Published in final edited form as:

Epidemiology. 2019 July ; 30(4): 582–589. doi:10.1097/EDE.0000000000001008.

Physical Exertion Immediately Prior to Early Preterm Delivery: A Case–Crossover Study

Harpreet S. Chahal^{1,2,*}, Bizu Gelaye^{1,*}, Elizabeth Mostofsky^{1,3}, Sixto E. Sanchez^{4,5}, Juan F. Mere⁶, Francisco G. Mercado⁷, Percy Pacora⁸, and Michelle A. Williams¹

¹Department of Epidemiology, Harvard TH Chan School of Public Health, Boston, MA, USA

²Mississauga Academy of Medicine, University of Toronto Mississauga, Mississauga, ON, Canada

³Cardiovascular Epidemiology Research Unit, Beth Israel Deaconess Medical Center, Boston, MA, USA

⁴Universidad Particular San Martin de Porres, Lima, Peru

⁵Asociación Civil PROESA, Lima, Peru

⁶Universidad Peruana Cayetano Heredia, Lima, Peru

⁷Universidad Peruana de Ciencias Aplicadas, Lima, Peru

⁸Department of Obstetrics and Gynecology, San Marcos University, Lima, Peru

Abstract

Background: Occupational exertion is associated with a higher risk of preterm delivery, while studies of leisure time activities generally document reduced risks. Less is known about the risk of preterm delivery immediately following episodes of moderate or heavy physical exertion.

Methods: We conducted a case–crossover study of 722 women interviewed during their hospital stay for early preterm delivery, defined by a gestational age before 34 weeks, and after 20 weeks. Interviews occurred between March 2013 and December 2015 in seven hospitals in Lima, Peru.

Results: The incidence rate ratio (RR) of early preterm delivery was 5.82-fold higher (95% confidence interval [CI]: 4.29 – 7.36) in the hour following moderate or heavy physical exertion compared to other times and returned to baseline in the hours thereafter. The RR of early preterm delivery within an hour of physical exertion was lower for exertion at moderate intensity (RR=2.43, 95% CI: 1.50 – 3.96) than at heavy intensity (RR=23.62, 95% CI: 15.54 – 35.91, *P*

Corresponding author: Harpreet S. Chahal, MSc., Harvard T.H. Chan School of Public Health, Department of Epidemiology, 677 Huntington Avenue, Kresge 500, Boston, MA 02115, Tel: 617-432-1071, Fax: 617-566-7805, harpreet.chahal@mail.utoronto.ca.

*These authors contributed equally to this work

Author contributions:

MAW, BG, and SES were responsible for study conception and original data collection in Lima, Peru. MAW, BG, and SES contributed to the study design and protocol. SES, JFM, FGM, and PP contributed to the original data collection. HSC conducted the data analysis and drafted the manuscript. HSC, BG, EM, and MAW contributed to data analysis, interpretation and drafting the manuscript. All co-authors (HSC, BG, EM, SES, JFM, FGM, PP, MAW) reviewed the draft manuscript for important intellectual content and provided approval for this final version.

Conflicts of interest: None declared

The data and code are not available for replication because the data are not publicly available.

homogeneity < 0.001). The RR of early preterm delivery was lower in the hour following moderate physical exertion among women who habitually engaged in physical exertion more than 3 times per week in the year before pregnancy (RR=1.56, 95% CI: 0.81 – 3.00) compared to more sedentary women (RR=6.91, 95% CI: 3.20 – 14.92, *P*-homogeneity = 0.003).

Conclusions: Our study showed a heightened risk of early preterm delivery in the hour following moderate or heavy physical exertion.

Keywords

physical exertion; preterm delivery; preterm birth; case–crossover

Introduction

Early preterm deliveries, defined as deliveries before 34 weeks gestation, occur in roughly 2.8% of live births in the United States.¹ These deliveries are a subset of all preterm deliveries (<37 weeks) and have an even higher risk of infant morbidity and mortality compared to preterm infants born at later gestational ages.² Early preterm deliveries are associated with major neonatal complications, hospital readmissions, and death. Maternal factors for preterm deliveries include cigarette smoking,³ preeclampsia,⁴ obesity,⁵ previous preterm birth,⁶ psychiatric disorders,^{7,8} psychotropic medication use,⁹ and exposure to intimate partner violence.¹⁰ Despite several studies, the safety of physical exertion during pregnancy among women at risk of preterm deliveries remains unclear. For instance, occupational physical activity during pregnancy has been associated with an elevated risk of preterm delivery,¹¹ while leisure-time activity¹² – even at vigorous intensity¹³ – has been reported to reduce the risk of preterm delivery.

