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A prospective study of physical activity and fecundability in women with a history of pregnancy loss

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STUDY QUESTION: Is physical activity (PA) associated with fecundability in women with a history of prior pregnancy loss?

SUMMARY ANSWER: Higher fecundability was related to walking among overweight/obese women and to vigorous PA in women overall.

WHAT IS KNOWN ALREADY: PA may influence fecundability through altered endocrine function. Studies evaluating this association have primarily utilized Internet-based recruitment and self-report for pregnancy assessment and have yielded conflicting results.

STUDY DESIGN, SIZE, DURATION: This is a secondary analysis of the Effects of Aspirin in Gestation and Reproduction (EAGeR) trial (2007–2011), a multisite, randomized controlled trial of preconception-initiated low-dose aspirin.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Healthy women ($n = 1214$), aged 18–40 and with 1–2 prior pregnancy losses, were recruited from four US medical centers. Participants were followed for up to six menstrual cycles while attempting pregnancy and through pregnancy for those who became pregnant. Time to hCG detected pregnancy was assessed using discrete-time Cox proportional hazard models to estimate fecundability odds ratios (FOR) adjusted for covariates, accounting for left truncation and right censoring.

MAIN RESULTS AND THE ROLE OF CHANCE: The association of walking with fecundability varied significantly by BMI (P-interaction = 0.01). Among overweight/obese women, walking ≥10 min at a time was related to improved fecundability (FOR = 1.82, 95% CI: 1.19, 2.77). In adjusted models, women reporting >4 h/wk of vigorous activity had significantly higher fecundability (FOR = 1.69, 95% CI: 1.24, 2.31) compared to no vigorous activity. Associations of vigorous activity with fecundability were not significantly different by BMI (P-interaction = 0.9). Moderate activity, sitting, and International Physical Activity Questionnaire (IPAQ) categories were not associated with fecundability overall or in BMI-stratified analyses.

LIMITATIONS, REASONS FOR CAUTION: Some misclassification of PA levels as determined by the short form of the IPAQ is likely to have occurred, and may have led to non-differential misclassification of exposure in our study. Information on diet and change in BMI was not collected and may have contributed to some residual confounding in our results. The generalizability of our results may be limited as our population consisted of women with a history of one or two pregnancy losses.

WIDER IMPLICATIONS OF THE FINDINGS: These findings provide positive evidence for the benefits of PA in women attempting pregnancy, especially for walking among those with higher BMI. Further study is necessary to clarify possible mechanisms through which walking and vigorous activity might affect time-to-pregnancy.

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Key words: time-to-pregnancy / anovulation / pregnancy loss / physical activity / exercise

Introduction

The female reproductive system may be influenced by environment, lifestyle, behavior and other factors. Such effects may impact time-to-pregnancy (TTP), which is used to estimate couple fecundability or cycle-specific conception probability (Wilcox, 2010; Buck Louis and Platt, 2011; Sapra *et al.*, 2014). Approximately 60% of couples achieve pregnancy within three menstrual cycles, 80% within six menstrual cycles, and 90% within 12 menstrual cycles, with the remainder meeting the definition for clinical infertility (Wilcox, 2010). Understanding potential modifiable factors for a lengthened TTP may be of particular importance for women with a history of pregnancy loss, since TTP following a loss may be increased (Sapra *et al.*, 2014). Further, the relationship between physical activity (PA) and fecundability has not been evaluated in a population of women with a history of pregnancy loss.

PA has been proposed to influence fecundability through alterations in endocrine function. PA, recognized for maintaining and improving cardiorespiratory and muscular fitness, may represent a widely available strategy for promoting general health (Office of Disease Prevention and Health Promotion, 2017). The '2008 Physical Activity Guidelines for Americans' offer specific guidance for participation in moderate and vigorous-intensity aerobic PA along with muscle-strengthening activity for adults (Office of Disease Prevention and Health Promotion, 2017), and the American College for Obstetrics and Gynecology (ACOG) similarly recommends PA during pregnancy (ACOG Committee Obstetric Practice, 2002). While there are no specific guidelines for women with a history of pregnancy loss who are planning a pregnancy, ACOG offers general information about preconception care, suggesting that overweight women consider losing weight and becoming more physically active prior to pregnancy (Good Health Before Pregnancy: Preconception Care, 2017).

