

Men's body mass index and infertility

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BACKGROUND: In men, excess weight may be linked with altered testosterone, estradiol levels, poor semen quality and infertility. We investigated whether higher BMI among men is associated with infertility and if so, to what extent that effect might be mediated by altered sexual function. **METHODS:** A retrospective cohort study of pregnancies from 1999 through 2005 based within the Norwegian Mother and Child Cohort Study (MoBa). Questionnaires assessed mother's and father's height and weight and time to pregnancy. Our sample comprises 26 303 planned pregnancies. Couples were considered infertile if they took ≥ 12 months to achieve pregnancy or received infertility treatment. **RESULTS:** After adjusting for the woman's BMI, coital frequency and the ages and smoking habits of both partners, the odds ratio for infertility was 1.20 for overweight men [BMI 25–29.9; 95% confidence interval (CI) = 1.04–1.38] and 1.36 for obese men (BMI 30–34.9; 95% CI = 1.13–1.63) relative to men with low-normal BMI (20.0–22.4). When BMI was divided into eight categories, there was a trend of increased infertility with increased male BMI. The effect of men's BMI was nearly identical when coital frequency was not included indicating that the effect is not mediated by sexual dysfunction in heavier men. **CONCLUSIONS:** This study adds further support that men with excess body weight are at increased risk of infertility. Values may be underestimated because the most severe cases, couples who do not conceive, are not included in this birth cohort. Research is needed to see if weight loss improves fertility for these men.

Keywords: body mass index; infertility; time to pregnancy; body weight

Introduction

Obesity is rapidly increasing worldwide (Ogden *et al.*, 2006; Prentice, 2006). Excess weight is not only linked to increased risk of chronic disease (Must *et al.*, 1999), but has also been shown to increase risk of reproductive problems (Catalano, 2007). Several studies have shown that women with excess body weight are more likely to have fertility problems (Jensen *et al.*, 1999; Bolumar *et al.*, 2000; Rich-Edwards *et al.*, 2002; Pasquali, 2006; Gesink Law *et al.*, 2007). The adverse effects may be reversible with weight loss (Norman *et al.*, 2004; Ramlau-Hansen *et al.*, 2007). It is less clear whether men also experience reduced fertility with excess weight.

Similar to women, (Azziz, 1989) a sex hormone imbalance may affect reproduction in men, and excess weight can affect male hormone levels (Jensen *et al.*, 2004; Roudebush *et al.*, 2005; Fejes *et al.*, 2006). A significantly reduced testosterone to estradiol ratio has been observed among overweight or obese men (BMI > 25) when compared with men with lower BMI (Fejes *et al.*, 2006). Men with higher BMI have also exhibited altered quantity and quality of sperm (Jensen *et al.*,

2004; Magnusdottir *et al.*, 2005; Fejes *et al.*, 2006; Kort *et al.*, 2006).

There is sparse population-based data on the effect of men's body mass on a couple's fertility (Sallmen *et al.*, 2006; Ramlau-Hansen *et al.*, 2007). In a study of US farmers, risk of infertility increased with each 3-unit category of BMI, but there was some attenuation in the very highest BMI category. The strongest effect was for men with BMI of 32–34 who had twice the risk of infertility as men with BMI of 20–22 (Sallmen *et al.*, 2006). However, their data on infertility status were limited by lack of precise timing of the beginning of the pregnancy attempt, and their BMI data were collected as much as 4 years after the start of the pregnancy attempt. In a study based on data from the Danish National Birth Cohort, Ramlau-Hansen *et al.* (2007) also found increased infertility among men with excess weight (an ~50% increase in infertility for obese compared with normal weight men). However this study also lacked timely assessment of men's BMI since women were not asked to report partner's height and weight until 18 months post-partum. In neither report are data

presented on coital frequency, so mediating effects of sexual dysfunction in obese men could not be evaluated.

We examine the association between men's BMI and couples' infertility in a study that collected somewhat more timely BMI data as well as information on frequency of sexual intercourse around the time of conception.

Materials and Methods

Fertility is assessed in large population-based studies by collecting data on how long it takes couples to conceive (Joffe *et al.*, 2005). On average, couples who conceive quickly (measured in number months or menstrual cycles) are more fertile than couples who take longer to conceive. Such studies are often based within pregnancy cohorts because time-to-pregnancy data can be collected for the index pregnancy. (Zhu *et al.*, 2007) We used data from a large pregnancy cohort in Norway.