A recent, patient-level meta-analysis of randomized controlled trials found that women who received leisure physical activity-based interventions during pregnancy were less likely to develop gestational diabetes and to deliver by cesarean delivery. However, there was no evidence of a reduced risk of preterm delivery.¹⁴ In fact, the authors reported a modest, albeit imprecisely measured, increased risk of preterm delivery among women who received the exercise intervention as compared to those who did not (odds ratio [OR] = 1.29, 95% confidence interval [CI] 0.90 – 1.85). These studies were experimental and therefore could not include women with contraindications for exercise,¹⁵ which often overlap as risk factors for preterm delivery.⁶ To address this concern, we conducted a case–crossover study; because this design is observational, it allows for inclusion of women with high-risk pregnancies and because it is self-matched, it eliminates confounding by stable and slow-varying characteristics.¹⁶ Hernandez-Diez *et al.* (2014)¹⁷ used this approach and found a higher risk of preterm birth following skipped meals, disturbed sleep, sexual activity, and intake of spicy foods. Several case–crossover studies have also noted an acutely increased risk of preterm birth following exposure to high ambient temperature^{18–22} and air pollution.²³

In a cohort of 722 women in Peru who experienced early preterm delivery,²⁴ we hypothesized that episodes of physical exertion are followed by an acutely higher risk of early preterm delivery that varies by exertion intensity, but that this is mitigated by habitual

physical activity. To assess this, we first examined whether the risk of early preterm delivery was higher in the hour following moderate or heavy physical exertion compared to periods of light exertion or rest and determined the length of time between moderate or heavy physical exertion and the onset of symptoms (induction time). We then examined whether, compared to periods of light exertion or rest, the risk of early preterm delivery in the hour following heavy physical exertion was different from the risk following moderate exertion. We also examined whether habitual physical activity in the year before pregnancy modified the risk of early preterm delivery in the hour following moderate physical exertion compared to periods of light exertion or rest, and then did the same for the risk following heavy physical exertion.

Materials and Methods

Source population

We recruited women receiving care for early preterm delivery for the Placental Abruption Genetic Epidemiology and Triggers (PAGE) study. We recruited women from the following seven hospitals in Lima, Peru, South America: Instituto Nacional Materno Perinatal, Hospital Edgardo Rebagliati Martins, Hospital San Bartolome, Hospital Hipolito Unanue, Hospital Arzobispo Loayza, Hospital Dos de Mayo, and Hospital Maria Auxiliadora. Between March 2013 and December 2015, women were identified as eligible for interview during the in-patient labor and delivery period by the following procedures. Research staff identified eligible women by reviewing admission logbooks for the emergency room, labor and delivery, antepartum wards, and surgery. Early preterm delivery cases were identified by daily monitoring of all new admissions to antepartum wards, emergency room wards (intensive care unit) and labor and delivery wards of the study hospitals. Early preterm delivery was defined as a pregnancy ending before 34 weeks gestation, and after 20 weeks. We measured weeks of gestation using the mother's reported last menstrual period in the interview combined with 20 weeks gestation as reported in the ultrasound. When dating by both methods agreed within 14 days, we used last menstrual period to assign gestational age. When the two methods differed by > 14 days, we used the ultrasound date for gestational age. Using detailed information collected from medical records, we categorized early preterm delivery cases according to two pathophysiological groups: 1) early preterm premature rupture of membranes, those with physician diagnosis of rupture of fetal membranes prior to the onset of labor; and 2) early spontaneous preterm deliveries, those with physician diagnosis of spontaneous onset of labor before rupture of fetal membranes. We excluded women who had a multi-fetal pregnancy and who were not residents of Lima (i.e., women transferred from remote areas of Peru). During their hospital stay, we invited eligible women to participate in a 30-minute in-person interview and we obtained written informed consent. The procedures used in this study were approved by the research ethics boards of all participating institutions and the Swedish Medical Center, Seattle, WA (IRB#5123), where the study was administratively based.

Case–crossover design

We conducted a case–crossover study, a design that compares each case to herself at other times. The method was developed to estimate the transient effect of an intermittent exposure

on events with an identifiable, abrupt onset.¹⁶ Since the approach involves a comparison of the same person at different times, there is no confounding by fixed or slowly varying characteristics such as socioeconomic status or educational attainment. This design involves collecting information on exposure (e.g., participation in heavy physical exertion) immediately preceding the event (e.g., early preterm delivery) and comparing this with the expected frequency of exposure based on women's exposure pattern during similar referent time periods (Figure 1).

Interview

Trained female interviewers conducted the standardized-structured questionnaire in Spanish. We obtained information about a variety of potential triggers as well as sociodemographic, medical, reproductive, and lifestyle factors. Information collected during the interview included maternal age, educational attainment, marital status, employment during pregnancy, personal reproductive and medical histories, as well as history of hypertensive disorders. We also collected information regarding substance use before and during pregnancy. At the time of the interview, interviewers completed a brief physical exam protocol designed to measure maternal standing height, weight, and mid-arm circumference of each participant. To help standardize reporting of the intensity of physical exertion, women were shown a 15-point visual analogue Borg Scale (scores ranging from 6 – 20) which was used to rate all types of physical activity.²⁵ Then we provided examples of physical exertion at each level of intensity to help women classify episodes as light (scores 6 – 11, e.g., mopping), moderate (12 – 16, e.g., dancing) or heavy (17 – 20, e.g., sprinting). To record the usual frequency of physical exertion, we adapted a questionnaire that was designed for the Determinants of Myocardial Infarction Onset Study.²⁶ We started by asking each woman about her usual frequency of light exertion, with the question “During the year before pregnancy, on average, how many times per week did you participate in light exertion physical activity?”. Then we asked her about her frequency of light exertion during the first 3 – 6 months of pregnancy, during months 6 – 9 of pregnancy, and during the week before early preterm delivery. Next, we asked about her usual frequency of moderate exertion and then her usual frequency of heavy exertion physical activity, asking the same questions as for light exertion. Later, we asked when was the last time she was engaged in light exertion physical activity before symptom onset of early preterm delivery (e.g., labor pains or broken water-bag). We categorized the responses for last time engaged in activity as: never, at the time of event onset, ½ hour, 1 hour, 2 hours, 3–6 hours, 6–24 hours, 1–2 days, 3–4 days, or 5 days before. We then asked about the last time engaged in moderate exertion, and then heavy exertion physical activity. An English and/or Spanish language version of the relevant questions will be available upon request.

