EXAMINING THE ASSOCIATION BETWEEN VIGOROUS PHYSICAL ACTIVITY AND PREGNANCY-RELATED OUTCOMES

By

Sifang Kathy Zhao

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Approved:

Digna Velez Edwards, PhD, MS

Katherine Hartmann, MD, PhD

Pingsheng Wu, PhD

Loren Lipworth, PhD

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LIST OF ABBREVIATIONS

BMI	Body mass index
CATI	Computer-assisted telephone interview
CI	Confidence interval
DAG	Directed acyclic graph
EGA	Estimated gestational age
FR	Fecundability ratio
FSH	Follicle stimulating hormone
GnRH	Gonadotropin-releasing hormone
HR	Hazard ratio
h/wk	Hours per week
IRB	Institutional review board
IVF	In vitro fertilization
IP(W)	Inverse probability (weights)
IQR	Interquartile range
LH	Luteinizing hormone
LMP	Last menstrual cycle
m	month
MET	Metabolic equivalent of task
min/wk	Minutes per week
NHANES	National Health and Nutrition Examination Survey
pdf	Probability density function
pdf	Probability mass function

RCS	Restricted cubic splines
RFTS	*Right from the Start*
SES	Socioeconomic status
TTP	Time to pregnancy
VPA	Vigorous physical activity
vs.	Versus

CHAPTER I

SPECIFIC AIMS

Little is known about the influence of vigorous physical activity (VPA) in pregnancy. Medical association guidelines specifically avoid giving recommendations on the optimal frequency or amount of vigorous activity for women planning or carrying a pregnancy.[1,2] Approximately 35% of women who were pregnant or planning pregnancies reported engaging in first-trimester VPA (defined as activities that cause large increases in breathing and heart rate) at least once per week based on recent work from our group.[3] While the national estimate of pregnant women engaging in VPA is unknown, close to 50% of women of reproductive age report engaging in *recreational* VPA (defined as activities with a duration of at least 10 minutes that cause heavy sweating or large increases in breathing or heart rate) at least once per week, according to the National Health and Nutrition Examination Survey (NHANES).[4] This proportion may be higher when including other potentially more common forms of exertion, such as occupational and household activities that can cause large increases in breathing and heart rate. Given how little we know and how many women of reproductive age engage in VPA, this work aim to better understand the influence of multiple modes of VPA on pregnancy outcomes including time to pregnancy (TTP) and miscarriage, and the infant outcome of birthweight.

This work studies the association between VPA and pregnancy-related outcomes in *Right from the Start* (RFTS), a community-based prospective cohort of pregnant women in North Carolina, Texas, and Tennessee (2000-2012).[5] Study participants were asked during their first trimester to report the type, frequency, and amount of each mode of VPA (recreational, occupational, indoor/outdoor household, child/adult care, or other activities) using structured recall items in a computer-assisted telephone interview (CATI). Among all enrolled participants (n=5,780), over 94% (n=5,457) reported their VPA status (any vs. none). Missing VPA status was primarily due to not completing the interview (n=301). Participants were also asked how many cycles they tried before conceiving. The timing of miscarriage and infant birthweight at delivery were obtained from participants and medical or vital records. Study participants also self-reported important covariates including sociodemographic, reproductive, behavioral, and lifestyle factors. The **overarching hypothesis** is that VPA prior to conception is associated with TTP and that VPA during the first trimester is associated with miscarriage and infant birthweight (Figure 1).

