July 2017

A Prospective Study of Physical Activity and Fecundability

Lindsey M. Russo
University of Massachusetts Amherst

A Prospective Study of Physical Activity and Fecundability

A Thesis Presented

by

LINDSEY M. RUSSO

Submitted to the Graduate School of the
University of Massachusetts Amherst in partial fulfillment
of the requirements for the degree of

Master of Science

May 2017

Public Health

Epidemiology

A Prospective Study of Physical Activity and Fecundability

A Thesis Presented

by

LINDSEY M. RUSSO

Approved as to style and content by:

____

Brian W. Whitcomb, Chair

____

Marquis Hawkins, Member

____

Susan E. Hankinson, Department Chair
Department of Biostatistics & Epidemiology
School of Public Health & Health Sciences

ACKNOWLEDGEMENTS

I would like to thank my advisor, Dr. Brian Whitcomb, for the unique opportunity to work on a project from the EAGeR Study with his colleagues from NICHD, and for his support throughout my time as both a graduate and undergraduate student at the University of Massachusetts Amherst. I am most appreciative for his patience and enthusiasm for teaching, and above all, for the inspiration to pursue a career in epidemiology. I would also like to express my gratitude to my committee member, Dr. Marquis Hawkins, for his contribution to my understanding of the methods and practices in physical activity epidemiology, which were essential to the fulfillment of this project. Finally, I would like to extend my appreciation to the faculty, staff, and fellow students who have also supported and inspired me to continue learning in this area.

ABSTRACT

A PROSPECTIVE STUDY OF PHYSICAL ACTIVITY AND FECUNDABILITY

MAY 2017

LINDSEY M. RUSSO, B.S., UNIVERSITY OF MASSACHUSETTS AMHERST

M.S., UNIVERSITY OF MASSACHUSETTS AMHERST

Directed by: Dr. Brian W. Whitcomb

Background:

Physical activity (PA) may influence fecundability through alterations in endocrine function. The limited studies that have evaluated PA and fecundability in non-clinical populations have utilized internet-based recruitment, contain potential issues in measurement, and have yielded inconclusive results.

Methods:

We evaluated the association between PA and time-to-pregnancy in the Effects of Aspirin in Gestation and Reproduction trial, which included 1228 women attempting pregnancy ages 18–40 with prior pregnancy loss. PA was measured at baseline using the short form of the International Physical Activity Questionnaire to determine hours/week of activity (vigorous, moderate, and walking) and hours/day of sedentary (sitting) behavior. Pregnancy was assessed using urine hCG assays. Discrete time Cox models were used to estimate fecundability odds ratios (FORs) adjusted for marital status and parity, accounting for left truncation and right censoring.

Results:

We observed a positive association between fecundability and vigorous PA of ≥ 4 hrs/week vs. none (FOR= 1.55, 95% CI: 1.17, 2.07) adjusted for marital status and parity. In stratified multivariable models, this association was most pronounced among overweight/obese women reporting vigorous PA of ≥ 4 hrs/week compared to none (FOR=2.27, 1.41, 3.65); however, there was no significant effect modification. Fecundability was not associated with categorical measures of moderate PA, walking, or sitting.

Conclusion:

In this study, fecundability was positively associated with vigorous PA. Further study is necessary to clarify possible mechanisms to explain the relationship through which vigorous PA might affect time-to-pregnancy; however, such improvements in fecundability may be related to a reduction in ovulatory disorders.

TABLE OF CONTENTS

LIST OF TABLES

Table **Page**

LIST OF FIGURES

Figure **Page**

CHAPTER I

INTRODUCTION

Physical activity (PA) has been proposed to influence fecundability, the single-cycle probability of conception, through alterations in endocrine function. Time-to-pregnancy (TTP), defined as the number of menstrual cycles of unprotected intercourse required to reach pregnancy, provides an approximate endpoint to estimate a couple's fecundability.[1–3] Approximately 60% of couples achieve pregnancy within three menstrual cycles, about 80% within six menstrual cycles, and about 90% within twelve menstrual cycles.[2] Understanding potential modifiable factors for a lengthened TTP may be of particular importance for women with a history of pregnancy loss, as recent evidence indicates that TTP following a loss may be increased.[1]

Established risk factors related to reduced fecundability as measured by a lengthened TTP include extremes in maternal age and BMI, low caloric intake, occupational exposures, environmental exposures, smoking, and alcohol and caffeine consumption to a lesser extent.[1,3] Suggested modifiable risk factors include body weight, dietary factors,[4] and physical activity.[5]

Physiology of Exposure-Outcome Relationship

There are two potential mechanisms through which physical activity may impact fecundability. The first mechanism relates to disruption in normal endocrine function,[6–12] while the second mechanism relates to the effects of moderate physical activity on stress and anxiety.[14]

The first possible mechanism prefaces that physical activity may interrupt normal endocrine function through increased follicular phase length, [11] decreased luteal phase length,[10] and increased total menstrual cycle length,[9] ultimately increasing risk for amenorrhea.[15] These factors, which may be observed in competitive athletes have been related to decreased fecundability.[15,16] The second mechanism relates to the reduction of stress and anxiety through moderate physical activity which may result in an increased implantation and live birth rate, as has been demonstrated among an ART population.[14]

Epidemiology of Exposure-Outcome Relationship

To date, only two prospective cohort studies have evaluated the association between physical activity and TTP in non-clinical population.[15,16] Among the two studies that have evaluated this association, both utilized internet-based recruitment.[15,16] Both studies used general questionnaires to measure physical activity and relied on retrospective report to determine TTP. The first of these studies found an inverse association between vigorous physical activity and fecundability.[16] In the second of these studies, the results were null for moderate and vigorous activity with fecundability; however a significant association was reported between vigorous activity and TTP among overweight/obese women.[15]