Statistical analysis

In a case–crossover analysis, data are stratified by individual persons.^{16,27} In the analysis of this self-matched design, each woman forms her own stratum. Thus, for every calculation of an incidence rate ratio, each woman contributed her own 2-by-2 table with the a-cell equal to 1 if she was exposed immediately before onset of early preterm delivery (and 0 if she was unexposed), and the b-cell equal to 1 if the a-cell was 0 (or 0 if the a-cell was 1), while the values in the c and d cells represented the relative amount of exposed versus unexposed

time, respectively, in the referent period. Such an analysis requires an assumption about the average duration of the hazard period (the exposure duration plus the average duration of its effect). We chose a 1-hour duration for the hazard period, based on prior work on physical exertion, and then later tested this assumption when calculating the induction time. Thus, a woman was classified as exposed in the case window ($a = 1$) if she said her last time of moderate or heavy exertion was “at the time of symptom onset”, “ $\frac{1}{2}$ hour before”, or “1 hour before”, and classified as unexposed ($b = 1$) if she said her last time was “2 hours before” or more. We multiplied the usual weekly frequency of physical exertion by the hypothesized duration of its physiologic effect (1 hour) to calculate weekly hours of exposure for the c-cell, and subtracted this value from total hours in a week to get the unexposed hours for the d-cell. Using methods for sparse data analysis, we calculated the Mantel-Haenszel incidence rate ratio (RR) for person-time and 95% confidence intervals (95% CIs).²⁸

To estimate the hypothesized induction time from physical exertion to the onset of symptoms of early preterm delivery, RRs were calculated by comparing exposure to moderate or heavy physical exertion within the 1st-, 2nd-, and 3rd- to 6th-hour windows before early preterm delivery to the estimated person-time exposed in the previous week. We also conducted analyses to assess whether the association between physical exertion and early preterm delivery differed according to the intensity of physical exertion (heavy vs moderate). In addition, we conducted subgroup analyses to assess whether observed associations varied by self-reported history of habitual physical activity, defined as either moderate or heavy intensity physical exertion (≤ 3 vs. > 3 times per week in the year before pregnancy). Further, we conducted subgroup analyses to determine the extent to which, if at all, risks of types of early preterm delivery (i.e., early preterm premature rupture of membranes, early spontaneous preterm deliveries) differed and if the risk of early preterm delivery varied by maternal age (< 35 vs. ≥ 35 years). For these subgroup analyses we used the Wald χ^2 test of homogeneity.²⁸ To evaluate whether other potential triggers could account for the observed associations, we conducted sensitivity analyses excluding women who engaged in other potentially triggering activities in the hour before early preterm delivery. These potentially triggering activities were as follows: sexual intercourse, cigarette smoking, alcohol, coffee, tea, cola, cocaine, marijuana and terokal (an adhesive that is inhaled recreationally) consumption. All statistical analyses were conducted using SAS (version 9.4; SAS institute, Cary, NC). All reported *P*-values are two-sided.

Results

The characteristics of women who experienced early preterm delivery are described in Table 1. The mean frequency of physical activity decreased after conception and over the course of pregnancy (Figure 2). Of the 722 enrolled women who had early preterm delivery, 10 provided no information on usual physical exertion so were excluded from the final analyses. Of the 712, 335 (46%) reported that they engaged in moderate or heavy physical exertion (exertion causing deep breathing or panting, overheating, and sweating respectively) in the week before early preterm delivery. Among the 335 who engaged in moderate or heavy physical exertion, 213 (64%) reported engaging in such activity once that week and 68 (20%) reported more than three times that week.

Among 335 women who engaged in moderate or heavy physical exertion in the week before early preterm delivery, 41 (12%) women reported having engaged in moderate or heavy physical exertion in the hour before symptoms of early preterm delivery. Compared to periods of light exertion or rest, the immediate risk of early preterm delivery was 5.82-fold higher (95% CI: 4.29 – 7.36) within an hour of moderate or heavy physical exertion (Figure 3). Compared to periods of light exertion or rest, the RR was 1.08 (95% CI: 0.56 – 2.08) in the second hour after moderate or heavy physical exertion and 1.17 (95% CI: 0.81 – 1.69) in the 3–6 hours following moderate or heavy physical exertion. In a sensitivity analysis excluding women who were exposed to other potential triggers in the hour before symptom onset of early preterm delivery, the association between moderate or heavy physical exertion in the past hour and early preterm delivery was attenuated but remained strong (RR=4.63, 95% CI: 3.30 – 6.51).

