

Appendix 1. Supplemental Methods

Women in NHS3 who report they are currently pregnant are invited to participate in the MHS. Approximately 90% of eligible women participate. On gestation week 20, these women are sent an initial pregnancy questionnaire with questions concerning the pregnancy and exposures during the first and early second trimester. Women are also asked about their intention to become pregnant and, if the pregnancy was planned, the duration of their pregnancy attempt. To date, 2,148 women with planned pregnancies have enrolled in the MHS and retrospectively (on the gestation week 20 questionnaire) reported their time to pregnancy. Cox proportional hazards models for discrete survival time (PROC PHREG with ties=discrete in SAS) were used to estimate the fecundability odds ratios (FORs) and 95% confidence intervals (CI). FORs estimate the odds of becoming pregnant each month among exposed women compared to unexposed women, conditional on not being pregnant in the previous month. FORs <1 denote a reduction in fecundity or a longer TTP, and FORs >1 denote a shorter TTP. Women were considered at risk of pregnancy for the duration of their pregnancy attempt until they became pregnant.

Appendix 2. Sensitivity Analysis for the Association Between Weight Change Since Age 18, Current Body Mass Index (BMI), and BMI at Age 18 and Median Duration of Pregnancy Attempt

Adjusted Time Ratio (95% CI)	Weight Change Since Age 18 (per 5 kg)	P-interaction	Current BMI (per 5 kg/m²)	P-interaction	BMI at Age 18 (per 5 kg/m²)	P-interaction
All women (n=1950)	1.04 (1.02, 1.06)		1.08 (1.04, 1.12)		1.03 (0.98, 1.09)	
Age		0.64		0.10		0.06
< 37 years (n=1130)	1.06 (1.03, 1.09)		1.11 (1.05, 1.16)		1.07 (0.99, 1.15)	
≥37 years (n=820)	1.04 (1.01, 1.06)		1.06 (1.00, 1.11)		0.99 (0.91, 1.08)	
Smoking Status		0.20		0.11		0.13
Never Smoker (n=1513)	1.04 (1.02, 1.07)		1.06 (1.02, 1.11)		1.01 (0.95, 1.08)	
Ever Smoker (n=432)	1.05 (1.02, 1.09)		1.13 (1.05, 1.22)		1.11 (0.98, 1.25)	
Pregnancy history		0.46		0.31		0.09
Nulligravid (n=1137)	1.05 (1.02, 1.08)		1.11 (1.06, 1.17)		1.07 (1.00, 1.15)	
Gravid (n=813)	1.05 (1.02, 1.08)		1.06 (1.00, 1.12)		0.98 (0.89, 1.07)	

Accelerated failure time models were used to estimate the time ratios and 95% confidence intervals (CI). All models are adjusted for age (years), race (white vs. other), smoking status (never, former, current, missing), and marital status (married, not married). Weight change models are further adjusted for BMI at age 18.

Appendix 3. Comparison of the Demographic Characteristics of Women in the Current Duration and Retrospective Cohorts

Demographic Characteristics	Current Duration Cohort n=1,950	Retrospective Cohort n=2,148	P
Age at study entry (years)	34.1 (4.9)	33.1 (3.9)	<0.001
< 30 years	361 (18.5)	378 (17.6)	
30-37 years	1129 (57.9)	1464 (68.2)	
> 37 years	460 (23.6)	306 (14.3)	
Body mass index (kg/m ²)	26.2 (6.7)	25.0 (5.2)	<0.001
Underweight (<18.5 kg/m ²)	31 (1.6)	44 (2.1)	
Normal weight (18.5-24.9 kg/m ²)	1058 (54.3)	1308 (60.9)	
Overweight (25-29.9 kg/m ²)	429 (22.0)	461 (21.5)	
Obese (>30 kg/m ²)	432 (22.2)	335 (15.6)	
Smoking status, n (%)			0.01
Never	1513 (77.6)	1685 (78.5)	
Former	88 (4.5)	58 (2.7)	
Current	344 (17.6)	399 (18.6)	
Marital status, n (%)			<0.001
Never married	333 (17.1)	287 (13.4)	
Married	1478 (75.9)	1753 (81.8)	
Divorced/Separated/Widowed	83 (4.3)	52 (2.4)	
Domestic partnership	54 (2.8)	51 (2.4)	
Race, n (%)			<0.001
White	1755 (91.9)	2009 (94.9)	
Black	42 (2.2)	21 (1.0)	
Asian	59 (3.1)	37 (1.8)	
American Indian	3 (0.2)	9 (0.4)	
Hawaiian or Pacific Islander	5 (0.3)	2 (0.1)	
Mixed Race	46 (2.4)	40 (1.9)	
Hispanic Ethnicity, n (%)	82 (4.2)	79 (3.7)	0.40
Pregnancy History, n (%)			<0.001
0 pregnancies	1137 (59.4)	1093 (51.6)	
1 pregnancy	433 (22.6)	549 (25.9)	
2 pregnancies	196 (10.3)	281 (13.3)	
3+ pregnancies	147 (7.7)	195 (9.2)	
Ever Diagnosed with PCOS, n (%)	199 (10.2)	133 (6.2)	<0.001
Regular Menstrual Cycle Pattern, n (%)	1091 (78.4)	972 (81.5)	0.05

Differences across cohorts were assessed using a Chi square test and a Fisher's exact test where appropriate (when a cell count was < 5).