The mechanisms through which increasing PA may impact TTP are unclear. Very high levels of exercise may result in disruption of menstrual cyclicity and increase risk for amenorrhea and subfertility (De Souza *et al.*, 1998; Warren and Perlroth, 2001). Conversely, PA may have beneficial effects on fecundability through reduction of stress and anxiety and/or impacts on lipid profiles and inflammation (Sorensen *et al.*, 2003), though information on thresholds for the amount and intensity of activity to achieve optimal fertility is not known (Warren and Perlroth, 2001; Gudmundsdottir *et al.*, 2009).

To date, few studies have examined the association between PA and conception probability in a population of women not being treated for infertility (Gudmundsdottir *et al.*, 2009; Wise *et al.*, 2012; McKinnon *et al.*, 2016). Results of studies of PA and TTP vary, with some suggesting higher conception probability with moderate intensity activity (Gudmundsdottir *et al.*, 2009), and conflicting results regarding vigorous intensity activity (Wise *et al.*, 2012; McKinnon *et al.*, 2016). Questions remain regarding the association of PA and intensity-specific domains with TTP. Women with a history of pregnancy loss are at risk for protracted subfertility/infertility and may end up requiring clinical care for fertility. For these women, interventions that improve TTP may have significant impact both as an intervention and for making decisions regarding treatment. Clarifying the role and etiology of PA in conception may help to provide recommendations for women with a history of pregnancy loss when attempting pregnancy.

Thus, we aimed to evaluate the relationship between PA and fecundability among a large cohort of reproductive-aged women with a history of pregnancy loss.

Materials and Methods

Study setting and population

This is a secondary analysis of the Effects of Aspirin in Gestation and Reproduction (EAGeR) trial, a multisite, randomized controlled trial of preconception initiated low-dose aspirin (LDA) among women aged 18–40 and with a history of one to two prior documented miscarriages. Participants in the EAGeR study were recruited from four US university medical centers from 2007 to 2011. A total of 1228 women were randomized. Of these, 14 women dropped out of the study shortly after randomization, and the remaining 1214 were considered in these analyses.

For the current analysis, we consider data on conception attempts among participants in the EAGeR trial who were followed for up to six menstrual cycles while attempting pregnancy and through pregnancy for those who became pregnant. Follow-up during the first two menstrual cycles of observation entailed collection of daily first-morning urine samples and use of a fertility monitor (Clearblue Easy Fertility Monitor; Inverness Medical) for timing intercourse and to inform scheduling of clinic visits to coincide with expected ovulation. Participants who did not become pregnant during months 1 and 2 of follow up continued for 4 additional months of less intensive 'passive' follow up with continued use of a fertility monitor and data collection, but no daily urine collection. Visits during the passive follow up were scheduled on Days 2–4 of menstruation. Clinic visits throughout both phases of follow up entailed completion of questionnaires, collection of biospecimens (spot urine samples and blood samples by venipuncture) and assessment of anthropometry. Biospecimens including urine samples from self-collection and clinic visits were frozen and stored at −80°C. From among 1228 women in the EAGeR trial, women were excluded from multivariable models of fecundability due to dropout prior to observation ($n = 14$) or for missing information on trying time prior to study entry ($n = 86$). As a result, a total of 1128 women were included in the Cox models of fecundability.

Ethics approval

Written informed consent was acquired from all participants and Institutional Review Board approval was provided at each study site and the data coordinating center. The design, methods and participant characteristics of the EAGeR Study have been previously described (Schisterman

et al., 2013); the trial was registered with clinicaltrials.gov (number NCT00467363).

Assessment of PA

PA was assessed at baseline using the self-administered, last 7-day, short form version of the International Physical Activity Questionnaire (IPAQ-SF) (International Physical Activity Questionnaire, 2005). The IPAQ-SF contains seven questions that measure the frequency and duration of walking, moderate intensity activity and vigorous intensity activity that occurred for at least 10 min at a time over the previous week, in addition to time spent in sedentary activities. Vigorous intensity PA was defined as 'activities that take hard physical effort and make you breathe much harder than normal'. Moderate intensity PA was defined as 'activities that take moderate physical effort and make you breathe somewhat harder than normal'. Walking included '[walking] at work and at home, walking to travel from place to place, and any other walking that you might do solely for recreation, sport, exercise or leisure'. Sedentary activity was defined as 'time spent [sitting] at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading or sitting or lying down to watch television'. Responses to activity questions from the IPAQ-SF were used to calculate metabolic equivalent of task (MET)-min/week using standard approaches (International Physical Activity Questionnaire, 2005).