A total of three observational studies have evaluated the relationship between physical activity and infertility or subfertility.[4,17,18] The outcomes of these studies have included ovulatory disorder infertility,[4] cases of infertility, subfertility and involuntary childlessness,[17] and lifetime infertility.[18] All three studies used self-administered questionnaires for the assessment of physical activity and all used in-person recruitment strategies.[4,17,18] Each of these studies produced null findings.[4,17,18]

In the most recent study to date, McKinnon et al. recruited a group of 2,062 pregnancy planners from the United States and Canada to study the impact of physical activity on TTP.[15] This was an internet-based prospective cohort study that required participants to complete a self-administered lifestyle questionnaire at baseline which asked subjects about participation in moderate physical activity, vigorous physical activity, and sedentary (sitting) behavior. Results were null except among overweight/obese women, in which vigorous physical activity was associated with improved fecundability (≥5 hrs/week vs. <1 hr/week; Fecundability Ratio (FR)= 1.27, 95% CI 1.02–1.57).[15]

Prior studies of this association are inconclusive and are limited from a methodologic standpoint through 1.) lack of a validated measure of PA and 2.) use of retrospective report of time-to-pregnancy (TTP). Large prospective cohort studies with detailed assessment of physical activity and human chorionic gonadotropin (hCG) pregnancy are needed to gain a clearer understanding of the true impact of physical activity on TTP. Therefore, the aim of this analysis was to evaluate the relationship between physical activity and fecundability among a large cohort of reproductive-aged women with a history of pregnancy loss in the Effects of Aspirin in Gestation and Reproduction (EAGeR) Study. The primary strengths of the current study include the use of a validated measurement tool to assess physical activity and the use of longitudinal urine specimen collection during the first two menstrual cycles for outcome assessment of hCG pregnancy.[19]

CHAPTER II

METHODS

Study Design

Using a prospective cohort design, we examined the association between physical activity and detection of hCG-positive pregnancy among 1228 women in the EAGeR Study from 2006 to 2012. The EAGeR Study was a multisite, double-blind, randomized controlled trial which examined the impact of low-dose aspirin (LDA) use on live birth rates. Participants were randomized to receive daily low dose aspirin (LDA) (81 mg/day) or a matching placebo, and all were provided with daily 400-mcg folic acid.[19] Recruitment for this study occurred between June 15, 2007 and July 15, 2011, and follow-up was concluded in 2012.[19]

Study Population

The target study population included regularly menstruating women ages 18-40 with one to two prior pregnancy losses who were trying to conceive. Participants for the EAGeR Study were recruited from four different states which included university medical centers in Utah, New York, Pennsylvania, and Colorado. Study recruitment was performed using physician/nurse referrals within clinical sites among participating medical centers, along with community-based recruitment that included household mailings, local health promotion events, posters, social media, brochures, and local media. The primary outcome of the EAGeR Study was live birth, while an hCG-positive pregnancy was a secondary outcome. The Institutional Review Board at each participating study center approved the study and a Data Safety and Monitoring Board provided supervision over patient safety in this study. Written informed consent was obtained from all participants.

Following randomization, patients were seen at study sites for a baseline visit and then followed either until pregnancy or up to six menstrual cycles without becoming pregnant. At the baseline visit, after signing informed consent forms and undergoing a more in-depth screening, eligible participants completed questionnaires, provided biospecimens, and had anthropometric measurements taken by study personnel. Participant follow-up after randomization was divided into two phases: active follow up and passive follow up. During active follow up, clinic visits were scheduled to coincide with ovulation. Active follow up included daily first-morning urine collection during the first two menstrual cycles. This was followed by four months of passive follow up during which participants were only required to come in for a monthly clinic visit. During the first two months after randomization, subjects came in for clinic visits every two weeks, and once every month during the next four menstrual cycles. Visits during passive follow up were scheduled as “end-cycle” visits on days 2-4 of menstruation. Participants were provided fertility monitors (Clearblue Easy Fertility Monitor; Inverness Medical) to help determine timing of ovulation to inform timing of intercourse and coordinate midcycle clinic visit scheduling.

To be eligible for the EAGeR Study, women needed to be between the ages of 18 and 40 and must have had one or two documented pregnancy losses (at any gestational age).[19] Participants with one to five pregnancies including pregnancy losses, or up to two pregnancies that did not end in a loss could participate in this study.[19] Women were required to have both tubes intact, both ovaries, and a uterus in order to meet study inclusion criteria. Women could not be pregnant at the baseline or randomization visits (as determined by negative urine pregnancy tests at both visits) and needed to be actively trying to conceive. Women were required to have regular menstrual cycles (21-42 days in length) and may not have missed more than one menses over the previous year. Women had to be willing to be randomized and agree to follow the study protocol. Finally, participants had to be within the first four days of menstrual flow at the randomization visit in order to meet inclusion criteria.[19]

There were a number of exclusion criteria for this study including: history of infertility or subfertility, undergoing or planning to use medical fertility therapies during trial (including clomiphene intra-uterine insemination, or in vitro fertilization), diagnosis of a major medical disorder (regardless of severity) or an unstable mental disorder, known current or recent alcohol abuse or illicit drug use, known allergy to aspirin or non-steroidal anti-inflammatory agents (NSAIDs), clinical indication for chronic use of NSAIDs (e.g., rheumatoid arthritis) or for additional folic acid supplementation, taking medication for a seizure disorder, medical contraindication to aspirin therapy or anticoagulant therapy, or a diagnosis of a sexually transmitted infection.[19] For the purposes of the current analysis, we also excluded women who were missing data from the International Physical Activity Questionnaire.