Appendix 4. Supplemental Discussion

Our study was not without limitations. As with all studies of time to pregnancy, our study consisted entirely of women who were planning a pregnancy. To address the possibility of planning bias, we looked at differences in body weight and weight change by pregnancy planning status among women enrolled in our Maternal Health Study.

Women with planned and unplanned pregnancies had similar weight changes since age 18 (median: 5.4 vs. 6.8 kg, p-value=0.09) and BMIs at age 18 (median 21.4 vs. 21.6 kg/m², p-value=0.29); however women with unplanned pregnancies had slightly higher current BMIs (median= 24.0 kg/m²) than women with planned pregnancies (median=23.6 kg/m²) (p-value=0.01). If unplanned pregnancies reflect a shorter time-to-pregnancy, our results would have been biased towards finding reduced fecundity with higher current BMIs. However, if women with unplanned pregnancies have a longer time-to-pregnancy our observed results are likely an underestimate of the true effect. Second, due to the observational nature of our study, residual confounding is possible, particularly regarding the ability of some women to lose weight. Unintentional weight loss can be present in women with undetected chronic wasting conditions. However, the demographic profile of these women along with the fact that the majority of women who lost weight were overweight or obese in adolescence strongly suggests that weight loss in this study was most likely intentional. We also did not collect information on frequency of sexual intercourse or characteristics of the male partner. While a previous study found no differences in frequency of sexual intercourse across BMI categories (1), other studies have found a positive correlation between partners' BMIs (2). As higher male

BMI has been related to impaired fertility (3), our results could have been an overestimation of the true effect since we were unable to account for this potential confounder. We also did not have information on current use of infertility treatment. If use of infertility treatment shortens or lengthens a woman's time to pregnancy, then our results could be biased in either direction. Of note, we tried to minimize the effect of this by assigning all women with a current duration of pregnancy attempt > 3 years to 3 years and in sensitivity analyses we changed this cut-off to 1 and 2 years. In all analyses, results remained similar. Finally, since we only used one assessment of current weight we assumed that weight was constant for the duration of the woman's pregnancy attempt (4). If women changed their weight in response to having experienced longer pregnancy attempts, this could have resulted in exposure misclassification. Fortunately, exposure was assessed at least 6 months prior to pregnancy duration assessment, thus it is unlikely that this exposure misclassification was differential with respect to duration of pregnancy attempt.

The strengths of our study are also worth noting. Our study was the first to use a current duration methodology to investigate the question of how adult weight change influences fertility. By using a current duration approach, we were able to include both women with high fertility (who are excluded from many prospective cohorts) and those who are involuntarily infertile (who are excluded from retrospective pregnancy cohorts). We were also able to compare the results from our current duration analysis to a more typical retrospective time-to-pregnancy analysis. Our consistent results in both cohorts strengthens our conclusions regarding causality. Third, our study collected information

on menstrual cycle characteristics and subclinical markers of PCOS which allowed us to investigate potential mechanisms linking adult weight change and fecundity. Finally, due to the homogenous nature of this cohort, many socio-economic factors were inadvertently controlled for in the design of this cohort.

References

1. Brunner Huber LR, Stanley WA, Broadhurst L, Dmochowski J, Vick TM, Scholes D. No association between body size and frequency of sexual intercourse among oral contraceptive users. *Ann Epidemiol* 2014; 24:655-9.
2. Abrevaya J, Tang H. Body mass index in families: spousal correlation, endogeneity, and intergenerational transmission. *Empir Econ* 2010; 41:841-864.
3. Sermondade N, Faure C, Fezeu L, Shayeb AG, Bonde JP, Jensen TK, Van Wely M, Cao J, Martini AC, Eskandar M, et al. BMI in relation to sperm count: an updated systematic review and collaborative meta-analysis. *Hum Reprod Update* 2013; 19:221-31.
4. Slama R, Ducot B, Carstensen L, Lorente C, de La Rochebrochard E, Leridon H, Keiding N, Bouyer J. Feasibility of the current-duration approach to studying human fecundity. *Epidemiol* 2006; 17:440-9.