As per standard IPAQ scoring protocols, participants were classified by overall activity into three categories based on a combination of duration and intensity: high, medium, and low (International Physical Activity Questionnaire, 2005). The criteria for high activity are (i) vigorous-intensity activity on at least 3 days achieving a minimum total PA of at least 1500 MET-min/week, or (ii) 7 or more days of any combination of walking, moderate-intensity or vigorous-intensity activities achieving a minimum total PA of at least 3000 MET-min/week. The criteria for medium activity are (i) 3 or more days of vigorous-intensity activity of at least 20 min per day, or (ii) 5 or more days of moderate-intensity activity and/or walking of at least 30 min per day, or (iii) 5 or more days of any combination of walking, moderate-intensity or vigorous intensity activities achieving a minimum total PA of at least 600 MET-min/week. A 'low' activity level indicates not meeting the criteria for medium or high activity (International Physical Activity Questionnaire, 2005).

Hours/week of walking, moderate intensity PA and vigorous intensity PA were determined using questions from the IPAQ-SF regarding duration and days per week of at each type of activity performed for at least 10 min at a time, and categorized for statistical analyses. Hours/day of sedentary behavior was modeled both continuously and categorically. To address implausibly high values (>3 h/day), such observations were truncated and all set to 3 h/day, permitting a maximum of 21 h/wk in any activity category, as per IPAQ guidelines (International Physical Activity Questionnaire, 2005).

Assessment of fecundability

Anovulatory cycles were determined using a combination of approaches (Radin et al., 2017). Urinary hormone concentrations and data from fertility monitors were used to determine anovulatory cycles among women without a positive pregnancy test. Cycles were considered to be anovulatory if the maximum luteal phase urinary pregnanediol glucuronide (PdG) was <5 ug/mL (n = 259 cycles) (Johnson et al., 2015). For cycles without luteal phase PdG measures, fertility monitor data on LH were used to determine anovulation. Cycles with maximum LH concentrations <2.5 times the mean of the previous 5 days were considered to be anovulatory (Park et al., 2007).

Fecundability was assessed as discrete time intervals (i.e. number of menstrual cycles) to pregnancy (Schisterman et al., 2015). Pregnancy was determined by a positive urine hCG test, which was sensitive to 25 mIU/mL hCG (Quidel Quickvue; Quidel Corp). Pregnancy tests were conducted (i) at home or at the clinic if a participant reported a missed menses, (ii) from batched augmented urine hCG testing using daily first-morning urine collected at home, or (iii) using spot urine samples obtained at all clinic visits. Free beta hCG was also measured in these urine samples to assist with detection of very early pregnancy. To verify pregnancy, two free beta-hCG laboratory assays (catalog number RIS0011R; BioVendor; catalog number 4221-16; Diagnostic Automation Inc.) were used first to identify 'potentially positive' values and then 'true positive' values for early hCG-detected pregnancy (Schisterman et al., 2015).

Covariates

At the baseline visit, women in the EAGeR trial were asked to complete several questionnaires assessing information on demographics, health and reproduction, lifestyle, occupation and the IPAQ-SF. Specifically, information was collected from participants on age, marital status, high school education, race, income, parity, number of previous pregnancy losses, smoking in the past year, alcohol consumption in the past year, current partner's age, and time from last loss to randomization. BMI was calculated using height and weight measurements from the baseline anthropometric assessment.

Statistical analysis

Descriptive analysis was performed for all variables in the dataset. Characteristics were compared by hCG-detected pregnancy status using chi-square tests and t-tests (Table I). In order to avoid potential complications arising from interactions of PA with LDA treatment, we performed tests for interaction. Because our tests showed no significant differences of effect between the treatment and placebo groups, the analysis was combined and performed in the entire cohort.