Compared to periods of light exertion or rest, the RR of early preterm delivery within an hour of physical exertion was lower for exertion at moderate intensity (RR=2.43, 95% CI: 1.50 – 3.96) than at heavy intensity (RR=23.62, 95% CI: 15.54 – 35.91, P -homogeneity < 0.001). The RR of early preterm delivery within an hour of moderate physical exertion compared to periods of light exertion or rest was lower for women who habitually engaged in physical exertion more than 3 times per week in the year before pregnancy (RR=1.56, 95% CI: 0.81 – 3.00) compared to women who engaged in physical exertion three or fewer times (RR=6.91, 95% CI: 3.20 – 14.92, P -homogeneity = 0.003) (Table 2). The RR of early preterm delivery within an hour of heavy physical exertion compared to periods of light exertion or rest was lower for women who habitually engaged in physical activity more than three times per week in the year before pregnancy (RR=17.12, 95% CI: 10.24 – 28.60) compared to women who engaged in physical activity three or fewer times (RR=75.91, 95% CI: 32.30 – 178.40, P -homogeneity = 0.003). Additionally, the RR associated with moderate or heavy physical exertion in the past hour compared to periods of light exertion or rest was higher for early preterm premature rupture of membranes (RR=8.40, 95% CI: 5.60 – 12.61) than it was for early spontaneous preterm deliveries (RR=3.55, 95% CI: 2.15 – 5.86, P -homogeneity < 0.001). The RR associated with moderate or heavy physical exertion in the past hour compared to periods of light exertion or rest was similar for women aged < 35 years (RR=5.82, 95% CI: 4.10 – 8.28) to women 35 and older (RR=5.82, 95% CI: 3.17 – 10.68, P -homogeneity = 1.00).

Discussion

Episodes of moderate or heavy physical exertion were associated with an acutely heightened risk of early preterm delivery that was 5.82-fold higher in the subsequent hour compared to periods of light exertion or rest, and the risk returned to baseline in the hours thereafter. The heightened risk following moderate or heavy physical exertion was mitigated by habitual physical activity before pregnancy. Lastly, the association between exertion and ePPROM was stronger than the association between exertion and esPTD.

There has only been one other study examining the acute risk of preterm delivery following episodes of exertion. Hernandez-Diaz *et al.* (2014)¹⁷ conducted a study of 100 women who experienced preterm (<37 weeks) deliveries. They reported no association between preterm

birth and physical activity in the past 24 hours when they compared to the previous 48 to 72 hours. Because there is consistent evidence of a biologic effect of exertion within one hour of exertion,²⁴ we included a one-hour hazard period for our analysis and found a heightened risk in that time period. Therefore, it is possible that the lack of association in the prior study may have been due to the fact that they assumed only a 24-hour hazard period.

Prior studies have reported that the heightened risk of cardiovascular disease following episodes of exertion is modified by habitual physical activity.²⁴ For instance, Baylin *et al.* (2007)²⁹ studied the acute risk of myocardial infarction in Costa Rica and found a 27.5-fold higher risk (95% CI: 18.7 – 40.5) in the hour after heavy exertion among people who they classified as sedentary; similarly, we estimated a 23.62-fold higher risk (95% CI: 15.54 – 35.91) in the hour after heavy exertion among women who did little or no other heavy physical activity in the week prior.

Associations between chronic physical exertion and preterm delivery provide valuable insight into the total risk across different populations. For example, a study in Denmark found that women who participated in more than one sport and who performed moderate to heavy physical exertion during their pregnancy had a lower baseline risk of preterm delivery than those who were more sedentary.³⁰ These findings are consistent with the hypothesis of a modifying effect of physical fitness, as is our finding that women who were more habitually active (and presumably more physically fit) had lower or no statistically significant acute increase in risk of early preterm delivery from each individual episode of moderate and heavy physical exertion. This finding is consistent with current clinical practice guidelines that recommend a gradual introduction into an exercise program for pregnant women who are sedentary.¹⁵

Physical exertion elicits a release of catecholamines and prostaglandins that may stimulate preterm labor due to their effects on uterine motility.^{31–34} However, circulating levels of catecholamines correlate better with the relative intensity of physical exertion than the absolute intensity, and the relative intensity can also be reduced after an exercise training program.³⁵ This training effect is concordant with our finding of effect modification by habitual physical activity, and with results seen in studies of cardiovascular events,²⁴ suggesting that habitual physical activity results in a tolerance to the acute effects of physical exertion. Women with collagen vascular disorders, or even higher amounts of endogenous protein that degrades collagen – matrix metalloproteinases – are at higher risk of preterm premature rupture of membranes due to impaired integrity of the fetal membranes.³⁶ Integrity can also be impaired from inflammatory mediators, among other causes. Although speculative, it is possible that the transient physiologic response from physical exertion – which includes a release of inflammatory mediators, shear stress, and oxidative stress – is more likely to induce early preterm delivery through premature rupture of membranes than spontaneously, which may explain the findings we observed in this study.