Assessment of Physical Activity

Physical activity participation was measured at baseline using the self-administered, last-7 day, short form version of the International Physical Activity Questionnaire (IPAQ-SF). The IPAQ-SF contains seven questions that measure participation in walking, moderate physical activity, vigorous physical activity, and time spent in sedentary (sitting) behavior over the last seven days. For example, "During the last 7 days, did you do moderate activities like carrying light loads, bicycling at a regular pace, or doubles tennis? If yes, please specify on how many days." As based on standard IPAQ protocol, baseline total exercise was categorized by total MET-minutes/week using the following cut-points: low (<600 MET-minutes/week), moderate (≥600 MET-minutes/week and <3000 MET-minutes/week), and high (≥3000 MET-minutes/week). Hours/week of walking, moderate physical activity, and vigorous physical activity were assessed categorically to allow non-linearity. Hours/day of sedentary (sitting) behavior was assessed both continuously and categorically.

Assessment of Pregnancy

The occurrence of pregnancy was determined by a daily spot urine pregnancy test (Quidel Quickvue, Quidel Corporation, San Diego, CA) during a woman's first two menstrual cycles following study entry. HCG pregnancy tests were also conducted: 1) when women reported missing a period on any after-cycle visit, 2) in batched augmented urine hCG testing completed on the last 10 days of each woman's first cycle of study participation from daily first-morning urine collected at home, and 3) for spot urine samples taken at all after-cycle visits. A dichotomous variable was used to indicate the presence or absence of an hCG positive pregnancy result (Table 2).

Covariate Assessment

At the baseline visit, women in the EAGeR Study were asked to complete several questionnaires including a demographics questionnaire, a health and reproduction questionnaire, a physical measurements questionnaire, a lifestyle questionnaire, an occupation questionnaire, and an exercise questionnaire (IPAQ-SF). Information on age, marital status, high school education, race, income, parity, number of previous pregnancy losses, smoking in past year, alcohol consumption in the past year, current partner's age, and time from last loss to randomization was collected from participants. Body mass index (BMI) was calculated using height and weight measurements obtained from the baseline anthropometric assessment.

Statistical Analysis

Baseline exercise levels were determined based on standard IPAQ protocol. As has been previously described,[20,21] reported minutes of walking, moderate physical activity, and vigorous physical activity were presented in hours/week and modeled categorically. Hours/day of sedentary (sitting) behavior were modeled both continuously and categorically. Time-to-pregnancy was modeled in discrete time intervals defined by menstrual cycles.

Descriptive analysis was performed for all variables in the dataset. We compared the distribution of each covariate across subjects with high, moderate, and low IPAQ total baseline exercise level using ANOVA and chi-square tests, as applicable (Table 1). We further evaluated the distribution of covariates by hCG-detected pregnancy status using chi-square tests and t-tests (Table 2).

In order to avoid potential complications arising from interactions of physical activity with LDA, we performed tests for interaction. Because our tests showed no significant differences of effect between the treatment and placebo groups, we utilized the full population for evaluation. We used multivariable discrete Cox proportional hazards models to estimate fecundability odds ratios (FORs) and 95% confidence intervals (CI) for the respective associations between total baseline exercise level (IPAQ), categorical measures of walking, moderate physical activity, and vigorous physical activity (Table 3), and continuous and categorical measures of sitting with fecundability (Table 4).

A FOR represents the odds of becoming pregnant among exposed women compared to unexposed women.[3] A FOR above one indicates increased fecundability (a shorter TTP), whereas a FOR below one indicates reduced fecundability (a longer TTP).[3] Delayed entry was allowed in our models as the time at risk for some women was initiated prior to study entry. Our analyses accounted for both left truncation and right censoring.

Potential confounders were chosen based on a review of the prior literature. Variables significant at the 0.10 level for total baseline exercise level (IPAQ) and hCG-detected pregnancy status were included in the final models. We also conducted stratified analyses to examine whether the association between physical activity and fecundability varied by BMI (Table 5) and whether the relationship between sitting and time-to-pregnancy varied by BMI (Table 6). To examine whether participants' physical activity levels changed over time, we calculated Spearman correlation coefficients for menstrual cycles 3-6 of follow-up (Figure 1).

Two approaches were used to address values above the cutpoint set by IPAQ protocol to identify implausibly high values (>3 hours/day). In one set of analyses, these observations were censored and considered as missing (vigorous PA (n=23), moderate PA (n=145), and walking (n=143)) and in another set of analyses these values were truncated and all set to 3, permitting a maximum of 21 hours/week in any activity category.

Data on covariates were missing for alcohol (n=15), BMI (n=20), current partner's age (n=38), education (n=1), exercise (n=1), income (n=1), smoking (n=10), and time from last loss to randomization (n=19). Two-sided P values ≤ 0.05 were considered statistically significant. All analyses were conducted using SAS version 9.4 (SAS Institute, Inc.).

CHAPTER III

RESULTS

Among the 1227 subjects with recorded total baseline exercise levels (IPAQ), 797 women (65.0%) achieved an hCG-detected pregnancy. Across IPAQ total baseline exercise levels, 210 women in the low baseline exercise group (65.2%) became pregnant, compared with 327 in the moderate baseline exercise level group (65.4%), and 260 in the high baseline exercise group (64.2%).

Across participants in the EAGeR Study, 26.2% (n=322) of women were categorized as having a low total baseline exercise level (IPAQ), 40.8% (n=500) as having a moderate total baseline exercise level, and 33.0% (n=405) as having a high total baseline exercise level. On average, women in the EAGeR study reported 1.2 hours/week of participation in vigorous physical activity, 2.7 hours/week in moderate physical activity, 3.5 hours/week in walking, and 5.5 hours/day in sitting (sedentary) behavior.

