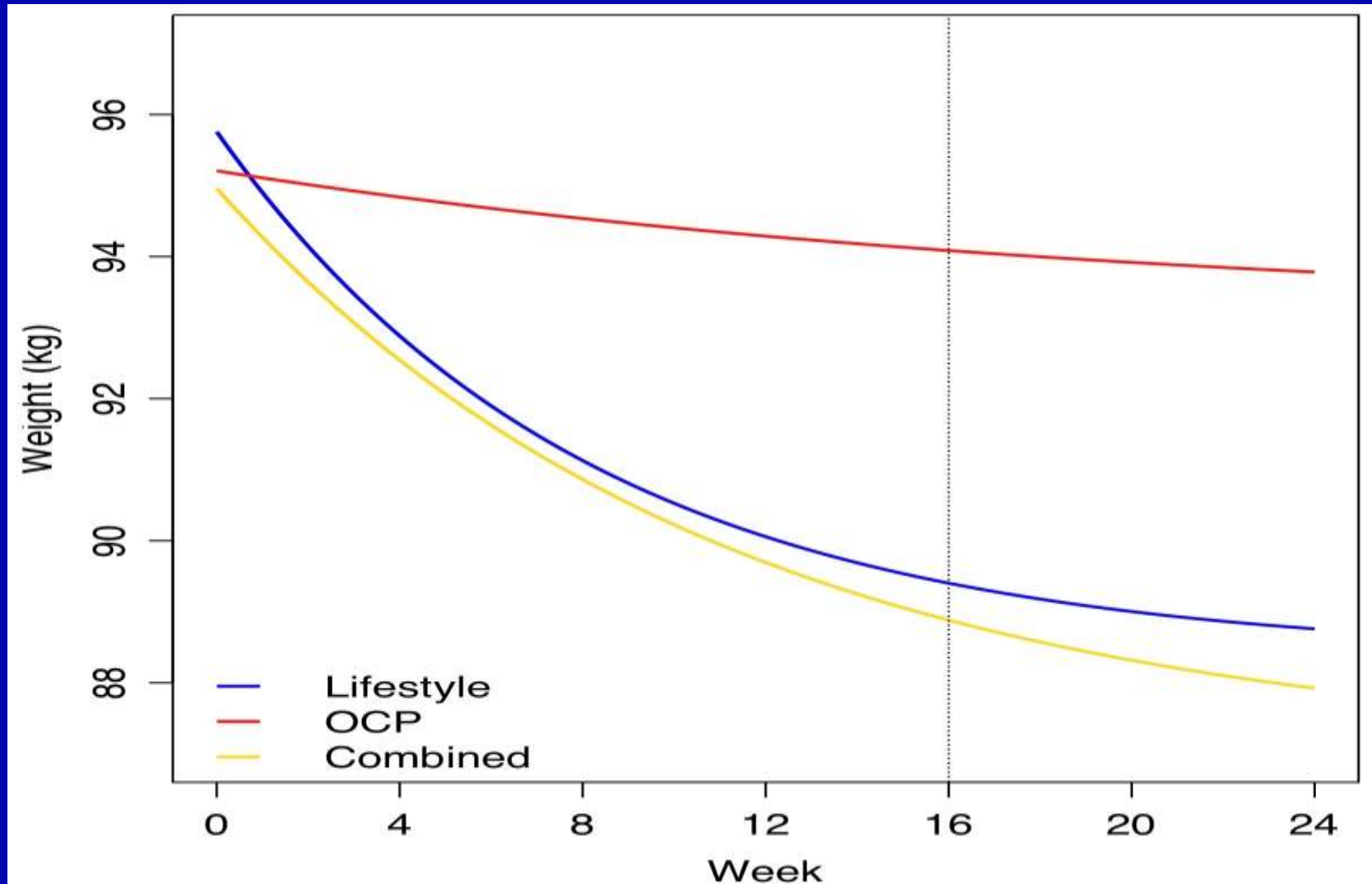
Conclusions: Clinical Care

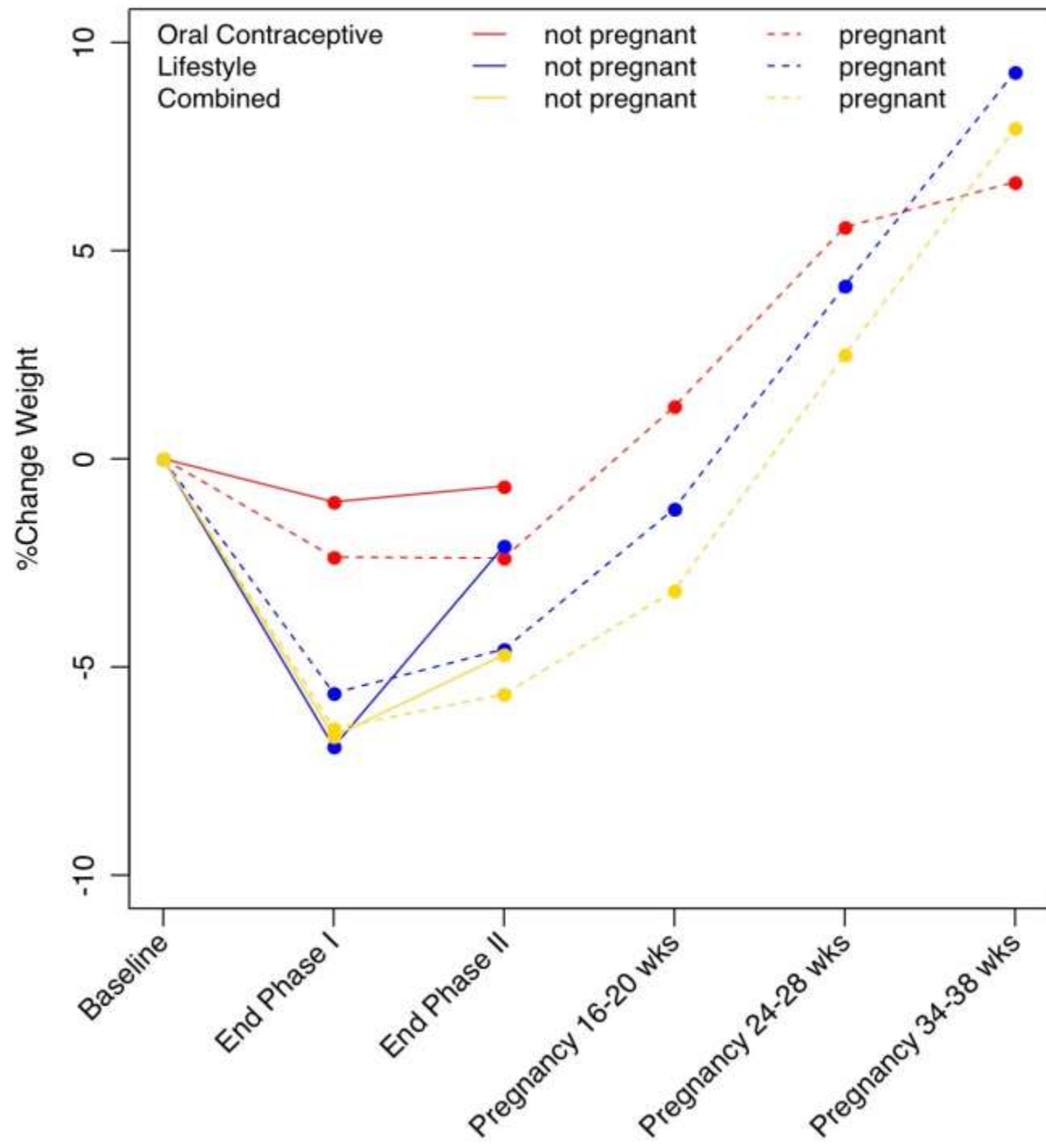
- Preconception lifestyle modification in overweight/obese women with PCOS improves ovulation rates with clomiphene vs pretreatment with OCP
 - ◆ Treatment is relatively simple, safe and well tolerated.
- OCP pretreatment likely offers little benefit versus immediate treatment with ovulation induction.
- Concurrent Lifestyle Modification should be recommended for overweight/obese women with PCOS on OCP therapy.
 - ◆ Eliminates adverse metabolic effects of OCP



**...and now,
a word
from
our
Sponsors...**

Modeling of Projected Weight Loss with Longer Interventions





**Weight will
Rebound
during
Infertility
Treatment
and
Pregnancy**

FIT PLEASE

Obese Women (BMI ≥ 30 and Age ≤ 40 y)
with Unexplained Infertility (N = 380)

Phase II
Lifestyle:
16 weeks

Intensive Lifestyle Modification:
Weight Loss AND Increased
Physical Activity (N = 190)

Standard Lifestyle Modification:
Increased Physical Activity
(N = 190)

Phase III: Infertility
Treatment

3 cycles of Ovarian Stimulation with Clomiphene /Insemination
(Clamp physical activity and weight during this phase)

Phase III:
Pregnancy

Pregnancy (3 visits): One per trimester for weight, blood
pressure, and glycemic measures

Phase IV:
Infancy

Primary Outcome: Good Birth Outcome: Healthy singleton or
twin Live Birth (≥ 37 weeks, 2500-4000g, no major anomaly)

Infant Follow up