The Norwegian Mother and Child Cohort (MoBa) Study

The ongoing Norwegian MoBa was started in 1999 as a research platform for studies on the health of mothers and their children. Women were sent an invitation to participate and a written consent form at the same time they were given an appointment for their routine second trimester ultrasound examination (carried out around the 17th week of gestation for nearly all women in Norway). The study aims to enroll 100 000 pregnant women from hospitals and birthing units with >100 births annually. Fifty of the 52 eligible centers participate in recruitment.

The participation rate for the MoBa was 45% during the time of recruitment for this analysis sample (Magnus *et al.*, 2006). Preliminary analysis of data from the Norwegian Medical Birth Registry (which covers all births nationwide) indicated that MoBa participants tended to be older than non-participants, more likely to be married or living with the father of the child, and less likely to smoke. Participating women complete a series of self-administered questionnaires about themselves and the father of the child. The present analysis is based on the initial questionnaire (completed at about 17 weeks' gestation). More details about the MoBa can be found at <http://www.fhi.no/morogbarn>.

Exclusions

Data on 45 132 women were available for analysis. We selected each woman's first pregnancy in the study (not necessarily the woman's first pregnancy in her lifetime). We also made a series of exclusions because of missing data or to improve data quality and to reduce the potential for bias. These exclusions included women who were non-native Norwegian speakers, women who were not living with the father of their child (to increase the validity of women's report of their partner's height and weight), unplanned pregnancies and women aged <18 or ≥ 40 years old (to limit inclusion of couples with low fecundability due to age extremes). Details of exclusions are provided in Fig. 1.

Definition of infertility

Women who planned their pregnancy were asked, 'How many months did you have regular intercourse without contraception before you became pregnant?'. Women were able to choose '<1, 1–2, 3 or more months'. If the woman reported >3 months, she was then asked to report the number of months. We analysed time to pregnancy as a dichotomy (infertile or not), where infertility was defined as taking 12 or more months to conceive the pregnancy. Couples who received any type of infertility treatment for the current pregnancy

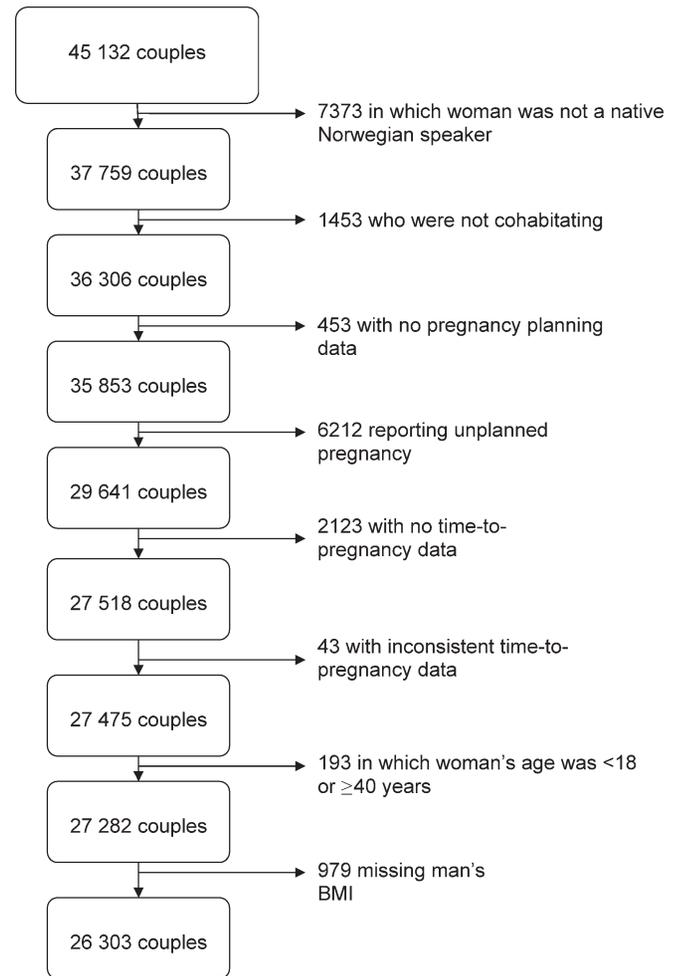


Figure 1: Flow chart of exclusions from the study sample resulting in 26 303 Norwegian couples, 1999–2005. The first three exclusion categories also include some women who were missing data for that variable

were also defined as infertile. Retrospective collection of time-to-pregnancy data has been shown to be reasonably accurate (Joffe *et al.*, 1993). Joffe *et al.* (1993) found that women's retrospective report of infertility (taking >12 months to achieve pregnancy) had a sensitivity of 80% and a specificity of 95% when compared with prospectively collected information.