We examined the distribution of demographics and reproductive characteristics of participants by total baseline exercise level (IPAQ) and found significant associations between age ($P = 0.01$), marital status ($P = 0.03$), high school education ($P < 0.001$), race (0.03), and alcohol consumption in past year ($P = 0.01$) (Table 1). Overall, those with moderate and high total baseline exercise levels tended to be younger, married, white, and more educated compared to those with a low total baseline exercise level.

We further evaluated participants by hCG pregnancy status, and noted significant differences according to BMI (kg/m^2) ($P < .001$), parity ($P < .001$), marital status ($P < .001$), high school education ($P < .01$), race ($P < .001$), annual income ($P = 0.01$), smoking in past year ($P <.001$), and time from last loss to randomization ($P <. 001$) (Table 2). Across participants, women with a positive hCG pregnancy test tended to be married, white, more parous, had a lower BMI, were more educated, and smoked less during the past year compared to those with a negative hCG pregnancy test.

Our findings were similar when using the two approaches described earlier to address values above the cutpoint set by IPAQ protocol (>3 hours/day) to identify implausibly high values; therefore, results are only presented for the first set of analyses in which values above 3 hours/day were censored and considered as missing.

We observed a positive association between fecundability and vigorous PA of ≥ 4 hrs/week vs. none (FOR= 1.55, 95% CI: 1.17, 2.07) adjusted for marital status and parity, with similar findings in unadjusted models. In stratified multivariable models, this association was most pronounced among overweight/obese women reporting vigorous PA of ≥ 4 hrs/week compared to none (FOR=2.27, 1.41, 3.65) and vigorous PA of > 0 hrs/week and <1 hr/week (FOR: 1.39, 1.04, 1.86); however, there was no significant effect modification. Fecundability was not associated with categorical measures of moderate physical activity or walking with adjustment for marital status and parity. Neither continuous nor categorical measures of sedentary (sitting) behavior were associated with TTP adjusted for marital status and parity. According to IPAQ total baseline exercise level, no differences were observed between high or moderate baseline exercise levels compared to low baseline exercise level in models with the same adjustment factors.

CHAPTER IV

DISCUSSION

It has been suggested that physical activity may impact the likelihood of conception through various mechanisms; moderate physical activity is associated with generally healthy behavior and has been proposed to improve fecundability through reduction of stress or anxiety in small studies.[14] In contrast, vigorous physical activity beyond some threshold of intensity has been proposed to improve fecundability in some populations[15] and worsen it in others.[16] In this study of physical activity and time-to-pregnancy among women with one or two prior pregnancy losses, our results suggest that vigorous physical activity is associated with fecundability. However, we observed no association between moderate physical activity, walking, or time spent in sedentary (sitting) behavior and probability of conception. In comparisons by IPAQ categories, no differences were observed between high or moderate baseline exercise levels compared to low baseline exercise levels in adjusted models.

Our stratified results are largely consistent with that of McKinnon et al. 2016, who reported results from the Pregnancy Study Online (PRESTO), a prospective cohort study of N=2,062. Similar to McKinnon et al., our findings were significant in adjusted models of vigorous physical activity and fecundability for obese/overweight women. Our null results for moderate activity are consistent with both McKinnon et al. 2016 and Wise et al. 2012.[15,16] Wise et al. did not consider sedentary activity, but our finding of no association between sedentary activity and fecundability agrees with that reported by McKinnon et al. 2016.

However, our findings are inconsistent with regard to vigorous activity.[15,16] Wise et al. 2012 described an inverse association between vigorous PA and fecundability in the internet-based 'Snart' Gravid cohort whereas our results showed a positive association between vigorous PA and fecundability.[16] Comparing women reporting $\geq$ 5 hours/week of vigorous activity (n=194) vs. none (n=720) in the 'Snart' Gravid cohort, an FR of 0.68 (95% CI: 0.54, 0.85) was observed, though primarily for women with a BMI less than 25 kg/m².[16]

Strengths of our study include use of a prospective cohort design with detailed information collected at baseline and longitudinal collection of biospecimens in a relatively large study population. In this study, we utilized the baseline IPAQ-SF for physical activity assessment, and some misclassification of physical activity levels is likely. Physical activity is inherently challenging to measure; however, the IPAQ has been used extensively in studies of physical activity.[14,18] A limitation in our study is that the IPAQ-SF was administered at baseline only. Although we have additional measures of moderate and vigorous physical activity for menstrual cycles 3-6, these assessments were taken from a different questionnaire and have limited comparability to the baseline IPAQ assessment. However, our comparison of time points suggests that minimal changes in physical activity occurred throughout the study period (Figure 1).

The IPAQ has shown fair correlation with Computer Science and Application's Inc. (CSA Model 7164) accelerometer data (N=781, $\rho = 0.30$, 95% CI 0.23–0.36), and is a reliable measurement tool ($\rho = 0.76$, 95% CI 0.73–0.77, test-retest). With regard to our population of interest, the IPAQ has been validated against the Modified Active Australia Survey (MAAS) among young women ages 18-25 from Victoria, Australia, demonstrating moderate agreement for both categorical (κ=.48, p<.001) and continuous data (r=.69, p<.001).[22]

Despite the validity of the IPAQ-SF, there are likely to be errors associated with self-report of physical activity; for example, women may have incorrectly reported their physical activity participation based on different interpretations of survey questions (resulting in an underestimation or overestimation of physical activity levels) or social desirability (resulting in an overestimation of physical activity levels), resulting in misreported activity levels. Misclassification of physical activity participation due to self-report and use of a baseline-only physical activity questionnaire is a concern in our study, and we believe the degree of impact on our results to be moderate to high. However, misclassification resulting from inaccurate exposure measurement is likely to be non-differential, biasing our results toward the null.