Frequency of each activity as performed for at least 10 min at a time was categorized based on observed distributions. Categories for vigorous and moderate activity frequency were: none; >0 to ≤1 h/wk; >1 to ≤2 h/week; >2 to ≤3 h/wk; >3 to ≤4 h/wk; and >4 h/wk. Frequency of walking for at least 10 min at a time was dichotomized as none or some, and hours/day of sitting was evaluated in quartiles. We used multivariable discrete-time Cox proportional hazards models to estimate fecundability odds ratios (FOR) and 95% CI for the respective associations between total baseline exercise level (IPAQ), categorical measures of walking, moderate intensity PA, and vigorous intensity PA, and continuous and categorical measures of sitting with fecundability (Table II). 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 and consideration of relevant biological relations. Variables considered for inclusion into multivariable models were selected based on bivariate relations ($P < 0.10$) with both exercise and hCG pregnancy. To examine whether the relationship between PA and fecundability varied by adiposity, we conducted analyses stratified on BMI (<25 and ≥25 kg/m^2) (Table III). In these models, we additionally adjusted for continuous BMI to control residual confounding, and used likelihood ratio tests as tests of multiplicative interaction.

In order to evaluate potential mechanisms, we conducted anovulation analyses. Associations of PA variables with cycle-specific risk of anovulation were assessed using generalized estimating equations with an unstructured initial working correlation matrix. Risk ratios were determined by log-binomial regression with weights specified as the inverse of the number of cycles contributed in order to address repeated observations with informative cluster size (Williamson et al., 2003), as previously described for these data (Radin et al., 2017). Multiple imputation was used to address

Table I Characteristics of participants (*N* = 1214) by hCG-detected pregnancy; EAGeR Study, 2007–2011.

Characteristics	− hCG test *N* = 417	+ hCG test *N* = 797	*P* value[a]
Age, y	29.0 ± 5.1	28.7 ± 4.6	0.35
BMI (kg/m^2)	27.9 ± 7.1	25.5 ± 6.1	<0.001
BMI (kg/m^2) category[b]			
Underweight (<18.5)	11 (2.7)	31 (3.9)	<0.001
Normal (18.5–24.9)	166 (40.9)	418 (53.1)	
Overweight (25.0–29.9)	94 (23.2)	187 (23.7)	
Obese (≥30.0)	135 (33.3)	152 (19.3)	
Parity			
Nulliparous	227 (54.4)	327 (41.0)	<0.001
1	133 (31.9)	304 (38.1)	
2+	57 (13.7)	166 (20.8)	
Marital status			
Living with partner	41 (9.8)	31 (3.9)	<0.001
Married	361 (86.6)	752 (94.4)	
Other	15 (3.6)	14 (1.8)	
More than high school education	342 (82.0)	707 (88.7)	<0.01
Race			
White	382 (91.6)	769 (96.5)	<0.001
Nonwhite	35 (8.4)	28 (3.5)	
Annual income (US $)			
≥ $100 000	163 (39.2)	326 (40.9)	0.01
$75 000–$99 999	34 (8.2)	114 (14.3)	
$40 000–$74 999	64 (15.4)	116 (14.6)	
$20 000–$39 999	117 (28.1)	187 (23.5)	
≤ $19 999	38 (9.1)	54 (6.8)	
Smoking in past year			
Never	351 (85.2)	706 (89.1)	0.01
Sometimes	29 (7.0)	57 (7.2)	
Often	32 (7.8)	29 (3.7)	
Alcohol consumption in past year			
Never	265 (64.6)	532 (67.4)	0.37
Sometimes	138 (33.7)	238 (30.2)	
Often	7 (1.7)	19 (2.4)	
Number of prior documented miscarriages[c]			
1	289 (69.3)	524 (65.8)	0.21
2	128 (30.7)	273 (34.3)	
Current partner's age, y	30.5 ± 5.8	30.1 ± 5.3	0.27
Time from last loss to randomization (months)			
≤4	166 (40.2)	474 (60.6)	<0.001
5–8	77 (18.6)	136 (17.4)	
9–12	52 (12.6)	53 (6.8)	
>12	118 (28.6)	119 (15.2)	

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* = 28), education (*n* = 1), income (*n* = 1), smoking (*n* = 10) and time from last loss to randomization (*n* = 19).
[a]*P* values were calculated from *t*-test or χ^2 test.
[b]BMI category (WHO classification).
[c]Clinically recognized pregnancy losses were documented using a combination of verification from a woman's physician and medical records.