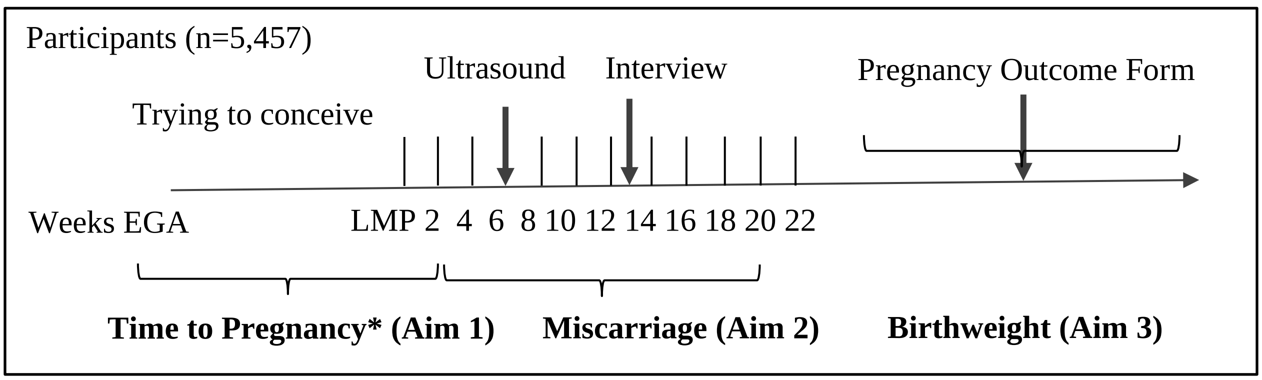

Figure 1. Flow chart of study events and pregnancy-related outcomes, RFTS, 2000-2012. *Abbreviations: EGA, estimated gestational age; LMP, last menstrual cycle. *VPA immediately prior to first trimester is approximated using first-trimester VPA measures reported during CATI*

Specific Aim 1: To assess whether VPA prior to conception, estimated using VPA during the first trimester, is associated with TTP, defined as number of cycles of trying before conception, among women who were pregnant. This work uses discrete-time proportional hazard models to estimate fecundability ratios (FR) and 95% confidence intervals (CI).

Specific Aim 2: To determine the association between VPA during the first trimester, combining all modes, and risk of miscarriage, defined as pregnancy loss prior to 20 weeks of gestation. This work uses inverse probability weighted marginal structural Cox models to compare risk of miscarriage among women engaging in different amounts of VPA, adjusting for candidate confounders.

Specific Aim 3: To evaluate whether frequency and amount of VPA during the first trimester are associated with infant birthweight. This work uses a linear regression to model birthweight, adjusting for gestational age and other candidate confounders using inverse probability weighting.

In summary, this work leverages a large well-established pregnancy cohort to investigate VPA and its relationship with important pregnancy-related outcomes. With detailed information on VPA for more than five thousand women, this is the largest cohort in the United States appropriate for examining the impact of VPA on TTP, miscarriage, and birthweight. These results advance understanding of physical exertion around conception and during pregnancy, which informs individual women and health care providers about the risks and benefits of engaging in VPA early in pregnancy. This research also has important public health implications since VPA is a readily modifiable risk factor. Individual behavioral changes in VPA on a population level could improve pregnancy and infant outcomes for all women planning or carrying pregnancies.

CHAPTER II

BACKGROUND

Limited guidelines on VPA

Pregnant women are advised to engage in moderate intensity physical activity for at least 20-30 minutes per day on most or all days of the week by the American College of Obstetricians and Gynecologists.[6] Similarly, the U.S. Department of Health and Human Services recommends 150 to 300 minutes a week of moderate intensity physical activity for healthy pregnant and postpartum women.[2] However, no guidelines are available on the optimal frequency or amount of VPA. The *2018 Physical Activity Guidelines Advisory Committee Scientific Report* specifically states that risks and benefits of VPA in pregnancy cannot be evaluated due to limited literature and stresses the need for future research on the safety and benefits of VPA before and during pregnancy on maternal and fetal outcomes.[7] The only mention of VPA in current guidelines is that pregnant women who habitually engage in VPA before pregnancy "can continue physical activity during pregnancy and the postpartum period."[2] This stand-alone comment provides no guidance on the optimal frequency or amount of VPA and excludes women who did not habitually engage in VPA before pregnancy.

Large proportion of women engaging in VPA

While current guidelines do not directly address the safety and benefits of VPA, they can be used to estimate the proportion of pregnant women engaged in VPA when combined with results from the NHANES. According to NHANES, 44% of women aged 18 to 24 years and 41% of women aged 25 to 44 years report engaging in VPA at least once a week, defined as recreational physical activities with a duration of at least 10 minutes that cause heavy sweating or large increases in breathing or heart rate.[4] NHANES also revealed that 25% of women aged 18-24 years and 24% of women aged 25-44 years report engaging in recreational VPA regularly, meaning at least three times per week for at least 20 minutes each episode.[4] Assuming women and health care providers are aware of the current guideline for the continuation of VPA in pregnancy for women habitually engaged in VPA, the number of pregnant women engaging in *recreational* VPA should be similar to that of women of reproductive age. This number may be underestimating the proportion of pregnant women engaging in all modes of VPA, meaning also including occupational, household, child/adult care, or other activities that cause large increases in breathing and heart rate. The proportion of women engaging in VPA during pregnancy is as high as 48% in the literature.[3,8,9]

Health benefits of physical activity

Physical activity is a protective factor against a range of chronic diseases including cardiovascular diseases and type 2 diabetes.[10-14] Physical activity is also associated with numerous health benefits by improving physiological, metabolic, and psychological function. Pregnant women benefit physiologically from physical activity similarly to non-pregnant women.[15] According to the 2018 Physical Activity Guidelines Advisory Committee, physical activity-related health benefits for pregnant women includes reduced risk of excessive weight gain and gestational diabetes.[7] In addition, physical activity can also help women adapt to anatomic and physiological changes in pregnancy (Table 1, page 6).