Height and weight

Women were asked to report their own height (cm) and weight (kg) prior to the pregnancy, and the height and weight of the child's father at the time of the questionnaire (during the second trimester of pregnancy). BMI was calculated as weight (kg) divided by height (m) squared. In addition to the 979 exclusions due to missing reports of men's BMI (Fig. 1), we set BMI as missing if a woman reported any of the following outlying values (determined by our frequency distributions of height and weight): for women, height <117 or >196 cm (60 excluded), or weight <38 or >150 kg (13 excluded), and for men, height <136 or >220 cm (74 excluded), or weight <50 or >200 kg (11 excluded).

Categories of BMI

We used the classification of BMI recommended by the World Health Organization (WHO) and the Centers for Disease Control for

'overweight' (25–29.9), 'obese' (30–34.9) and 'severely obese' (≥ 35). We categorized men with BMI < 20 as 'underweight' (comprising 1% of our sample), and *a priori* we selected 'low normal' BMI (20–22.4) as the referent in analyses. Since our sample size was large, we split each of the broad WHO categories of normal, overweight and obese into a total of eight BMI categories (< 20.0 , 20.0–22.4, 22.5–24.9, 25.0–27.4, 27.5–29.9, 30.0–32.4, 32.5–34.9 and 35+).

Validity of women's report for men's BMI

We evaluated the accuracy of the women's report of her partner's height and weight by taking advantage of a recent revision of the men's questionnaire. Starting in 2005, men were asked to report their own height and weight. While there are not enough couples with these additional data for a full analysis, we were able to use these data for a validity study. We selected 300 couples using the same inclusion criteria as in our main study, and compared the calculated BMI from the woman's report of her partner's height and weight with the calculated BMI from the men's own report (using the same eight categories of BMI as in the analysis). The women's report agreed well with the men's own report (82% agreement, kappa value of 77%). This high level of agreement may reflect our general restriction to married and cohabitating couples, and the fact that women completed the questionnaires at home, where they could ask their partners for this information.

Statistical analysis

We developed a logistic regression model for infertility that adjusted for several important potential confounders. Covariates included *a priori* in the model (based on published literature) were men's and women's ages and smoking status and women's BMI. (Baird and Wilcox, 1985; Jensen *et al.*, 1999; Rich-Edwards *et al.*, 2002; Hassan and Killick, 2003; Dunson *et al.*, 2004; The Practice Committee of the American Society for Reproductive Medicine, 2004; European Society of Human Reproduction and Embryology Capri Workshop Group, 2005; Axmon *et al.*, 2006) In addition, we evaluated (using either adjustment or restriction) the influence of the following women's factors: education level, alcohol use in the three months prior to pregnancy, recreational drug use in the month before pregnancy, diseases that might affect fertility (asthma, diabetes, heart disease, high blood pressure, hypo- or hyperthyroidism, lupus, fallopian tube infection, endometriosis, epilepsy and cancer) and the use of medications for these conditions. None of these factors substantially changed the relationship between men's BMI and fertility and were not included in the logistic model. Women were not asked such detailed questions about their partner's exposure factors, so we were unable to assess the effect of these factors in men. Coital frequency (daily, 5–6 times/week, 3–4 times/week, 1–2 times/week, 1–2 times every other week, $< 1-2$ times every other week) was added to the model to investigate possible mediating effects of sexual dysfunction. All analyses were performed using STATA/SE 8.0 (College Station, TX, USA).

Results

Characteristics of the 26 303 eligible couples are shown in Table 1, stratified by infertility status. Twelve percent (3113) of couples were infertile, with 1322 of these (42%) having received infertility treatment for the current pregnancy. Among the infertile group, 37% (1143) were having their first child compared with 31% (7162) in the fertile group.

Overall, the median time to pregnancy was two months, and it was two months for each category of men's BMI with the exception of the highest categories (32.5–34.9 and ≥ 35); for those categories median time was three months.

