Dietary Energy Density and Fertility: Results from the Lifestyle and Fertility Study

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ABSTRACT

Background: Diet is a modifiable lifestyle factor linked with fertility in a growing number of studies.

Objective: The objective of this study was to evaluate the association between dietary energy density (ED), a summary measure of diet quality that estimates the amount of energy per unit food (kcal/g) consumed, and conception and pregnancy outcomes.

Methods: A prospective cohort study of couples planning their first pregnancy was conducted in the Northeast region of the USA. Dietary data were collected prior to conception via 3 unannounced interviewer-administered 24-h dietary recalls. Multivariable-adjusted logistic regression (ORs and Cox proportional hazards models [HR] and 95% CIs) were estimated for continuous and categorical (tertile [T]) variables of dietary ED.

Results: The majority of women (n = 80; 61%) achieved clinical pregnancy. Median time to conception of a clinical pregnancy (TTC) for those who conceived was 4.64 mo with an IQR of 4.37 mo. ED modeled as a continuous variable was not associated with clinical pregnancy, live birth, or TTC after controlling for race, physical activity, and male partner’s ED. When ED was categorized to consider nonlinear associations, 60%, 73%, and 50% of the participants in the tertiles (from lowest ED to highest) achieved clinical pregnancy. In multivariable logistic analyses with the middle group as the referent (ED = 1.37–1.60), membership in the highest ED group (ED > 1.60) was associated with lower odds of clinical pregnancy (OR = 0.30; 95% CI: 0.11, 0.81; P = 0.02). In Cox proportional hazards analyses, membership in the highest ED group was associated with significantly longer TTC compared with the middle category (HR = 0.41; 95% CI: 0.21,0.82, P = 0.01).

Conclusions: These results suggest that high dietary ED is associated with reduced fertility. This study evaluated associations between dietary energy density and the probability of conceiving clinical pregnancy, having a live birth, and the time to conception among couples planning pregnancy.

Keywords: diet, energy density, calorie density, fertility, pregnancy

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Abbreviations used: AHEI-P, Alternative Healthy Eating Index for Pregnancy; ED, energy density; NDSR, Nutrition Data System for Research software; T, tertile; TTC, time to conception of a clinical pregnancy.

Introduction

Infertility is the failure to conceive after 12 mo of regular unprotected sexual intercourse (1). Impaired fecundity additionally includes difficulty carrying an infant to full term (1). There is a 20–25% probability of conception per month for healthy young couples with no known infertility conditions (1). Nevertheless, data from the US National Survey of Family Growth indicate that ~6% and 15–18% of women aged under 35 y experience infertility and impaired fecundity, respectively (2). For nearly 1/3 of infertile couples the origin remains unknown (3).

Diet is a modifiable lifestyle factor linked with fertility in a growing number of studies (4). A recent review of the epidemiologic literature on nutrition and fertility concluded that, based on the limited data available, concordance with overall healthful dietary patterns higher in fish, poultry, whole grains, vegetables, and fruits may be positively associated with female fertility and improved semen quality in males (4). The review also highlighted that no prospective studies have jointly assessed measures of female and male diet quality on infertility or impaired fecundity.

In the current study, we evaluated the association between dietary energy density (ED), assessed prior to attempting conception, on the
probability of conceiving a clinical pregnancy and having a live birth, and the time to conception among couples planning their first pregnancy. We hypothesized that higher ED would be associated with unfavorable outcomes. Dietary ED is a summary measure of diet quality that estimates the amount of energy per unit food (kcal/g) consumed (5). Low-ED diets are generally lower in fat and higher in fiber, fruits, and vegetables (6), consistent with the healthful dietary patterns that have been linked to better fertility (4). Consuming an energy-dense diet has been positively associated with body weight in both children and adults and may be a contributing factor to risk of chronic disease (7–10).