Table II Association between physical activity and fecundability; EAGeR Study, 2006–2012 (n = 1128).

	n	+hCG	Cycles	Unadjusted FOR	*P*[a]	Adjusted FOR[b]	*P*[a]
Vigorous activity (bouts of ≥10 min)[c]							
None	586	368	3727	Referent	0.03	Referent	0.04
>0 to ≤1 h/wk	146	105	967	1.22 (0.95, 1.57)		1.21 (0.94, 1.55)	
>1 to ≤2 h/wk	139	94	883	1.09 (0.85, 1.41)		1.07 (0.82, 1.38)	
>2 to ≤3 h/wk	116	76	717	1.05 (0.80, 1.39)		1.08 (0.81, 1.43)	
>3 to ≤4 h/wk	52	38	315	1.13 (0.77, 1.65)		1.08 (0.73, 1.59)	
>4 h/wk	89	69	583	1.69 (1.25, 2.29)		1.69 (1.24, 2.31)	
Moderate activity (bouts of ≥10 min)							
None	375	242	2420	Referent	0.43	Referent	0.33
>0 to ≤1 h/wk	166	101	1117	0.96 (0.74, 1.25)		0.98 (0.75, 1.27)	
>1 to ≤2 h/wk	141	104	917	1.28 (0.98, 1.67)		1.30 (1.00, 1.70)	
>2 to ≤3 h/wk	92	68	578	1.19 (0.87, 1.61)		1.18 (0.87, 1.61)	
>3 to ≤4 h/wk	56	38	315	1.10 (0.75, 1.62)		1.15 (0.78, 1.71)	
>4 h/wk	298	197	1845	1.06 (0.85, 1.31)		1.00 (0.80, 1.24)	
Walking (bouts of ≥10 min)							
None	129	78	875	Referent	0.14	Referent	0.17
Some	998	671	6311	1.22 (0.94, 1.58)		1.20 (0.92, 1.56)	
Sitting (h/day)[d]	1128	–		1.00 (0.97, 1.02)	0.82	1.01 (0.98, 1.04)	0.41
Sitting categories[d]							
1 (0–2.5 h/day)	239	168	1447	Referent	0.78	Referent	0.55
2 (3–4.5 h/day)	287	181	1877	0.90 (0.71, 1.15)		0.90 (0.71, 1.15)	
3 (5–7.5 h/day)	280	196	1739	0.99 (0.78, 1.25)		1.06 (0.83, 1.36)	
4 (>8 h/day)	322	205	2129	0.92 (0.73, 1.16)		1.02 (0.79, 1.32)	
Total baseline exercise[e]							
Low	297	200	1882	Referent	0.88	Referent	0.85
Medium	457	303	2920	0.95 (0.78, 1.16)		0.98 (0.80, 1.20)	
High	374	247	2390	0.96 (0.78, 1.19)		0.94 (0.76, 1.17)	

Notes: Fecundability odds ratios (FOR) are presented as estimate (95% CI) adjusted for marital status and parity. Among 1228 participants, there were 14 withdrawals, whose last visit day was at randomization leaving no observable time 'at risk' of pregnancy; thus, these women were excluded from the TTP analyses. In addition, 86 women were excluded due to missing information on trying time.
Information was missing for walking (n = 1).
[a]*P*-values were calculated from likelihood ratio tests of overall model fit.
[b]Adjusted for marital status and parity.
[c]Further adjusted for sitting.
[d]Further adjusted for IPAQ total baseline exercise level.
[e]IPAQ standard categorization.

missingness of anovulation status (Van Buuren, 2007); for 18% of observed cycles, issues with the fertility monitors such as infrequent usage, mistimed testing or testing malfunction resulted in missing anovulation. For this analysis, 20 datasets were imputed and estimates were made across datasets using SAS MI procedures, as has been described for these data previously (Radin *et al.*, 2017).