Infertility was significantly related to men's BMI. After adjusting for the woman's own BMI and the ages and smoking habits of both partners, overweight men had an adjusted odds ratio (adj. OR) for infertility of 1.19 [95% confidence interval (CI) = 1.03–1.37] relative to men with low normal BMI. For obese men, the adj. OR was 1.36 (95% CI = 1.12–1.62). Adding coital frequency to this model resulted in essentially identical estimates (1.20 for overweight men and 1.36 for obese men). Fig. 2 provides adjusted ORs of infertility at each of the eight categories of men's BMI. The association shows an elevated risk of infertility in very thin men (BMI < 20), and then a general increase in ORs with higher BMI, with a plateau above a BMI of 32.4. (The slightly lower infertility among the 1% of men with BMI above 35 is not significantly different from the peak OR of 1.36 for men with excess weight). As expected, women's prepregnancy BMI in the adjusted model was an important predictor of infertility with significant effects beginning in the overweight category (BMI 25.0–27.4; adj. OR = 1.12, 95% CI: 0.98–1.26) and continuing through the remaining four highest BMI categories (1.26, 1.08–1.47; 1.59, 1.33–1.91; 1.86, 1.49–2.32; 2.46 and 2.0–3.04, respectively).

We also conducted analyses to evaluate in more detail factors that might affect our results. First, we considered women's BMI. Though we controlled for women's BMI with the same eight categories as used for men's BMI, there could still be residual confounding, so we restricted analyses to couples in which the woman had a normal BMI (20.0–24.9). The effect of men's BMI was essentially unchanged (adj. OR for obese men = 1.38 versus 1.36 in the unrestricted sample). We also evaluated possible interaction between men's and women's BMI using interaction terms for each and found no significant interaction ($P = 0.36$). Secondly, we considered parity. It is generally inappropriate to adjust for parity in evaluating risk factors for infertility; adjusting for parity may result in over-adjustment since factors that affect the index pregnancy may have had similar effects at the time of previous pregnancy attempts (Weinberg, 1993). Results do not change when we do adjust for parity (adj. OR for obese men = 1.36 both with and without parity in model). We also restricted analysis to nulliparous couples and again results remained unchanged (adj. OR for obese men = 1.36). Finally, to further evaluate possible mediating effects of coital frequency we limited analyses to couples who had frequent intercourse (≥ 3 times per week). The effect for obese men again remained unchanged (adj. OR = 1.36).

Discussion

Our data suggest that men's excess weight may contribute to infertility. Aside from the underweight men (the thinnest 1%) who themselves had increased risk of infertility, we found that infertility increased with men's BMI, with some attenuation at the highest BMI category. The elevated risk of

Table 1: Characteristics of 26 303 couples with planned pregnancies in Norway, 1999–2005

	Men		Women	
	Fertile <i>n</i> = 23 190 (%)	Infertile <i>n</i> = 3113 (%)	Fertile <i>n</i> = 23 190 (%)	Infertile <i>n</i> = 3113 (%)
Age (years) at beginning of time-to-pregnancy				
<20	38 (0.2)	10 (0.3)	218 (1.0)	54 (1.8)
20–24	1449 (6.5)	248 (8.3)	3406 (14.9)	541 (17.8)
25–29	7428 (33.2)	971 (32.7)	9953 (43.6)	1279 (42.2)
30–34	8792 (39.3)	1093 (36.7)	7526 (33.0)	914 (30.2)
35–39	3533 (15.8)	470 (15.8)	1730 (7.6)	246 (8.1)
≥40.0	1114 (5.0)	182 (6.1)	0	0
Missing	836	139	357	79
Completed education at interview				
<High school	2259 (10.7)	384 (13.4)	1491 (6.7)	231 (7.7)
High school graduate	8588 (40.5)	1205 (42.0)	6429 (29.0)	997 (33.3)
High school graduate	6016 (28.4)	759 (26.5)	9932 (44.9)	1257 (42.0)
Up to 4-year college	4357 (20.5)	519 (18.1)	4285 (19.4)	508 (17.0)
4-year college plus missing	1970	246	1053	120
Smoking status^a				
Never	16 686 (72.4)	2117 (68.4)	12 047 (53.2)	1524 (49.8)
Former	1595 (6.9)	220 (7.1)	6239 (27.6)	572 (18.8)
Current	4774 (20.7)	757 (24.5)	4348 (19.2)	963 (31.4)
Missing	135	19	556	54
BMI^b				
<20.0	263 (1.1)	47 (1.5)	2523 (11.1)	312 (10.2)
20.0–22.49 (REF)	2528 (10.9)	283 (9.1)	6835 (29.9)	776 (25.3)
22.5–24.99	7432 (32.1)	938 (30.1)	6064 (26.6)	736 (24.0)
25.0–27.49	7165 (30.9)	924 (29.7)	3518 (15.4)	465 (15.2)
27.5–29.99	3661 (15.8)	539 (17.3)	1839 (8.1)	287 (9.4)
30.0–32.49	1381 (6.0)	238 (7.7)	1014 (4.4)	199 (6.5)
32.5–34.99	485 (2.1)	91 (2.9)	521 (2.3)	128 (4.2)
≥35.0	275 (1.2)	53 (1.7)	513 (2.3)	160 (5.2)
Missing	0	0	363	50
Couples' coital frequency during four weeks prior to pregnancy				
Daily			863 (3.8)	64 (2.1)
5–6 times/week			2033 (8.8)	166 (5.4)
3–4 times/week			8475 (37.0)	1050 (34.3)
1–2 times/week			8350 (36.5)	1154 (37.7)
1–2 times every 2 weeks			2563 (11.2)	485 (15.8)
<1–2 times every 2 weeks			615 (2.7)	145 (4.7)
Missing			291	49