By comparing each woman to herself at other times, the case–crossover design eliminates between-person confounding by fixed and slow-varying characteristics. However, since women may engage in other potentially harmful exposures at times when they are more

likely to be engaged in more exertion, we conducted a sensitivity analysis restricted to cases who were not also engaging in these activities in the hour prior to the onset of symptoms of early preterm delivery, and the results were similar. As in other studies, information on physical exertion was obtained via self-report, which may not be reported accurately. The intensity of physical exertion is also subjective, but because each woman is compared to herself it is possible that similar subjective interpretations are used for exposure ascertainment in both hazard and referent period.¹⁶ To our knowledge, there are no validated questionnaires for physical exertion in pregnant women that are amenable to case–crossover analysis. We adapted the questionnaire from the Determinants of Myocardial Infarction Onset Study²⁶ to obtain information about exertion during pregnancy. The pregnancy-related changes may impact quality of self-reported exertion, but it is reassuring that the self-reported patterns of physical activity during pregnancy in this study are similar to those observed in other studies.³⁷

Recall bias is possible, whereby women may overreport recent levels of exertion and underreport exertion levels for the referent period in the prior week. However, participants were not told the hypothesized window of effect, and the recall of usual exertion is based on only the prior week rather than the distant past. We did not have information on the kind of physical exertion performed before early preterm delivery, so we could not identify common exposures that merit attention and future study (e.g., heavy lifting). Because self-reported light intensity exertion may have lower correlation with actual light intensity physical exertion,^{38,39} we did not conduct analyses by light intensity physical exertion. A future study conducted with activity sensors that could reliably record the frequency and intensity of physical exertion could explore this question. Moreover, future studies may also incorporate a questionnaire on sedentary behavior. Last, our sample size may not have been sufficient to detect differences by maternal age or to more finely explore our secondary analysis on the etiology of early preterm delivery, but we did detect other instances of effect modification.

Despite these limitations, this study has many strengths. To our knowledge this is the first study on the short-term effect of physical exertion associated with early preterm deliveries (<34 weeks), a higher-risk subset of all preterm deliveries (<37 weeks). This study also included a relatively large sample of cases and therefore allowed stratification by both physical exertion intensity (moderate, heavy) and habitual physical activity (<3, >3 times per week) simultaneously. Due to the observational nature of this study, we were also able to examine the role of physical activity in the most unwell patients, who have been otherwise excluded from randomized controlled trials due to absolute and relative contraindications for exercise programs.^{40–44}

In this study, habitual activity before pregnancy lowered the risk associated with each episode of exertion. Therefore, preconception may serve as an ideal opportunity to encourage regular exercise, especially for women at high risk of preterm delivery. While folate supplementation before conception has considerably lowered the rate of neural tube abnormalities,⁴⁵ the feasibility of other interventions at preconception have been vastly underexplored.⁴⁶ Prepregnancy characteristics may explain up to 40% of preterm delivery⁴⁷ and evidence suggests that both primary care providers⁴⁸ and women⁴⁹ want more focus

placed on preconceptional care. Recent work on novel interventions at preconception has also found promising results in well⁵⁰ and unwell women^{51,52} alike. Based on our results regarding the health benefits of habitual activity and because evidence has not suggested that exercise programs during pregnancy decrease preterm delivery, a randomized controlled trial on the effects of preconceptional exercise on maternal outcomes seems warranted.

Acknowledgments:

The authors wish to thank the participating hospitals. The authors are indebted to the participants of the PAGE study for their cooperation. They are also grateful to Ms. Elena Sanchez and the dedicated staff members of Asociacion Civil Proyectos en Salud (PROESA), Peru for their expert technical assistance with this research. The authors also thank Ms. Julia Devorak for her help with figure illustration.

Source of funding: This work was supported by grants R01 HD059827 and T37 MD001449 from the National Institutes of Health.

Financial support

This research was supported by awards from the National Institutes of Health (R01 HD059827 and T37 MD001449).

References

1. Ananth CV, Friedman AM, Gyamfi-Bannerman C. Epidemiology of moderate preterm, late preterm and early term delivery. *Clin Perinatol* 2013;40(4):601–10. [PubMed: 24182950]
2. Shapiro-Mendoza CK, Lackritz EM. Epidemiology of late and moderate preterm birth. *Semin Fetal Neonatal Med* 2012;17(3):120–5. [PubMed: 22264582]
3. Williams MA, Mittendorf R, Stubblefield PG, Lieberman E, Schoenbaum SC, Monson RR. Cigarettes, coffee, and preterm premature rupture of the membranes. *Am J Epidemiol* 1992;135(8):895–903. [PubMed: 1585902]
4. Bilano VL, Ota E, Ganchimeg T, Mori R, Souza JP. Risk factors of pre-eclampsia/eclampsia and its adverse outcomes in low- and middle-income countries: a WHO secondary analysis. *PLoS One* 2014;9(3):e91198. [PubMed: 24657964]
5. Cnattingius S, Villamor E, Johansson S, Edstedt Bonamy AK, Persson M, Wikstrom AK, Granath F. Maternal obesity and risk of preterm delivery. *JAMA* 2013;309(22):2362–70. [PubMed: 23757084]
6. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet* 2008;371(9606):75–84. [PubMed: 18177778]
7. Sanchez SE, Puente GC, Atencio G, Qiu C, Yanez D, Gelaye B, Williams MA. Risk of spontaneous preterm birth in relation to maternal depressive, anxiety, and stress symptoms. *J Reprod Med* 2013;58(1–2):25–33. [PubMed: 23447915]
8. Yonkers KA, Smith MV, Forray A, Epperson CN, Costello D, Lin H, Belanger K. Pregnant women with posttraumatic stress disorder and risk of preterm birth. *JAMA Psychiatry* 2014;71(8):897–904. [PubMed: 24920287]
9. Calderon-Margalit R, Qiu C, Ornoy A, Siscovick DS, Williams MA. Risk of preterm delivery and other adverse perinatal outcomes in relation to maternal use of psychotropic medications during pregnancy. *Am J Obstet Gynecol* 2009;201(6):579 e1–8. [PubMed: 19691950]
10. Sanchez SE, Alva AV, Diez Chang G, Qiu C, Yanez D, Gelaye B, Williams MA. Risk of spontaneous preterm birth in relation to maternal exposure to intimate partner violence during pregnancy in Peru. *Matern Child Health J* 2013;17(3):485–92. [PubMed: 22527763]
11. Bonzini M, Coggon D, Palmer KT. Risk of prematurity, low birthweight and pre-eclampsia in relation to working hours and physical activities: a systematic review. *Occup Environ Med* 2007;64(4):228–43. [PubMed: 17095552]
12. da Silva SG, Ricardo LI, Evenson KR, Hallal PC. Leisure-Time Physical Activity in Pregnancy and Maternal-Child Health: A Systematic Review and Meta-Analysis of Randomized Controlled Trials and Cohort Studies. *Sports Med* 2017;47(2):295–317. [PubMed: 27282925]