Table 1. Changes in pregnancy and benefits of physical activity in pregnancy

Anatomic/physiological changes in pregnancy	Types of physical activity	Benefits
Gestational weight gain	Aerobic exercise	Enhance cardiorespiratory function.[16] Avoid excessive gestational weight gain.[17]
Musculoskeletal discomfort (back pain/pelvic girdle pain)	Resistive exercise; strength training; weight-bearing	Improve musculoskeletal fitness.[18]
	Pelvic floor muscle exercises	Decrease short-term risk of urinary incontinence.[19]

Physical activity also improves body composition, which is shown to influence fecundability,[20] as well as avoiding sedentary lifestyle-related comorbidities, preeclampsia, cesarean delivery, and giving birth to a macrosomic infant.[7] Physical activity is also shown to reduce stress and anxiety and enhance psychological well-being.[21,22]

Similar to physical activity, VPA can reduce stress and anxiety leading to increased implantation as studies have shown fecundity is influenced by psychosocial, sociobiological, and physiological factors, including stress levels.[23,24] VPA can also benefit reproductive function through its ability to regulate energy balance and improve insulin sensitivity.[25]

The benefits of physical activity are essential for maintaining health and preventing diseases for all stages of life, including pregnancy. On a population level, physical activity can lead to lower healthcare cost and less burden to our healthcare system.[26] However, we must also consider the risks of physical activity in pregnancy, especially for VPA.

Risks of physical activity in pregnancy

One third of injuries in pregnancy have been attributed to physical activity with an estimated incident rate of 4.1 injuries per 1,000 physical activity hours.[27] Although anatomic and physiological changes in pregnancies are necessary to create an ideal environment for the development of the fetus, women become more vulnerable to physical injuries such as falling and are at higher risk of other adverse events (Table 2, page 8).

Maternal VPA could adversely influence fetal health and potentially result in pregnancy loss through multiple pathways including hyperthermia,[28] release of hormones stimulating uterine contractility,[29,30] and fetal hypoglycemia due to increased glucose uptake in working muscles.[31-33] However, some of these risks are unlikely. While VPA is associated with ketone generation, small degrees and brief levels of ketonuria are unlikely to result in measurable deficits in newborns.[34] Similarly, thermoregulation is enhanced during pregnancy due to increased circulation to skin, minute ventilation, and plasma volume, which makes it hard for the body to reach a teratogenic temperature and experience hyperthermia.[35] Additionally, studies have shown that a normal fetus compensates for transient reduction in uteroplacental blood flow, independent of gestational age and intensity, making fetal bradycardia unlikely.[36-41]

Table 2. Changes in pregnancy and potential adverse consequence of physical activity for mother and fetus

Anatomic/physiological changes in pregnancy	**Risk factors**	**Consequence for mother**	**Consequence for fetus**
Gestational weight gain; poor balance[27]	Falling due to physical activity	Abdominal trauma	Placental abruption and potentially fetal death and comorbidity
Ligament laxity; joints supported less effectively	Joint stress from bearing weight or jumping	Sprains, joint injuries	
Increased basal metabolic rate and heat production[28,42,43]	Hot yoga; hot Pilate; prolonged VPA in hot conditions	Dehydration; hyperthermia (maternal body core temperature >102.2F)	Neural tube defect
Blood glucose levels decrease at faster rate[31-33]	VPA; >45 minutes of moderate physical activity	Reach hypoglycemic levels (<70 mg/dL or 3.9 mmol/L)	Miscarriage
Negative caloric balance[34]	VPA	Ketonuria	Deficits in newborns
Provide nutrition through uteroplacental blood flow[8,9,29,30,36,44]	VPA	Decreased uterine artery blood flow; increased blood pressure; increased intra-abdominal pressure; elevated catecholamines	Fetal hypoxemia; vagal stimulation; fetal bradycardia; miscarriage
		Increased uterine contraction	Preterm birth
		Reduced DNA methylation	Low birthweight