Results

As shown in Table I, among the 1214 women randomized, 797 women (65.7%) achieved an hCG-detected pregnancy. There were differences between women with and without a positive hCG test with regard to BMI (kg/m^2) ($P < 0.001$), parity ($P < 0.001$), marital status ($P < 0.001$), high school education ($P < 0.01$), race ($P < 0.001$), annual income ($P = 0.01$), smoking in past year ($P = 0.01$) and time from last loss to randomization ($P < 0.001$) (Table I). Women with a positive hCG pregnancy test were more likely to be married, white, parous, to have a lower mean BMI, to have more than high school education, higher income, to not have smoked within the past year, and a shorter time from last loss to randomization compared to those with a negative hCG test. These variables were considered for multivariable models. Alternative sets of covariate adjustments were tested but did not impact results.

We observed a positive association between fecundability and vigorous PA of >4 h/wk vs none (FOR = 1.69, 95% CI: 1.24, 2.31), adjusted for marital status, parity and sitting, with similar findings in unadjusted models (Table II). Other potential confounding factors including BMI were evaluated in multivariable models, but estimates

Table III Adjusted FOR and 95% CI for physical activity and fecundability, stratified by BMI: EAGeR Study, 2006–2012.

Exposure	Underweight/normal (BMI < 25 kg/m^2)			Overweight/obese (BMI ≥ 25 kg/m^2)			P^a
	+hCG	Cycles	Adj. FOR (95% CI)[b]	+hCG	Cycles	Adj. FOR (95% CI)[b]	
Vigorous activity (bouts of ≥10 min)[c]							
None	199	1697	Referent	165	1959	Referent	0.93
>0 to ≤1 h/wk	65	550	1.18 (0.85, 1.64)	38	405	1.03 (0.68, 1.56)	
>1 to ≤2 h/wk	52	478	0.97 (0.68, 1.39)	42	405	1.21 (0.82, 1.78)	
>2 to ≤3 h/wk	40	344	1.05 (0.70, 1.56)	35	367	1.05 (0.69, 1.59)	
>3 to ≤4 h/wk	23	195	0.88 (0.53, 1.46)	14	116	1.24 (0.65, 2.34)	
>4 h/wk	45	331	1.68 (1.12, 2.51)	24	232	1.57 (0.94, 2.63)	
Moderate activity (bouts of ≥10 min)							
None	131	1091	Referent	108	1296	Referent	0.36
>0 to ≤1 h/wk	67	603	1.10 (0.78, 1.56)	32	499	0.75 (0.49, 1.17)	
>1 to ≤2 h/wk	64	543	1.14 (0.80, 1.62)	40	356	1.58 (1.03, 2.42)	
>2 to ≤3 h/wk	37	287	1.11 (0.73, 1.70)	30	286	1.33 (0.84, 2.10)	
>3 to ≤4 h/wk	23	151	1.35 (0.80, 2.29)	14	153	0.93 (0.50, 1.73)	
>4 h/wk	102	920	0.98 (0.73, 1.32)	94	914	1.04 (0.76, 1.43)	
Walking (bouts of ≥10 min)							
None	47	343	Referent	29	513	Referent	0.01
Some	377	3252	0.83 (0.58, 1.19)	288	2985	1.82 (1.19, 2.77)	
Sitting categories							
1 (0–2.5 h/day)	93	801	Referent	72	625	Referent	0.27
2 (3–4.5 h/day)	115	1034	1.14 (0.83, 1.56)	65	829	0.68 (0.46, 1.00)	
3 (5–7.5 h/day)	115	896	1.19 (0.86, 1.64)	79	818	0.96 (0.66, 1.40)	
4 (>8 h/day)	101	864	1.22 (0.87, 1.71)	102	1232	0.93 (0.65, 1.34)	
Total baseline exercise							
Low	118	848	Referent	78	998	Referent	0.26
Medium	171	1497	0.87 (0.66, 1.15)	129	1381	1.12 (0.82, 1.54)	
High	135	1250	0.81 (0.60, 1.08)	111	1125	1.18 (0.85, 1.63)	

Notes: Fecundability odds ratios (FORs) are presented as estimate (95% confidence interval) adjusted for marital status, parity and BMI. Among 1228 participants, there were 14 withdrawals, whose last visit day was at randomization leaving no observable time 'at risk' of pregnancy; thus, these women were excluded from the TTP analyses. In addition, 86 women were excluded due to missing information on trying time. Information was missing for walking ($n = 1$) and BMI ($n = 17$).
[a]*P*-value for interaction; [b]adjusted for marital status, parity and BMI; [c]additionally adjusted for sitting.