13. Evenson KR, Siega-Riz AM, Savitz DA, Leiferman JA, Thorp JM Jr. Vigorous leisure activity and pregnancy outcome. *Epidemiology* 2002;13(6):653–9. [PubMed: 12410006]
14. International Weight Management in Pregnancy Collaborative G. Effect of diet and physical activity based interventions in pregnancy on gestational weight gain and pregnancy outcomes: meta-analysis of individual participant data from randomised trials. *BMJ* 2017;358:j3119. [PubMed: 28724518]
15. Evenson KR, Barakat R, Brown WJ, Dargent-Molina P, Haruna M, Mikkelsen EM, Mottola MF, Owe KM, Rousham EK, Yeo S. Guidelines for Physical Activity during Pregnancy: Comparisons From Around the World. *Am J Lifestyle Med* 2014;8(2):102–121. [PubMed: 25346651]
16. Maclure M The case–crossover design: a method for studying transient effects on the risk of acute events. *Am J Epidemiol* 1991;133(2):144–53. [PubMed: 1985444]
17. Hernandez-Diaz S, Boeke CE, Romans AT, Young B, Margulis AV, McElrath TF, Ecker JL, Bateman BT. Triggers of spontaneous preterm delivery--why today? *Paediatr Perinat Epidemiol* 2014;28(2):79–87. [PubMed: 24384058]
18. Avalos LA, Chen H, Li DK, Basu R. The impact of high apparent temperature on spontaneous preterm delivery: a case–crossover study. *Environ Health* 2017;16(1):5. [PubMed: 28143601]
19. Basu R, Chen H, Li DK, Avalos LA. The impact of maternal factors on the association between temperature and preterm delivery. *Environ Res* 2017;154:109–114. [PubMed: 28056406]
20. Basu R, Malig B, Ostro B. High ambient temperature and the risk of preterm delivery. *Am J Epidemiol* 2010;172(10):1108–17. [PubMed: 20889619]
21. Ha S, Liu D, Zhu Y, Kim SS, Sherman S, Mendola P. Ambient Temperature and Early Delivery of Singleton Pregnancies. *Environ Health Perspect* 2017;125(3):453–459. [PubMed: 27580125]
22. Kent ST, McClure LA, Zaitchik BF, Smith TT, Gohlke JM. Heat waves and health outcomes in Alabama (USA): the importance of heat wave definition. *Environ Health Perspect* 2014;122(2):151–8. [PubMed: 24273236]
23. Li S, Guo Y, Williams G. Acute Impact of Hourly Ambient Air Pollution on Preterm Birth. *Environ Health Perspect* 2016;124(10):1623–1629. [PubMed: 27128028]
24. Dahabreh IJ, Paulus JK. Association of episodic physical and sexual activity with triggering of acute cardiac events: systematic review and meta-analysis. *JAMA* 2011;305(12):1225–33. [PubMed: 21427375]
25. Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 1982;14(5):377–81. [PubMed: 7154893]
26. Mittleman MA, Maclure M, Tofler GH, Sherwood JB, Goldberg RJ, Muller JE. Triggering of acute myocardial infarction by heavy physical exertion. Protection against triggering by regular exertion. Determinants of Myocardial Infarction Onset Study Investigators. *N Engl J Med* 1993;329(23):1677–83. [PubMed: 8232456]
27. Mittleman MA, Maclure M, Robins JM. Control sampling strategies for case–crossover studies: an assessment of relative efficiency. *Am J Epidemiol* 1995;142(1):91–8. [PubMed: 7785679]
28. Rothman KJ, Greenland S, Lash TL. *Modern epidemiology*. 3rd ed Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2008.
29. Baylin A, Hernandez-Diaz S, Siles X, Kabagambe EK, Campos H. Triggers of nonfatal myocardial infarction in Costa Rica: heavy physical exertion, sexual activity, and infection. *Ann Epidemiol* 2007;17(2):112–8. [PubMed: 17236983]
30. Hegaard HK, Hedegaard M, Damm P, Ottesen B, Petersson K, Henriksen TB. Leisure time physical activity is associated with a reduced risk of preterm delivery. *Am J Obstet Gynecol* 2008;198(2):180 e1–5. [PubMed: 18226619]
31. Lotgering FK, Gilbert RD, Longo LD. Maternal and fetal responses to exercise during pregnancy. *Physiol Rev* 1985;65(1):1–36. [PubMed: 3880895]
32. Omer H Possible psychophysiologic mechanisms in premature labor. *Psychosomatics* 1986;27(8):580–4. [PubMed: 3018827]
33. Omer H, Everly GS Jr. Psychological factors in preterm labor: critical review and theoretical synthesis. *Am J Psychiatry* 1988;145(12):1507–13. [PubMed: 3057922]
34. Zuspan FP, Cibils LA, Pose SV. Myometrial and cardiovascular responses to alterations in plasma epinephrine and norepinephrine. *Am J Obstet Gynecol* 1962;84:841–51. [PubMed: 14004121]