### Methods

**Design and study participants**
The Lifestyle and Fertility Study (ISIS) was a multisite, prospective cohort study of healthy, nulliparous couples with no known infertility conditions, planning their first pregnancy. Other eligibility criteria for women included having regular menstrual periods and using contraception at the time of enrollment, and no history of polycystic ovary syndrome or PCOS, endometriosis, or serious medical conditions such as diabetes, cancer, or heart disease. We conducted preliminary telephone screening on 802 female participants between May 2008 and June 2012 at sites in Boston, MA, Lebanon, NH, and University Park, PA. Of these, 536 did not meet our eligibility criteria, 85 were not interested in participating, and the remaining 181 were invited for in-person screening. After in-person screening, 135 were interested in participating and eligible for enrollment. A total of 132 women aged 18–39 y and their male partners (all but 1, i.e. \(n = 131\)) were enrolled. Between the screening and the baseline visits 2 women became pregnant and 1 decided not to participate. The protocol was approved by the participating institutions’ human subjects review boards and all participants provided written informed consent. The study was conducted according to the guidelines laid down in the Declaration of Helsinki. The study was registered at clinicaltrials.gov as NCT00642590.

**Data collection**
Demographic characteristics, medical history, and lifestyle factors, including dietary intake, were self-reported at baseline (before attempting conception). Height (without shoes) and weight (in light clothing) were measured by trained technicians and used to calculate BMI (kg/m²). Physical activity was ascertained at baseline and scored as meeting guidelines set by the US Department of Health and Human Services (yes/no) (10, 11). Frequency of intercourse was captured prospectively. Couples were followed from the start of the study protocol until they either achieved a clinically confirmed pregnancy, completed 6 menstrual cycles of attempted conception, or were lost to follow-up.

**Pregnancy outcome**
We followed our participants to determine whether they conceived or not for 6 menstrual cycles with daily urine collection. Pregnancy (\(n = 80/52\) for yes/no pregnancy) was determined by a positive pregnancy test (human chorionic gonadotropin or hCG ≥20 mIU/ml; AIM MidStream OTC Professional, Craig Medical Distribution, Inc.) and confirmed clinically by each female participant’s physician either using a urine test, blood test, and/or ultrasound. Clinical pregnancies were followed to delivery (\(n = 69\)) or loss (\(n = 11\)) and the date recorded. Live birth was defined as a gasp, heartbeat, or sign of life at birth. Time to conception of a clinical pregnancy (TTC) was defined as the length of time from the date the couple began attempting conception (day 1 of the first menstrual cycle after the baseline visit) to the date of the last menstrual period plus 14 d for those who conceived a clinical pregnancy during the study. There were a total of 47 participants who completed follow-up, but did not conceive a clinical pregnancy. Five participants did not have follow-up to determine outcome and were censored at date of last contact.

**Dietary assessment**
Dietary intake was assessed at baseline using a standardized multipass process including a series of 3, unannounced, telephone 24-h dietary recalls administered on consecutive days (2 weekdays, 1 weekend day) by trained interviewers at the Diet Assessment Center, Penn State University (University Park, PA). Dietary intake assessment was attempted in all participants; however, 2 males did not provide dietary data. Dietary recalls included all foods, beverages, and supplements consumed by participants over the previous 24-h period. The Nutrition Data System for Research software (NDSR, Version 2012, Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN [12]) was used for data entry and nutritional analyses. NDSR output data were used to calculate average daily energy intake (in kcal) and average amount of food consumed (in g) for each participant from food alone, excluding beverages (e.g. differentiating between milk used in cereal compared with milk consumed as a beverage) (13). Beverages have a high water content, and the weight of the beverages, even caloric beverages, like regular soda (has an ED of 0.34 kcal/g which is lower than most vegetables) generally lowers the overall ED of the diet. Dietary ED was calculated as mean energy (kcal)/mean total amount (g) consumed (5).