HCG pregnancy status was determined by the QuickVue hCG Urine Test, a sensitive immunoassay which can detect a positive result in urine specimens with as low as 25 mlU/mL hCG (sensitivity >99%, specificity >99%).[23] The QuickVue hCG Urine Test was administered at baseline and then at each subsequent clinic visit during the active and passive follow up period. Although it is possible that the pregnancy test results were incorrect even when administered correctly, this is not likely because both sensitivity and specificity are very high for the QuickVue hCG Urine Test. Therefore, there is a very low likelihood of misclassification of the outcome due to this source; however, if present, the impact (bias to the null) would be minor.

Instead, a more likely source of non-differential misclassification is the misclassification of women who forgot to take the pregnancy test or took this test too early. For example, women who may have become pregnant in the third month of follow up that did not take the pregnancy test could have had an early pregnancy loss with minimal spotting and would not have been classified as pregnant. Alternately, women who became pregnant in the sixth month of follow up may have become pregnant before exiting the study and would have been misclassified as not pregnant if the hCG pregnancy test was taken before hCG levels were high enough to detect pregnancy. These situations would also result in a bias towards the null.

The situations described above are unlikely because hCG pregnancy status was determined using three different procedures: 1.) at home pregnancy tests, 2.) clinic hCG pregnancy tests, and 3.) hCG testing of stored spot/daily urine samples. While it is possible that some women who became pregnant in the sixth month were misclassified, we do not have data to examine the degree to which this situation may have impacted our results since these women had already exited the study.

Participants in the EAGeR study were required to complete a demographics questionnaire, a health and reproduction questionnaire, a physical measurements questionnaire, a lifestyle questionnaire, an occupation questionnaire, and an exercise questionnaire (IPAQ-SF) to gather information on covariates as well as potential confounders. Anthropometric measurements were taken to gather information on height and weight to calculate BMI, which was also considered as a confounder in our Cox models.

In our study, there may be residual confounding and potential confounding factors which were not accounted for; for example, intercourse frequency, which could have overestimated our results given our finding of a positive association between vigorous physical activity and fecundability. If vigorous PA is related to increased intercourse frequency, and increased intercourse frequency is related to improved fecundability, then exercisers could experience increased fecundability related to intercourse frequency rather than due to physical activity itself. If physical activity is truly related to improved fecundability, then this FOR>1 would be biased away from the null by intercourse frequency. The strength of confounding due to intercourse frequency would depend on how strongly it is related to physical activity and fecundability. However, Pearson correlation coefficients of vigorous physical activity and fecundability showed only weak correlations.

CHAPTER V

CONCLUSION

In this study, fecundability was positively associated with vigorous PA. Further study is necessary to clarify possible mechanisms through which vigorous activity might affect time-to-pregnancy; however, it is possible that such improvements in fecundability may be related to a reduction in ovulatory disorders. Generalizability in our study may be limited as our population consisted of women with a history of pregnancy loss.[23] If replicated, these findings have implications for lifestyle and behavior modifications for women trying to become pregnant.

Table 1. Demographics of Participants by Baseline Exercise Level[1]; EAGeR Study, 2006-2012

Characteristics	Total N= 1227	Low N= 322	Moderate N= 500	High N= 405	*P* Value[2]
Age, y	28.7 ± 4.8	29.1 ± 5.0	29.0 ± 4.9	28.2 ± 4.5	.01
BMI, kg/m²	26.3 ± 6.6	26.4 ± 6.7	26.2 ± 6.4	26.5 ± 6.7	.76
BMI category[3]					.97
Underweight/normal <25 kg/m²	632	163	259	210	
Overweight/obese ≥25 kg/m²	575	151	232	192	
Parity					.01
Nulliparous	562 (45.8)	131 (40.7)	260 (52)	171 (42.2)	
1	442 (36.0)	132 (41.0)	163 (32.6)	147 (36.3)	
2+	223 (18.2)	59 (18.3)	77 (15.4)	87 (21.5)	
Marital status					.03
Living with partner	74 (6.0)	25 (7.8)	31 (6.2)	18 (4.4)	
Married	1123 (91.5)	284 (88.2)	463 (92.6)	376 (92.8)	
Other	30 (2.4)	13 (4.0)	6 (1.2)	11 (2.7)	
High school education					
More than high school	1057 (86.2)	265 (82.3)	451 (90.2)	341 (84.4)	<.001
Race					.03
White	1162 (94.7)	296 (91.9)	478 (95.6)	388 (95.8)	
Nonwhite	65 (5.3)	26 (8.1)	22 (4.4)	17 (4.2)	
Annual income (US $)					.13
≥ $100,000	93 (7.6)	23 (7.1)	32 (6.4)	38 (9.4)	
$75,000–$99,999	312 (25.5)	84 (26.1)	116 (23.2)	112 (27.7)	
$40,000–$74,999	181 (14.8)	46 (14.3)	78 (15.6)	57 (14.1)	
$20,000–$39,999	149 (12.2)	39 (12.1)	75 (15.0)	35 (8.7)	
≤ $19,999	491 (40.1)	130 (40.4)	199 (39.8)	162 (40.1)	

Table 1 (Cont.)