Measuring physical activity

The multiple hormonal, physiological, and biomechanical changes induced by pregnancy make objective measurement of the intensity of physical activity difficult. Some physicians use 90 percent of maximum age-predicted heart rate as the safety cutoff for intensity.[45] While this method is often used by athletes for training purposes, it may not be the best way to characterize intensity among pregnant women. Some physicians use the metabolic equivalent of task (MET), based on the Compendium of Physical Activity, to monitor intensity for prescribed exercises (moderate intensity has MET of 3 to 4 and VPA has MET greater than 6).[46] Using activity-based MET developed in non-pregnant populations to estimate energy expenditure in pregnant women can result in significant over- or underestimation, depending on the activity.[47]

An alternative method to measure intensity is the talk test. Inability to carry on normal conversations easily indicates vigorous intensity. Accelerometers can also be used to measure intensity.[8] While some researchers believe accelerometers are more objective, accelerometers only capture certain movements. This method is also challenged by compliance and unvalidated cutoffs. In a recent study where women planning pregnancies were given accelerometers, almost none engaged in VPA based on *a priori* criteria (counts per second) and thus the impact of VPA on implantation could not be determined.[48]

Perceived exertion may be a more effective and practical indicator of physical activity intensity during pregnancy than heart rate parameters or estimated absolute energy requirements of specific activities.[6,49] To measure perceived exertion, the Borg scale of perceived exertion (ranges from 6 to 20) is often used by clinicians for exercise prescription.[50] A score of 13 to 14 (somewhat hard) indicates moderate intensity and 15 to 20 (hard or very hard) indicates vigorous intensity.[50] The scale is constructed to increase linearly with intensity, which only holds if oxygen consumption and heart rate increase linearly with work load. In addition, the Borg scale is shown to be associated with substantial increase in heart rate and oxygen uptake,[50] making it a valuable and widely-used method to gauge intensity.

Physiology of VPA

While moderate physical activity is beneficial for pregnant women, the effect of VPA is unclear. When energy demand exceeds dietary energy intake, a negative energy balance may occur and lead to hypothalamic dysfunction.[25] Specifically, VPA may disrupt normal endocrine function through increasing the follicular phase and thus increasing total menstrual cycle length, which in turn may cause disruption of normal endocrine function and ovulation.[51] Among women engaged in prolonged VPA for (>60min/day), VPA may result in anovulatory cycles.[52] Both prolonged cycles and anovulatory cycles increase TTP (Aim 1). The mechanism by which VPA disrupts ovulation in women with normal and low body mass index (BMI) via energy deficiency is summarized below (Figure 2, page 11).[52] For women with high BMI, moderate physical activity may improve insulin sensitivity and restore ovulation, but this may not be true for VPA.[53]

In addition to disrupting ovulation, biologic evidence suggests physical activity affects implantation and endometrial receptivity.[48] During implantation, glycodelin and insulin-like growth factor-binding protein 1 facilitate adhesion at the maternal-embryo interface.[54,55] The level of these molecules decreases in the absence of moderate activity as moderate activity can increase insulin sensitivity and reduce carbohydrate-induced hyperinsulinemia.[53] We do not know if the above mechanism holds for VPA. On the other hand, VPA lowers leptin levels, which may promote blastocyst adhesion and blastocyst outgrowth on fibronectin and stimulate trophoblast invasion.[56,57] Although the direction of influence is unclear and the effects may vary based on maternal body habitus, VPA may affect the quality of implantation and endometrial receptivity, thus potentially affecting the risk of miscarriage (Aim 2).