**Statistical analysis**
Statistical analyses were performed using SAS Institute, Inc. software (version 9.3). Dietary ED was evaluated as both a continuous variable and categorized into tertiles of intake with the middle tertile serving as the referent. Descriptive statistics were conducted for tertiles of ED and presented as mean § SD for continuous and percentages for categorical variables. Multivariable-adjusted logistic regression models (ORs and 95% CIs) were estimated for odds of clinical pregnancy and live birth by continuous and categories of ED. Time to clinical pregnancy was evaluated in Cox proportional hazards regression models. In these models, lower HRs (RR; 95% CI) can be interpreted as less likely to achieve pregnancy (longer TTC). The associations between pregnancy outcomes and dietary ED were evaluated in a series of multivariate models that adjusted for race/ethnicity (white, other), male partner’s dietary ED (continuous), physical activity (meeting guidelines versus not), and then with the addition of prepregnancy BMI (continuous kg/m²) or total energy intake (kcal/d). For categorical ED, the middle tertile (T2) was designated as the referent. A number of other potential covariates were evaluated but did not appreciably contribute to model fit or interpretation and were not included in final models. These variables included female educational status (=college, college degree, graduate degree), household income (<$60,000, $60,000–99,999, ≥$100,000), female smoking status (ever versus never), total and trans fat intakes (per cent kcal), animal and vegetable protein intake (g/d), and alcohol use (g/d). Attempts at conception per cycle were available for all.
but 9 couples who became pregnant in a short time period (<1 mo); thus, this variable was considered in sensitivity analyses. In Cox models, potential effect modification by age and BMI was evaluated by modeling multiplicative interaction terms between variables for ED and time.

**Results**

The majority of participants (n = 80 women; 61%) achieved clinical pregnancy. Among those who conceived, the median TTC was 4.64 mo with an IQR of 4.37 mo (data not presented). Compared with women consuming lower-ED diets, those who consumed higher-ED diets were more likely to be Caucasian (Table 1). Male partners of women reporting higher ED diets also reported higher ED diets. As expected, women consuming higher-ED diets reported intakes higher in total energy, total and trans fat, and lower in dietary fiber. From the lowest to the highest category (tertile) of ED, 60% (26/44), 73% (32/44), and 50% (22/44) of the participants achieved clinical pregnancy.

In logistic regression analyses (Table 2), ED modeled as a continuous variable was not significantly associated with either clinical pregnancy or live birth after adjustment for maternal race and activity level and male dietary ED. In the categorical ED analysis, women reporting ED diets in the highest tertile (T3: ED >1.60) were significantly less likely to achieve pregnancy (OR = 0.29; 95% CI: 0.11, 0.76, P < 0.01) than women in the middle category of ED (ED = 1.37–1.60). There was

**Table 1** Baseline characteristics of females by tertiles (range) of dietary energy density

| Characteristics1 | T1 (n = 44) (0.85–1.36) | T2 (n = 44) (1.37–1.60) | T3 (n = 44) (1.61–2.66) | P value | Overall |
|------------------|--------------------------|--------------------------|--------------------------|---------|---------|
| Age, y (mean ± SD) | 29.7 ± 3.2 | 29.8 ± 2.7 | 29.9 ± 3.7 | 0.92 | 29.8 ± 3.2 |
| Race, n (%) | | | | 0.004 | |
| White | 28 (21.2) | 38 (28.8) | 39 (29.6) | 105 (79.6) |
| African American | 3 (2.3) | 1 (0.8) | 3 (2.3) | 7 (5.3) |
| Asian | 12 (9.1) | 2 (1.5) | 2 (1.5) | 16 (12.1) |
| Other/unknown | 1 (0.8) | 3 (2.3) | 0 (0) | 4 (3.0) |
| Education, n (%) | | | | 0.08 | |
| <College degree | 5 (3.8) | 1 (0.8) | 9 (6.8) | 15 (11.4) |
| College degree | 15 (11.4) | 19 (14.4) | 18 (13.6) | 52 (39.4) |
| Graduate degree | 24 (18.2) | 24 (18.2) | 17 (12.9) | 65 (49.2) |
| Income, $ (n) (%) | | | | 0.36 | |
| <$60,000 | 15 (11.6) | 7 (5.4) | 13 (10.1) | 35 (27.1) |
| $60,000–$99,999 | 11 (8.5) | 16 (12.4) | 14 (10.9) | 41 (31.8) |
| ≥$100,000 | 16 (12.4) | 20 (15.5) | 17 (13.2) | 53 (41.1) |
| Smoking status, n (%) | | | | 0.69 | |
| Never | 37 (28.0) | 34 (25.8) | 33 (25.0) | 104 (78.8) |
| Past use | 7 (5.3) | 10 (7.6) | 10 (7.6) | 27 (20.5) |
| Current use | 0 (0) | 0 (0) | 1 (0.8) | 1 (0.8) |
| Alcohol use, n (%) | | | | 0.30 | |
| No | 12 (9.1) | 7 (5.3) | 7 (5.3) | 26 (19.7) |
| Yes | 32 (24.2) | 37 (28.0) | 37 (28.0) | 106 (80.3) |
| Activity score (PA), n (%) | | | | 0.43 | |
| Inactive | 9 (6.8) | 14 (10.6) | 10 (7.6) | 33 (25) |
| Active | 35 (26.5) | 30 (22.7) | 34 (25.8) | 99 (75) |
| BMI, kg/m², mean ± SD | 24.0 ± 5.4 | 24.4 ± 5.4 | 24.6 ± 5.4 | 0.86 | 24.3 ± 5.4 |
| Pregnancy outcomes | | | | 0.39 | |
| Attempts,3 mean/cycle ± SD | 9.7 ± 3.3 | 9.9 ± 3.5 | 6.2 ± 3.4 | 0.04 | 6.6 ± 4.3 |
| Pregnancy, n (yes) | 23 (17.4) | 23 (17.4) | 19 (14.5) | 0.23 | 69 (52.3) |
| TTC, mo, mean ± SD | 2.2 ± 0.9 | 2.4 ± 0.9 | 2.4 ± 0.9 | 0.65 | 2.4 ± 0.9 |
| Live birth, n (yes) | 15 (11.6) | 15 (11.6) | 10 (7.6) | 0.37 | 3.4 ± 2.5 |
| Male energy density | 1.5 ± 0.3 | 1.7 ± 0.4 | 1.9 ± 0.4 | <0.001 | 1.7 ± 0.4 |