Smoking in past year					.21
Never	1067 (87.7)	275 (86.2)	439 (88.9)	353 (87.4)	
Sometimes	87 (7.2)	20 (6.3)	36 (7.3)	31 (7.7)	
Daily	63 (5.2)	24 (7.5)	19 (3.9)	20 (5.0)	
Alcohol consumption in past year					.01
Never	806 (66.5)	202 (63.3)	310 (62.9)	294 (73.5)	
Sometimes	380 (31.4)	108 (33.9)	170 (34.5)	102 (25.5)	
Often	26 (2.2)	9 (2.8)	13 (2.6)	4 (1.00)	
Number of previous pregnancy losses					.11
1	824 (67.2)	201 (62.4)	345 (69.0)	278 (68.6)	
2	403 (32.8)	121 (37.6)	155 (31.0)	127 (31.4)	
Current partner's age, y	30.2 ± 5.5	30.7 ± 5.7	30.4 ± 5.5	29.7 ± 5.3	.06
Time from last loss to randomization (months)					.54
≤4	647 (52.7)	162 (50.3)	280 (56.0)	205 (50.6)	
5-8	235 (19.2)	65 (20.2)	85 (17.0)	85 (21.0)	
9-12	105 (8.6)	26 (8.1)	44 (8.8)	35 (8.6)	
>12	240 (19.6)	69 (21.4)	91 (18.2)	80 (19.8)	

Values are n (%) for categorical variables and mean ± SD for continuous variables. Information was missing for alcohol (n=15), BMI (n=20), current partner's age (n=38), education (n=1), exercise (n=1), income (n=1), smoking (n=10), and time from last loss to randomization (n=19).
[1]Baseline exercise level categorization (IPAQ standards)
[2]P values were calculated from ANOVA or χ^2 test.
[3]BMI category (WHO standards)

Table 2. Demographics of Participants by hCG-detected Pregnancy; EAGeR Study, 2006-2012

Characteristics	**Total N=1227**	**- hCG test N=430**	**+ hCG test N=797**	***P* Value**
Age, y	28.7 (4.8)	28.9 ± 5.1	28.7 ± 4.6	.52
BMI, kg/m²	26.3 (6.6)	27.9 ± 7.1	25.5 ± 6.1	<.001
BMI category				<.001
Underweight/normal <25 kg/m²	632	183	449	
Overweight/obese ≥25 kg/m²	575	236	339	
Parity				<.001
Nulliparous	562 (45.8)	235 (54.7)	327 (41.0)	
1	442 (36.0)	138 (32.1)	304 (38.1)	
2+	223 (18.2)	57 (13.3)	166 (20.9)	
Marital status				<.001
Living with partner	74 (6.0)	43 (10.0)	31 (3.9)	
Married	1123 (91.5)	371 (86.3)	752 (94.4)	
Other	30 (2.4)	16 (3.7)	14 (1.8)	
High school education				<.01
More than high school	1057 (86.2)	350 (81.6)	707 (88.7)	
High school graduate	144 (11.8)	67 (15.6)	77 (9.7)	
Not high school graduate	25 (2.0)	12 (2.8)	13 (1.6)	
Race				<.001
White	1162 (94.7)	393 (91.4)	769 (96.5)	
Nonwhite	65 (5.3)	37 (8.6)	28 (3.5)	

Table 2 (Cont.)

Annual income (US $)				0.01
≥ $100,000	93 (7.6)	39 (9.1)	54 (6.8)	
$75,000–$99,999	312 (25.5)	125 (29.1)	187 (23.5)	
$40,000–$74,999	181 (14.8)	65 (15.2)	116 (14.6)	
$20,000–$39,999	149 (12.2)	35 (8.2)	114 (14.3)	
Smoking in past year				<.001
Never	1067 (87.7)	361 (84.9)	706 (89.1)	
Sometimes	87 (7.2)	30 (7.1)	57 (7.2)	
Often	63 (5.2)	34 (8.0)	29 (3.7)	
Alcohol consumption in past year				0.36
Never	806 (66.5)	274 (64.8)	532 (67.4)	
Sometimes	380 (31.4)	142 (33.6)	238 (30.2)	
Often	26 (2.2)	7 (1.7)	19 (2.4)	
Number of previous pregnancy losses				0.15
1	824 (67.2)	300 (69.8)	524 (65.8)	
2	403 (32.8)	130 (30.2)	273 (34.3)	
Current partner's age, y	30.2 ± 5.5	30.5 ± 5.8	30.1 ± 5.3	0.32
Time from last loss to randomization (months)				<.001
≤4	647 (52.7)	173 (40.2)	474 (59.5)	
5-8	235 (19.2)	84 (19.5)	151 (19.0)	
9-12	105 (8.6)	52 (12.1)	53 (6.7)	
>12	240 (19.6)	121 (28.1)	119 (14.9)	

Values are n (%) for categorical variables and mean ± SD for continuous variables.
Data on covariates were missing for alcohol (n=15), BMI (n=20), current partner's age (n=38), education (n=1), income (n=1), smoking (n=10), and time from last loss to randomization (n=19).
P values were calculated from t-test or χ^2 test.

Table 3. Association between Physical Activity and Fecundability; EAGeR Study, 2006-2012

	n	**Unadjusted FOR**	**Adjusted FOR***
Vigorous activity**			
None	577	Referent	Referent
> 0 hrs/wk and <1 hr/wk	100	1.38 (1.03, 1.83)	1.39 (1.04, 1.86)
1- <2 hrs/wk	143	1.01 (0.79, 1.31)	1.01 (0.78, 1.31)
2 - <3 hrs/wk	115	1.19 (0.90, 1.57)	1.20 (0.91, 1.58)
3 - <4 hrs/wk	74	0.94 (0.67, 1.31)	0.92 (0.65, 1.29)
≥ 4 hrs/wk	105	1.61 (1.22, 2.12)	1.55 (1.17, 2.07)
Moderate activity			
None	370	Referent	Referent
> 0 hrs/wk and <1 hr/wk	211	0.99 (0.78, 1.26)	0.96 (0.76, 1.22)
1- <2 hrs/wk	175	1.23 (0.96, 1.58)	1.24 (0.97, 1.59)
2 - <3 hrs/wk	84	1.13 (0.82, 1.56)	1.14 (0.82, 1.58)
3 - <4 hrs/wk	79	1.01 (0.72, 1.40)	1.02 (0.73, 1.43)
≥ 4 hrs/wk	195	1.11 (0.87, 1.41)	1.07 (0.84, 1.36)
Walking			
None	126	Referent	Referent
> 0 hrs/wk and <1 hr/wk	264	1.23 (0.91, 1.65)	1.22 (0.90, 1.64)
1- <2 hrs/wk	217	1.12 (0.82, 1.52)	1.11 (0.81, 1.51)
2 - <3 hrs/wk	126	1.17 (0.83, 1.64)	1.15 (0.82, 1.62)
3 - <4 hrs/wk	120	1.44 (1.02, 2.02)	1.41 (1.00, 1.99)
≥ 4 hrs/wk	261	1.22 (0.91, 1.65)	1.21 (0.89, 1.63)