were not impacted and additional variables were not retained in final models for parsimony. Fecundability was not associated with categorical measures of moderate intensity PA or walking ≥10 min at a time with adjustment for marital status and parity. Neither continuous nor categorical measures of sedentary behavior were associated with TTP adjusted for marital status, parity and IPAQ total baseline exercise level. According to IPAQ total baseline exercise level, no differences were observed between high or medium baseline exercise levels compared to low baseline exercise level in models adjusted for marital status and parity.

The association of walking with fecundability differed significantly between subgroups of BMI (*P*-interaction = 0.01) (Table III). Among overweight/obese women, walking (median 3 h/wk) was associated with higher fecundability (FOR = 1.82, 1.19, 2.77), whereas among women with underweight/normal BMI, walking ≥10 min at a time was unrelated to fecundability when compared to walking <10 min at a time (FOR=0.83, 0.58, 1.19). Associations of vigorous activity with fecundability did not vary by BMI (*P*-interaction = 0.93). Moderate activity, sitting, and IPAQ categories were not associated with fecundability in the stratified analyses (Table III). Log-binomial regression models of anovulation suggested no associations with any of the PA variables (Supplemental Table SI).

Discussion

Among overweight or obese (BMI≥25) women with one or two prior pregnancy losses, compared to those who reported no walking for ≥ 10 min at a time, those reporting some walking had a higher conception probability. In addition, vigorous intensity PA of >4 h/wk was also associated with higher fecundability in women regardless of BMI. No associations were observed between overall activity (IPAQ categories), moderate intensity PA, or time spent in sedentary behavior. These results provide support for the benefits of engaging in PA prior to pregnancy and show that even walking may be helpful for overweight/obese women (Good Health Before Pregnancy: Preconception Care, 2017). For context, in our data we observe an FOR of 1.3 comparing

those with normal BMI to those considered overweight or obese. Prior studies observe nearly two fold higher conception probability for non-smokers compared to smokers (Alderete *et al.*, 1995).

Several of our observations are consistent with prior prospective cohort studies. Our BMI-stratified results are largely consistent with that of the Pregnancy Study Online (PRESTO), a prospective cohort study of US and Canadian women ($N = 2062$) (McKinnon *et al.*, 2016). Specifically, among women with overweight/obesity, vigorous PA was associated with higher fecundability. Also, our finding of no overall association between sedentary activity and fecundability agrees with results from the PRESTO study (McKinnon *et al.*, 2016). Similar to our results, the PRESTO and Danish cohorts found no association for moderate intensity activity and fecundability (Wise *et al.*, 2012; McKinnon *et al.*, 2016). However, a positive relationship was reported by Gudmundsdottir *et al.* (2009). In the North-Trøndaleg Health Study ($n = 3887$ participants), comparing women whose exercise duration was moderate (16–30 and 30–60 min) to women reporting activity duration of <15 min, odds ratios of 0.3 (95% CI: 0.2, 0.5) and 0.5 (95% CI: 0.3, 0.9) were found for subfertility or involuntary childlessness (Gudmundsdottir *et al.*, 2009).

In contrast to our findings, Wise *et al.*, 2012 described an inverse association between vigorous intensity PA and fecundability in the Internet-based cohort of Danish women, whereas our results showed a positive association between vigorous intensity PA and fecundability. Comparing women reporting ≥5 h/wk of vigorous activity ($n = 194$) vs none ($n = 720$) in the 'Snart' Gravid cohort, a fecundability ratio of 0.68 (95% CI: 0.54, 0.85) was observed, though primarily for women with a BMI < 25 kg/m^2 (Wise *et al.*, 2012). Discrepant findings may be related to differences in the instrument used for PA assessment and hCG determination of pregnancy. Notably, EAGeR was conducted at various sites in the US among women with a history of 1–2 prior losses, and differences with Danish women in the Snart Gravid cohort are important to consider, as well. Overall PA levels were higher in Snart Gravid than among participants in EAGeR and, unlike participants in EAGeR, participants in Snart Gravid were recruited without reproductive history based restrictions (Wise *et al.*, 2012) and prior pregnancy losses were less common.