1Values are mean ± SD for continuous variables or n (%) for categorical variables; n = 132 for most variables.

2Participants reported unknown incomes.

3Participants did not report pregnancy attempts.

PA, physical activity; TTC, time to conception of a clinical pregnancy in months.
TABLE 2  Association between energy density and odds of clinical pregnancy (n = 80) and live birth (n = 69) for participants of the Lifestyle and Fertility study

| Model                                      | Clinical pregnancy | Live birth |
|--------------------------------------------|--------------------|------------|
|                                            | OR 95% CI          | P value    | OR 95% CI          | P value |
| ED continuous                              |                    |            |                    |         |
| ED (Model 1)                               | 0.80 (0.31, 2.06)  | 0.64       |                    |         |
| ED + race + male ED + PA (Model 2)         | 0.40 (0.13, 1.26)  | 0.12       |                    |         |
| Model 2 + BMI (Model 3)                    | 0.39 (0.12, 1.26)  | 0.12       |                    |         |
| Model 2 + total energy (Model 4)           | 0.60 (0.16, 2.22)  | 0.44       |                    |         |
| Above Model (4) + attempts²                | 0.39 (0.08, 1.90)  | 0.24       |                    |         |
| ED categorical¹                             |                    |            |                    |         |
| ED low (<1.37)                             | 0.84 (0.32, 2.21)  | 0.72       | 1.10 (0.44, 2.80)  | 0.84 |
| ED high (>1.6)                             | 0.29 (0.11, 0.76)  | <0.01      | 0.43 (0.17, 1.07)  | 0.07 |
| Model 5 + BMI (Model 6)¹                   |                    |            |                    |         |
| ED low (<1.37)                             | 0.83 (0.32, 2.18)  | 0.70       | 1.09 (0.43, 2.77)  | 0.85 |
| ED high (>1.6)                             | 0.30 (0.11, 0.78)  | 0.01       | 0.44 (0.17, 1.10)  | 0.08 |
| Model 5 + total energy (Model 7)¹          |                    |            |                    |         |
| ED low (<1.37)                             | 0.80 (0.30, 2.19)  | 0.67       | 0.93 (0.35, 2.47)  | 0.89 |
| ED High (>1.6)                             | 0.30 (0.11, 0.81)  | 0.02       | 0.49 (0.19, 1.24)  | 0.13 |
| Above Model (7) + attempts²                | 0.99 (0.32, 3.09)  | 0.99       | 1.06 (0.35, 3.17)  | 0.92 |
| ED low (<1.37)                             | 0.26 (0.09, 0.77)  | 0.02       | 0.50 (0.17, 1.40)  | 0.18 |

¹For categorical ED the referent is the middle tertile (ED 1.37–1.60). All variables are female except for male ED. BMI is measured prepregnancy. OR <1 means odds of pregnancy/live birth are lower.
²Sensitivity analyses – conception attempts are missing for 9 couples.