35. Kohrt WM, Spina RJ, Ehsani AA, Cryer PE, Holloszy JO. Effects of age, adiposity, and fitness level on plasma catecholamine responses to standing and exercise. *J Appl Physiol* (1985) 1993;75(4):1828–35. [PubMed: 8282638]
36. Tchirikov M, Schlabritz-Loutsevitch N, Maher J, Buchmann J, Naberezhnev Y, Winarno AS, Seliger G. Mid-trimester preterm premature rupture of membranes (PPROM): etiology, diagnosis, classification, international recommendations of treatment options and outcome. *J Perinat Med* 2017.
37. Borodulin KM, Evenson KR, Wen F, Herring AH, Benson AM. Physical activity patterns during pregnancy. *Med Sci Sports Exerc* 2008;40(11):1901–8. [PubMed: 18845974]
38. Schmidt MD, Freedson PS, Pekow P, Roberts D, Sternfeld B, Chasan-Taber L. Validation of the Kaiser Physical Activity Survey in pregnant women. *Med Sci Sports Exerc* 2006;38(1):42–50. [PubMed: 16394952]
39. Stein AD, Rivera JM, Pivarnik JM. Measuring energy expenditure in habitually active and sedentary pregnant women. *Med Sci Sports Exerc* 2003;35(8):1441–6. [PubMed: 12900702]
40. Barakat R, Pelaez M, Lopez C, Montejo R, Coteron J. Exercise during pregnancy reduces the rate of cesarean and instrumental deliveries: results of a randomized controlled trial. *J Matern Fetal Neonatal Med* 2012;25(11):2372–6. [PubMed: 22715981]
41. Barakat R, Pelaez M, Montejo R, Luaces M, Zakynthinaki M. Exercise during pregnancy improves maternal health perception: a randomized controlled trial. *Am J Obstet Gynecol* 2011;204(5):402 e1–7. [PubMed: 21354547]
42. Barakat R, Stirling JR, Lucia A. Does exercise training during pregnancy affect gestational age? A randomised controlled trial. *Br J Sports Med* 2008;42(8):674–8. [PubMed: 18552370]
43. Perales M, Refoyo I, Coteron J, Bacchi M, Barakat R. Exercise during pregnancy attenuates prenatal depression: a randomized controlled trial. *Eval Health Prof* 2015;38(1):59–72. [PubMed: 24872442]
44. Ruiz JR, Perales M, Pelaez M, Lopez C, Lucia A, Barakat R. Supervised exercise-based intervention to prevent excessive gestational weight gain: a randomized controlled trial. *Mayo Clin Proc* 2013;88(12):1388–97. [PubMed: 24290112]
45. Czeizel AE. Ten years of experience in periconceptional care. *Eur J Obstet Gynecol Reprod Biol* 1999;84(1):43–9. [PubMed: 10413225]
46. Hussein N, Kai J, Qureshi N. The effects of preconception interventions on improving reproductive health and pregnancy outcomes in primary care: A systematic review. *Eur J Gen Pract* 2016;22(1): 42–52. [PubMed: 26610260]
47. Haas JS, Fuentes-Afflick E, Stewart AL, Jackson RA, Dean ML, Brawarsky P, Escobar GJ. Prepregnancy health status and the risk of preterm delivery. *Arch Pediatr Adolesc Med* 2005;159(1):58–63. [PubMed: 15630059]
48. Heyes T, Long S, Mathers N. Preconception care: practice and beliefs of primary care workers. *Fam Pract* 2004;21(1):22–7. [PubMed: 14760039]
49. Mazza D, Chapman A. Improving the uptake of preconception care and periconceptional folate supplementation: what do women think? *BMC Public Health* 2010;10:786. [PubMed: 21182797]
50. Weisman CS, Hillemeier MM, Downs DS, Feinberg ME, Chuang CH, Botti JJ, Dyer AM. Improving women's preconceptional health: long-term effects of the Strong Healthy Women behavior change intervention in the central Pennsylvania Women's Health Study. *Womens Health Issues* 2011;21(4):265–71. [PubMed: 21536455]
51. Hambidge KM, Krebs NF, Westcott JE, Garces A, Goudar SS, Kodkany BS, Pasha O, Tshetu A, Bose CL, Figueroa L, Goldenberg RL, Derman RJ, Friedman JE, Frank DN, McClure EM, Stolka K, Das A, Koso-Thomas M, Sundberg S, Preconception Trial G. Preconception maternal nutrition: a multi-site randomized controlled trial. *BMC Pregnancy Childbirth* 2014;14:111. [PubMed: 24650219]
52. Legro RS, Dodson WC, Kris-Etherton PM, Kunselman AR, Stetter CM, Williams NI, Gnatuk CL, Estes SJ, Fleming J, Allison KC, Sarwer DB, Coutifaris C, Dokras A. Randomized Controlled Trial of Preconception Interventions in Infertile Women With Polycystic Ovary Syndrome. *J Clin Endocrinol Metab* 2015;100(11):4048–58. [PubMed: 26401593]