^aSmoking status reflects first trimester for men and beginning of pregnancy attempt for women. For multivariable analysis, the never and former categories were combined among women to create the 'no' category for smoking at the beginning of pregnancy attempt. ^bBMI was reported by women for both men and women and reflects first trimester for men and pre-pregnancy for women. REF, reference BMI category.

infertility with both low and high BMI resembles the pattern seen with BMI for other health outcomes, including all-cause mortality and cancer incidence (Inoue *et al.*, 2004; Breeze *et al.*, 2006; Gu *et al.*, 2006). The increased risk seen in the lowest weight category presumably represents a different biological mechanism from those mechanisms accounting for the general increase with heavier weights.

Excess weight has been related directly or indirectly to biologic changes that could reduce male fertility. Several studies have reported reductions in testosterone with obesity (Jensen *et al.*, 2004; Roudebush *et al.*, 2005; Fejes *et al.*, 2006). A recent Danish study of young men completing their military physical examination found a higher rate of abnormal sperm among men with either low or high BMI (<20 or ≥25) (Jensen *et al.*, 2004). In another study, overweight and obese men had reduced sperm motility and increased sperm DNA fragmentation (Kort *et al.*, 2006).

While women's obesity has been studied with regard to infertility (Grodstein *et al.*, 1994; Jensen *et al.*, 1999; Rich-Edwards

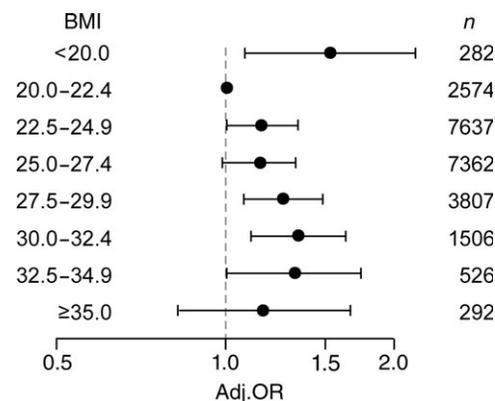


Figure 2: Adjusted OR, 95% CI and number of men by men's BMI categories among 23 986 men in Norway, 1999–2005. Model adjusted for women's BMI category (same eight categories as the men), women's and men's ages at the beginning of the pregnancy attempt, women's smoking at the beginning of pregnancy attempt, men's smoking during the first trimester of pregnancy and coital frequency. Reference BMI category is 20.0–22.49

et al., 2002; Pasquali *et al.*, 2003; Norman *et al.*, 2004), there is little population-based data for men. Sallmen *et al.* (2006) reported a dose-response increase in infertility with BMI, reaching a maximum OR of around 2.0 (somewhat higher than seen in our study). Unlike our study, Sallmen's study included infertile couples who were unable to conceive during the four year follow-up period. Since our analysis was based only on couples who successfully achieved a pregnancy, our results may underestimate the effect of BMI on infertility (Baird *et al.*, 1986). Contrary to our study, no increased risk was observed in this previous study among underweight men, although their sample size was only one-tenth of ours.