Discussion

In the first study to examine the role of dietary ED in achieving pregnancy, we observed that women who consumed high-ED diets preconceptually were less likely to achieve clinical pregnancy and experienced longer TTC. In addition, there was a suggestion that women who consumed high-ED diets prior to pregnancy were less likely to have a live birth; however, our numbers were more limited for those analyses and results should be interpreted cautiously.

Relatively few studies have examined the influence of preconceptual overall dietary quality on fertility. In general, our results are consistent with those of other investigators who noted that healthful dietary patterns promote fertility among healthy women without a history of infertility. Three previous studies have evaluated the association between preconceptual dietary patterns and fertility among healthy women planning pregnancy (14–16). Chavarro and colleagues (14) reported that among 17,544 women in the Nurses’ Health Study II (NHSII), diets featuring more vegetable protein and high-fat dairy sources, more MUFAs and fewer trans fatty acids, lower glycemic load, and including regular multivitamin supplements, were associated with a lower risk of ovulatory disorder infertility. Toledo and colleagues (15) found that greater concurrence (highest quartile – Q4) with a Mediterranean-type dietary pattern derived through factor analysis was associated with a lower risk of difficulty becoming pregnant (ORQ4versus1high = 0.56; 95% CI: 0.35, 0.90, P = 0.01) in a Spanish nested case-control study (n = 485). In contrast, we recently reported in the Lifestyle and Fertility Study that greater adherence with the Alternative Healthy Eating Index for Pregnancy (AHEI-P) was not significantly associated with achieving clinical pregnancy or TTC, even after adjustment for covariates (16). Although these are seemingly contradictory results, these 2 measures of diet quality likely capture different constructs. The AHEI-P is an a priori summary dietary index that includes several subscales scored individually and summed which focus on foods (e.g. vegetables, fruits, whole grains, sugar-sweetened beverages, nuts and legumes, red and
processed meats), macronutrients (PUFA-, trans-, and ω-3 fatty acids), and sodium, including components for nutrients important for pregnancy (e.g. calcium, folate, and iron) (17).

Dietary ED may play a role in fertility through interactions of modifiable dietary factors including total energy intake, diet composition, nutrient intakes as well as other characteristics of foods. Of the macronutrients, fat has the most influence on ED because it contributes the most energy by weight. Not surprisingly, consumption of high-ED diets contributes to increased energy intake and has been associated with obesity (10, 18, 19). Obese women (BMI ≥ 30) experience endocrine dysregulation and in previous research have demonstrated higher risk of infertility (20, 21). In our population, prepregnancy BMI and dietary ED were only modestly correlated (Spearman correlation 0.08; P = 0.35), and the associations we observed between consuming a high-ED diet and unfavorable fertility outcomes remained significant after adjustment for BMI or total energy intake (Tables 2 and 3). Notably, previous studies have shown that metabolic consequences associated with high-fat and high-ED diets such as unfavorable lipid profiles, insulin resistance, inflammation, and oxidative stress (19, 22, 23) might impact fertility, independent of obesity (24–26). Dietary patterns characterized by higher fat consumption and lower intakes of fiber-rich foods like fruits, vegetables, and whole grains also tend to be lower in antioxidants. A 2013 Cochrane review (27) evaluated 28 antioxidant trials and concluded that supplemental oral antioxidants were not associated with increased live birth or clinical pregnancy rates, but did not address antioxidant intake contributed by diet. There are many possibilities through which dietary antioxidants might influence fertility (28, 29). Clearly, this is an area that deserves further study. Finally, converging lines of evidence suggest that foods, particularly energy-dense, high-fat animal products, fast and processed foods, may be important routes of exposure to environmental contaminants, including those which are potential endocrine disruptors and may disrupt hormonally mediated physiological processes important in fertility (30–34). This is also an area in need of future research.