Figure 1. Schematic for calculating incidence rate ratio of event (e.g., early preterm delivery) in the hour following exposure (e.g., moderate or heavy physical exertion) compared to other times using the usual frequency of exposure over the past week.

Figure 2.

Mean frequency of self-reported habitual physical activity per week by period relative to pregnancy among women with early preterm delivery (N=722) in Peru, 2013 – 2015.

Figure 3.

Rate ratio of early preterm delivery after episodes of moderate or heavy physical exertion compared to periods of light exertion or rest among women in Peru with early preterm delivery (N=722), 2013 – 2015. Each period before the onset of early preterm delivery was assessed as an independent hazard period and physical exertion during these periods was compared with that during the prior week. The error bars indicate 95 percent confidence limits and the dashed line indicates the baseline risk. The n indicates the number of women exposed within the hazard period.

Table 1.

Characteristics of women with early preterm delivery (N=722) in Peru, 2013 – 2015.

	Moderate or Heavy Physical Exertion in Past Week	
	Yes (N=335) n (%)	No (N=377) n (%)
Maternal age, y		
<20	24 (7.2)	36 (9.7)
20–24	93 (28.0)	87 (23.3)
25–29	77 (23.2)	81 (21.7)
30–34	68 (20.5)	77 (20.6)
35–39	48 (14.5)	64 (17.2)
40	22 (6.6)	28 (7.5)
Pre-pregnancy BMI (kg/m ²)		
Underweight (< 18.5)	6 (2.3)	6 (2.1)
Normal (18.5 – 24.9)	138 (53.1)	167 (57.8)
Overweight (25.0 – 29.9)	81 (31.2)	82 (28.4)
Obese (≥ 30.0)	35 (13.5)	34 (11.8)
Education		
Less than high school	35 (10.5)	20 (5.4)
High school	205 (61.4)	236 (63.4)
More than high school	94 (28.1)	116 (31.2)
Gravida ^a		
1	88 (27.0)	107 (28.7)
2	108 (33.1)	99 (26.5)
3	130 (39.9)	167 (44.8)
Parity ^a		
0	28 (8.6)	25 (6.7)
1	121 (37.1)	148 (39.7)
2	177 (54.3)	200 (53.6)
Substance use during pregnancy		
Cigarette	15 (4.5)	12 (3.2)
Alcohol	83 (24.8)	65 (17.3)
Cocaine	5 (1.5)	5 (1.3)
Marijuana	5 (1.5)	6 (1.6)
Terokal	6 (1.8)	8 (2.1)
Employed during pregnancy	177 (53.2)	206 (55.4)
Preeclampsia/eclampsia	23 (7.0)	30 (8.1)
Chorioamnionitis	51 (15.6)	62 (16.8)
Premature rupture of membranes (PROM)	172 (53.3)	199 (54.7)
Prior placental abruption	0 (0.0)	3 (0.8)
Chronic hypertension	8 (2.4)	10 (2.7)

	Moderate or Heavy Physical Exertion in Past Week	
	Yes (N=335)	No (N=377)
	n (%)	n (%)
Anemia ^b	123 (42.6)	153 (47.2)
Prenatal care	276 (82.6)	316 (84.5)
Prenatal vitamin use	221 (68.0)	268 (72.8)
Gestational age, mean weeks $\pm$ SD	29.7 $\pm$ 3.5	29.9 $\pm$ 3.5

BMI, body mass index

^aIncluding current pregnancy

^bHemoglobin <11 g/dL in 2nd or 3rd trimester

Frequencies may not add to column total due to missing data

Table 2.

Rate ratio of early preterm delivery in the hour following physical exertion among women with early preterm delivery (N=722) in Peru, 2013 – 2015.

Intensity of physical exertion in past hour	No. exposed in past hour	Rate Ratio (95% CI)	P-homogeneity
Moderate			
Habitual physical activity before pregnancy ^a			
> 3 times/week	8	1.56 (0.81 – 3.00)	0.003
3 times/week	7	6.91 (3.20 – 14.92)	
Heavy			
Habitual physical activity before pregnancy ^a			
> 3 times/week	16	17.12 (10.24 – 28.60)	0.003
3 times/week	10	75.91 (32.30 – 178.40)	
Moderate or heavy			
Etiology			
ePPROM	25	8.40 (5.60 – 12.61)	< 0.001
esPTD	14	3.55 (2.15 – 5.86)	
Maternal age			
< 35	31	5.82 (4.10 – 8.28)	1.000
35	10	5.82 (3.17 – 10.68)	

ePPROM, early preterm premature rupture of membranes

esPTD, early spontaneous preterm deliveries

^aHabitual physical activity is the average frequency of moderate and heavy episodes of physical