Sallmen *et al.*'s finding of increased risk if their partner was overweight or obese was corroborated by Ramlau-Hansen *et al.* (2007). Although this Danish Birth Cohort study was large (it had twice as many couples as ours), it along with the Sallmen *et al.* (2006) study lacked information on frequency of sexual intercourse so obesity-related changes on sexual function could not be distinguished from obesity-related effects on fertility.

Obesity has been associated with both sexual and erectile dysfunction (Esposito and Giugliano, 2005; Bacon *et al.*, 2006), therefore reduced intercourse frequency could be a mediating factor by which obesity produces infertility. To assess the role of intercourse, we first examined the relationship between frequency of intercourse and men's BMI. After adjusting for men's age, we found no evidence that men with higher BMI had less frequent intercourse. This is consistent with our finding that adjusting for coital frequency did not reduce the strength of the BMI association with infertility, even though coital frequency was independently associated with infertility status [adj. OR = 1.28, (95% CI: 1.23–1.33) for each decrease in coital frequency on the 6-level variable]. We pursued this further by limiting the analysis to couples with frequent intercourse (three or more times per week). If sexual intercourse functions as a mediator of a BMI effect on fertility, the BMI effect would be expected to be much reduced in this group. However, the association of BMI and infertility remained essentially unchanged. Thus, any mechanism that explains the BMI effect is likely to involve hormones or semen changes rather than sexual function.

Our data have a number of limitations. There may be selection bias from restricting our sample to planned pregnancies. Unplanned pregnancy will occur more often in highly fecund couples. Thus, if heavy men tend to be over-represented in the unplanned sample, the observed association could arise through selection bias (highly fecund, heavy men would be under-represented in the analysis). However, the mean age-adjusted BMI in the unplanned pregnancy group was actually lower than that in the planned pregnancy group (25.8 versus 25.9), indicating that this bias would not explain our results.

Confounding is always a concern in observational studies, especially when the possible confounding variables are strongly correlated with the exposure of interest. Such is the case with a man's BMI being correlated with his partner's BMI, as well as with his own age and the age of his partner.

Because of this, we have not presented estimates unadjusted for these variables. Fortunately, our study has the advantage of a large sample size, which allows for careful adjustment of such confounders (Slama *et al.*, 2004). For example, there is little if any residual confounding by female BMI in our main analysis, as demonstrated by the analysis restricted to women of normal BMI. Nor were our results confounded by parity as demonstrated when we restricted to nulliparous couples and found that the association was essentially unchanged. Data on male alcohol and drug use and medical history were not available, so we cannot rule out unmeasured confounding from these male factors.

Our data on men's BMI have the limitation of being provided by the woman. Though these were shown to accurately reflect men's self-report, self-reports by both men and women tend to overestimate height and underestimate weight (Niedhammer *et al.*, 2000). To the degree that this misreporting is present in our data, it would tend to reduce an association between adiposity and infertility.

Another limitation of the men's BMI data is that the question was asked during the woman's pregnancy. The most relevant time-period for the BMI effect on fertility is before pregnancy, ideally at the time the couple first started to try to become pregnant. For some couples, that may have been years before the actual pregnancy. Future studies would benefit from collection of BMI data at the start of the pregnancy attempt.

We used BMI as a population-level indicator for overweight and obesity (Ogden *et al.*, 2006). However, BMI does not distinguish between weight associated with adipose tissue versus that from muscle. Our results using BMI therefore do not reflect the inter-individual differences in body composition. A true measure of body fat might be expected to have an even stronger association with infertility.

Only 45% of eligible women have enrolled in the Norway MoBa, and these participants differed from non-respondents in certain characteristics such as age and smoking habits. This raises a concern about the generalizability of our results to the whole population. In this context, it is reassuring that the well-established relation of women's smoking with reduced fertility was apparent in our data (Table 1), even though smokers are under-represented among participants.

In sum, male adiposity was associated with increased infertility. This is consistent with recent literature showing impairment of semen characteristics among overweight men and two other studies of men's BMI and infertility. Our data suggest that sexual dysfunction is not likely to be an important mediator in the relationship, but increased adiposity could produce other biologic changes in men that reduce their fertility. If such changes occur and are reversible, weight loss may improve their chances of conception.

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