Fecundability odds ratios (FORs) are presented as estimate (95% confidence interval).
*Adjusted for marital status and parity
**Further adjusted for sedentary (sitting) behavior

Table 4. Association between Sitting and Fecundability; EAGeR Study, 2006-2012

	n	Unadjusted FOR	Adjusted FOR*
Sitting (hrs/day)	1114	1.00 (0.97, 1.02)	1.01 (0.98, 1.04)
Sitting quartiles			
1 (0- 2.5 hrs/day)	237	Referent	Referent
2 (3- 4.5 hrs/day)	285	0.90 (0.71, 1.15)	0.89 (0.70, 1.14)
3 (5- 7.5 hrs/day)	276	0.99 (0.78, 1.25)	1.03 (0.81, 1.32)
4 (>8 hrs/day)	316	0.92 (0.73, 1.16)	0.99 (0.76, 1.30)

Fecundability odds ratios (FORs) are presented as estimate (95% confidence interval).
*Adjusted for marital status, parity, and exercise

Table 5. Adjusted FOR[a] and 95% CI for Physical Activity and Fecundability, Stratified by BMI: EAGeR Study, 2006-2012

Exposure	Underweight/normal[a] (BMI < 25 kg/m²) (n=589) n	FOR (95 % CI)	Overweight/obese (BMI ≥ 25 kg/m²) (n=525) n	FOR (95 % CI)	P
Vigorous activity[b]					
None	283	Referent	294	Referent	.08
> 0 hrs/wk and <1 hr/wk	62	1.61 (1.11, 2.34)	38	0.87 (0.53, 1.45)	
1- <2 hrs/wk	76	0.94 (0.66, 1.34)	67	1.09 (0.74, 1.61)	
2 - <3 hrs/wk	63	1.17 (0.80, 1.70)	52	1.21 (0.79, 1.85)	
3 - <4 hrs/wk	38	0.86 (0.53, 1.38)	36	0.93 (0.56, 1.53)	
≥ 4 hrs/wk	67	1.17 (0.81, 1.69)	38	2.27 (1.41, 3.65)	
Moderate activity					.70
None	182	Referent	188	Referent	
> 0 hrs/wk and <1 hr/wk	117	1.00 (0.73, 1.38)	94	0.90 (0.62, 1.31)	
1- <2 hrs/wk	95	1.24 (0.88, 1.75)	80	1.30 (0.89, 1.88)	
2 - <3 hrs/wk	54	1.27 (0.84, 1.93)	30	0.82 (0.46, 1.47)	
3 - <4 hrs/wk	44	0.97 (0.63, 1.52)	35	1.05 (0.62, 1.79)	
≥ 4 hrs/wk	97	1.00 (0.71, 1.41)	98	1.18 (0.83, 1.67)	
Walking					
None	60	Referent	66	Referent	.06
> 0 hrs/wk and <1 hr/wk	151	0.81 (0.54, 1.22)	113	1.81 (1.12, 2.92)	
1- <2 hrs/wk	111	0.76 (0.50, 1.17)	106	1.67 (1.02, 2.71)	
2 - <3 hrs/wk	69	0.91 (0.57, 1.45)	57	1.51 (0.88, 2.60)	
3 - <4 hrs/wk	57	0.81 (0.50, 1.33)	63	2.71 (1.61, 4.55)	
≥ 4 hrs/wk	141	0.88 (0.58, 1.33)	120	1.75 (1.08, 2.82)	

Fecundability odds ratios (FORs) are presented as estimate (95% confidence interval) adjusted for marital status, parity, and BMI
[a]BMI category (WHO standards)
[b]Additionally adjusted for sedentary (sitting) behavior

Table 6. Adjusted FOR and 95% CI for Sitting and Fecundability, Stratified by BMI: EAGeR Study, 2006-2012

Exposure	**Underweight/normal[*] (BMI < 25 kg/m²) (n=632)**		**Overweight/obese (BMI ≥ 25 kg/m²) (n=575)**		
	n	**FOR (95% CI)**	**n**	**FOR (95% CI)**	**P**
Sitting, hours/day	589	1.02 (0.98, 1.06)	525	1.01 (0.98, 1.05)	.68
Sitting, hours/day (quartiles)					.27
1 (0- 2.5 hrs/day)	134	**Referent**	103	**Referent**	
2 (3- 4.5 hrs/day)	161	1.14 (0.83, 1.56)	124	0.68 (0.46, 1.00)	
3 (5- 7.5 hrs/day)	152	1.19 (0.86, 1.64)	124	0.96 (0.66, 1.40)	
4 (>8 hrs/day)	142	1.22 (0.87, 1.71)	174	0.93 (0.65, 1.34)	

Fecundability odds ratios (FORs) are presented as estimate (95% confidence interval) adjusted for marital status, parity, and BMI
*BMI category (WHO standards)