In addition to high-ED diets there is a possibility that very low-ED diets may also have negative effects on conception. Women consuming the lowest ED diets (T1) showed some evidence of reduced fertility compared with the middle tertile, but results were not significant. Low-ED diets are generally higher in fiber and were so in this population. Previous studies have observed that diets higher in fiber may influence menstrual function and ability to conceive (35). For example, Andrews and colleagues reported a modestly positive association between higher intakes of dietary fiber and luteal phase deficiency, a menstrual cycle disturbance associated with recurrent miscarriages and infertility (36, 37), (OR = 1.10; 95% CI: 0.99, 1.23, P = 0.07) after adjustment for age, per cent body fat, and total energy intake, among 246 women in the BioCycle Study.

Strengths of our study include its prospective design, including dietary intake and lifestyle characteristics collected prior to attempting pregnancy, measured weight and height that allowed us to accurately assess BMI, and confirmation of clinical pregnancy. All women were nulliparous and planning their first pregnancy. We assessed dietary intake in detail with repeated, unannounced telephone 24-h recalls among both women and their male partners. Mean ED in this population of women (mean ED = 1.5) was comparable to that reported for US women at similar BMIs (~1.4) (10). Limitations are that this study was modest in size and includes mostly non-Hispanic white, healthy, and better-educated women aged 18–39 years planning pregnancy. These factors may have some implications for the generalizability of our observations to more diverse populations of women.

In summary, results of our study suggest that higher ED diets may be associated with lower probability of conceiving a clinical pregnancy

| Model | HR | 95% CI | P value |
|-------|----|--------|---------|
| ED continuous | | | |
| ED (Model 1) | 0.86 | (0.42, 1.71) | 0.66 |
| ED + race + male ED + PA (Model 2) | 0.48 | (0.20, 1.14) | 0.10 |
| Model 2 + BMI (Model 3) | 0.50 | (0.21, 1.18) | 0.12 |
| Model 2 + total energy (Model 4) | 0.54 | (0.21, 1.41) | 0.21 |
| Above Model (4) + attempts² | 0.51 | (0.19, 1.32) | 0.16 |

ED categorical¹

| Model | HR | 95% CI | P value |
|-------|----|--------|---------|
| ED + race + Male ED + PA (Model 5)¹ | | | |
| ED low (<1.37) | 0.77 | (0.41, 1.42) | 0.40 |
| ED high (>1.6) | 0.41 | (0.21, 0.80) | 0.009 |
| Model 5 + BMI (Model 6)¹ | | | |
| ED low (<1.37) | 0.76 | (0.41, 1.40) | 0.38 |
| ED high (>1.6) | 0.42 | (0.22, 0.82) | 0.01 |
| Model 5 + total energy (Model 7)¹ | | | |
| ED low (<1.37) | 0.67 | (0.34, 1.30) | 0.24 |
| ED high (>1.6) | 0.42 | (0.22, 0.82) | 0.01 |
| Above model (5) + attempts² | 0.87 | (0.46, 1.68) | 0.69 |
| ED high (>1.6) | 0.44 | (0.23, 0.87) | 0.02 |

¹For categorical ED the referent is the middle tertile (ED 1.37–1.60). All variables are female except for male ED. BMI is measured prepregnancy. HR < 1 means TTC is longer. HR < 1 means delayed TTC.
²Sensitivity analyses – conception attempts are missing for 9 couples.
ED, energy density; PA, physical activity.
and longer time to conception among couples planning their first pregnancy. Additional research is needed to corroborate these findings and to identify potential underlying mechanisms for dietary ED in fertility-related outcomes. Future research in large, well-characterized prospective birth cohorts may wish to explore whether dietary ED is associated with additional maternal pregnancy-related outcomes, including gestational weight gain and pregnancy complications such as pre-eclampsia or gestational diabetes, or with infant characteristics, such as preterm birth and birth size.

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The authors’ responsibilities were as follows—all authors: participated in the study concept and research design; WF and TJH: analyzed the data; TJH: had primary responsibility for writing the manuscript; all authors: contributed to interpretation of data and read, edited, and approved the final manuscript.

Data Availability
The data underlying this article may be shared at a later date upon reasonable request to the corresponding author and after final approval by the principal investigator.

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