It has been suggested that PA may impact the likelihood of conception through various mechanisms; PA is associated with generally healthy behavior and has been proposed to improve fecundability and reduce TTP through reduction of stress or anxiety in small studies (Kucuk *et al.*, 2010). In contrast, PA beyond some threshold of intensity may improve fecundability in some populations (McKinnon *et al.*, 2016) and worsen it in others (Wise *et al.*, 2012). Whereas extreme high levels of activity may be related to menstrual cycle disturbances, we observed no associations with anovulation; thus the mechanisms through which PA affects fecundability are unclear.

Use of the EAGeR cohort provided detailed information collected at baseline and longitudinal collection of biospecimens in a relatively large study population for use in these analyses. We utilized the IPAQ-SF for PA assessment, which has been used extensively in studies of PA and has been observed to have good reliability (Craig *et al.*, 2003) and agreement with assessment by accelerometer (Craig *et al.*, 2003) and other instruments (Hartley *et al.*, 2015). Given the inherent limitations of self-report instruments, some misclassification of PA levels as determined by the IPAQ is likely (Kucuk *et al.*, 2010; Esmaeilzadeh *et al.*, 2013). Additionally, the IPAQ-SF was administered at baseline only; however, comparison of other measures of PA during months 3–6 of follow-up suggests that PA varied only minimally throughout the study period (data not shown). Though direct observation and accelerometers can provide a more objective measure of activity than self-report instruments (Sallis and Saelens, 2000), it is often more feasible to use PA questionnaires in large epidemiological studies. For these analyses, misclassification of PA is likely to be non-differential, given the prospective design of the EAGeR study. Our study is further limited in that information on diet and change in BMI was not collected which may have led to some residual confounding in our results. In addition, we note that use of the IPAQ allowed us to consider multiple dimensions of PA, i.e. overall categories of energy expenditure, as well as intensity-specific activity, which may act through different physiological pathways. However, this also resulted in a relatively large number of analyses, raising the probability of chance findings related to multiple comparisons.

The extensive biospecimens from EAGeR is also a strength of our study. Pregnancy status was determined by the QuickVue hCG urine test, a sensitive immunoassay with sensitivity and specificity >99% (Zarek *et al.*, 2015). The QuickVue hCG urine test was administered at baseline and then at each subsequent clinic visit during the active and passive follow-up period. Participants provided extensive information at baseline and during follow-up for use in statistical models. Though some uncontrolled confounding is likely, available data included a demographics questionnaire, a health and reproduction questionnaire, a lifestyle questionnaire, an occupation questionnaire, and anthropometric measurements to calculate BMI, enabling consideration of a large number of covariates; however, ultimately, few of these appeared to represent substantial confounding.

Our study population is unique as it consisted only of women with a history of one or two documented miscarriages. In the EAGeR study, of 1214 participants, ~65.7% achieved pregnancy within 6 months. The overall generalizability in our study is limited as our population may not be representative of the general population with regard to fecundability (Issa *et al.*, 2010). In addition, exercise habits may differ in women with prior miscarriage compared to those without.

In conclusion, in this cohort of women with a history of one to two prior pregnancy losses, walking ≥ 10 min at a time was associated with improved fecundability among women with BMI of 25 kg/m^2 or greater. Vigorous intensity PA of >4 h/wk was also associated with improved fecundability. No associations were observed between PA and anovulation. Further study is necessary to clarify possible mechanisms through which walking and vigorous activity might affect TTP. These findings provide positive evidence for the benefits of PA in women attempting pregnancy, especially those with higher BMI.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Authors' roles

L.M.R.: design, analysis and interpretation of data; drafting of article; final approval of the version to be published. B.W.W.: conception and design of study; analysis and interpretation of data; drafting of article; final approval of version to be published. S.L.M., M.H., R.G.R., K.C.S., N.J.P., K.K., U.R.O., D.L.K., T.L.H., L.A.S.: interpretation of data; revising the article critically for important intellectual content; final

approval of the version to be published. R.M.S., E.F.S.: conception and design of study; acquisition and interpretation of data; revising the article critically for important intellectual content, final approval of the version to be published.

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Conflict of interest

The authors report no conflicts of interest in this work.

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