Figure 1. Correlations of measures of activity during cycles 3 – 6 of follow-up

Vigorous physical activity	Spearman correlation coefficient estimate (P-value)		
	Cycle 4	Cycle 5	Cycle 6
Cycle 3	$r_{3\text{-}4}$ = .60 (P <.001)	$r_{3\text{-}5}$ = .51 (P <.001)	$r_{3\text{-}6}$ = .51 (P <.001)
Cycle 4		$r_{4\text{-}5}$ = .66 (P <.001)	$r_{4\text{-}6}$ = .57 (P <.001)
Cycle 5			$r_{5\text{-}6}$ = .67 (P <.001)

Moderate physical activity	Spearman correlation coefficient estimate (P-value)		
	Cycle 4	Cycle 5	Cycle 6
Cycle 3	$r_{3\text{-}4}$ = .66 (P <.001)	$r_{3\text{-}5}$ = .59 (P <.001)	$r_{3\text{-}6}$ = .59 (P <.001)
Cycle 4		$r_{4\text{-}5}$ = .66 (P <.001)	$r_{4\text{-}6}$ = .63 (P <.001)
Cycle 5			$r_{5\text{-}6}$ = .73 (P <.001)

BIBLIOGRAPHY

1. Sapra, K. J., McLain, A. C., Maisog, J. M., Sundaram, R. & Buck Louis, G. M. Successive time to pregnancy among women experiencing pregnancy loss. *Hum. Reprod. Oxf. Engl.* **29,** 2553–2559 (2014).

2. Wilcox, A. *Fertility and Pregnancy: An Epidemiologic Perspective*. (Oxford University Press, 2010).

3. Buck Louis, G. & Platt, R. W. *Reproductive and Perinatal Epidemiology*. (Oxford University Press, 2011).

4. Chavarro, J. E., Rich-Edwards, J. W., Rosner, B. A. & Willett, W. C. Diet and lifestyle in the prevention of ovulatory disorder infertility. *Obstet. Gynecol.* **110,** 1050–1058 (2007).

5. Rich-Edwards, J. W. *et al.* Physical activity, body mass index, and ovulatory disorder infertility. *Epidemiol. Camb. Mass* **13,** 184–190 (2002).

6. Frisch, R. E. *et al.* Delayed menarche and amenorrhea of college athletes in relation to age of onset of training. *JAMA* **246,** 1559–1563 (1981).

7. Loucks, A. B. Effects of exercise training on the menstrual cycle: existence and mechanisms. *Med. Sci. Sports Exerc.* **22,** 275–280 (1990).

8. Dadgostar, H., Razi, M., Aleyasin, A., Alenabi, T. & Dahaghin, S. The relation between athletic sports and prevalence of amenorrhea and oligomenorrhea in Iranian female athletes. *Sports Med. Arthrosc. Rehabil. Ther. Technol. SMARTT* **1,** 16 (2009).

9. Cooper, G. S., Sandler, D. P., Whelan, E. A. & Smith, K. R. Association of physical and behavioral characteristics with menstrual cycle patterns in women age 29-31 years. *Epidemiol. Camb. Mass* **7,** 624–628 (1996).

10. De Souza, M. J. *et al.* High prevalence of subtle and severe menstrual disturbances in exercising women: confirmation using daily hormone measures. *Hum. Reprod. Oxf. Engl.* **25,** 491–503 (2010).

11. Liu, Y., Gold, E. B., Lasley, B. L. & Johnson, W. O. Factors affecting menstrual cycle characteristics. *Am. J. Epidemiol.* **160,** 131–140 (2004).

12. De Souza, M. *et al.* High frequency of luteal phase deficiency and anovulation in recreational women runners: blunted elevation in follicle-stimulating hormone observed during luteal-

follicular transition. *J. Clin. Endocrinol. Metab.* **83,** 4220–32 (1998).

13. Hjollund, N. H. *et al.* Spontaneous abortion and physical strain around implantation: a follow-up study of first-pregnancy planners. *Epidemiology* **11,** 18–23 (2000).

14. Kucuk, M., Doymaz, F. & Urman, B. Effect of energy expenditure and physical activity on the outcomes of assisted reproduction treatment. *Reprod Biomed Online* **20,** 274–279 (2010).

15. McKinnon, C. J. *et al.* Body mass index, physical activity and fecundability in a North American preconception cohort study. *Fertil. Steril.* **106,** 451–459 (2016).

16. Wise, L. A. *et al.* A prospective cohort study of physical activity and time to pregnancy. *Fertil. Steril.* **97,** 1136-1142–4 (2012).

17. Gudmundsdottir, S. L., Flanders, W. D. & Augestad, L. B. Physical activity and fertility in women: the North-Trøndelag Health Study. *Hum. Reprod. Oxf. Engl.* **24,** 3196–3204 (2009).

18. Esmaeilzadeh, S., Delavar, M. A., Basirat, Z. & Shafi, H. Physical activity and body mass index among women who have experienced infertility. *Arch. Med. Sci. AMS* **9,** 499–505 (2013).

19. Schisterman, E. F. *et al.* A randomised trial to evaluate the effects of low-dose aspirin in gestation and reproduction: design and baseline characteristics. *Paediatr. Perinat. Epidemiol.* **27,** 598–609 (2013).

20. Craig, C. L. *et al.* International physical activity questionnaire: 12-country reliability and validity. *Med. Sci. Sports Exerc.* **35,** 1381–1395 (2003).

21. Ainsworth, B. E. *et al.* Compendium of physical activities: an update of activity codes and MET intensities. *Med. Sci. Sports Exerc.* **32,** S498-504 (2000).

22. Hartley, S. *et al.* A Comparison of Self-Reported and Objective Physical Activity Measures in Young Australian Women. *JMIR Public Health Surveill* **1,** (2015).

23. Zarek, S. M. *et al.* Is Anti-Müllerian Hormone Associated With Fecundability? Findings From the EAGeR Trial. *J. Clin. Endocrinol. Metab.* **100,** 4215–4221 (2015).