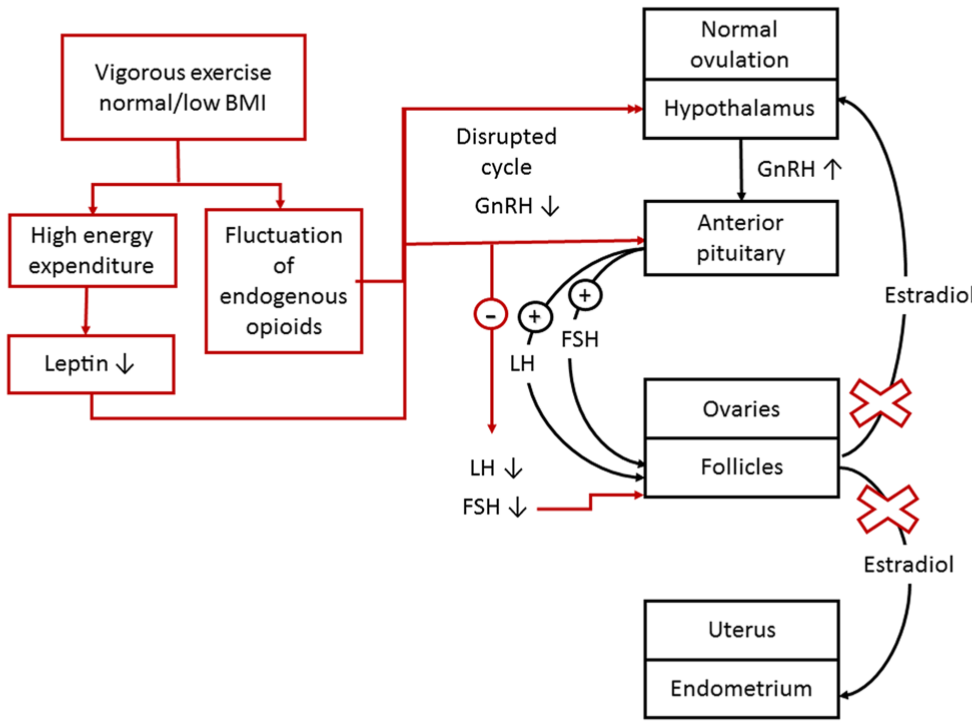

Figure 2. Proposed mechanism of disrupted ovulation by VPA

Adapted from Hakimi, 2017. Abbreviations: GnRH, gonadotropin-releasing hormone; FSH, follicle stimulating hormone; LH, luteinizing hormone. The arrows indicate direction of change in hormone levels.

Whether VPA is beneficial for the fetus is also unknown. As an important indicator of fetal health, fetal heart rate during VPA has been widely studied. One study found VPA was associated with a 10-30 beat/minute increase in fetal heart rate that resolved within 20 minutes after cessation of VPA (gestational age 25.2±3.0 weeks).[36] Authors hypothesized that increase in fetal heart rate is in response to transient decrease in uteroplacental blood flow and transplacental passage of maternal catecholamines, which increase blood flow and facilitate exchange of respiratory gasses across the placenta. Monitoring of fetal heart rate electronically can be obscured by artifacts. In a study where internal scalp electrodes were applied to the fetus, researchers found 60% maximum aerobic capacity during labor is safe. Another study indicated that 90% maximum heart rate between 23 to 29 weeks gestation resulted in a 50% reduction in mean uterine artery blood flow and led to fetal bradycardia. While the temporary reduction is large, fetal heart rate and umbilical artery Doppler index normalized quickly after cessation of VPA.[58]

VPA may also potentially influence infant birthweight (Aim3) through several mechanisms. For example, VPA can enhance placental growth and vascularity in healthy pregnant women leading to higher birthweight,[59,60] decrease birthweight through suboptimal perfusion,[9] increase the probability of having normal- vs. high-birthweight infants by mediating maternal weight gain and energy excess.

Time to pregnancy

TTP, or the number of menstrual cycles of trying before achieving pregnancy, is a measure of reproductive fitness.[61] Couples planning pregnancies and their health care providers are often focused on this time interval, especially in the context of difficulty conceiving. Women with lean body composition and irregular cycles may have trouble to conceive. Thus, knowledge about the effect of VPA on TTP is critical. Similarly, this knowledge can benefit women with a history of pregnancy loss since TTP following a loss may be longer compared with TTP before a loss.[62] Factors associated with TTP include opportunity to conceive such as timing and frequency of unprotected intercourse, overall health such as body weight and medical conditions, semen quality, and ovulatory quality as influenced by factors such as age, toxic exposures, and endocrine disorders.[63] The influence of lifestyle factors such as nutrition and VPA on TTP is less clear.

While multiple studies have suggested that competitive female athletes have increased risks of oligomenorrhea and amenorrhea and thus delayed TTP,[64-67] few studies evaluated the association between VPA and TTP in the general population.[68,69] Two prospective cohorts recruited women online prior to conception and relied on self-reported measures of physical activity and TTP. Physical activity levels were based on hour/week of VPA reported. The first study observed an inverse association between VPA and fecundability (≥5 hour/week vs. none: FR=0.68; 95% CI: 0.54, 0.85).[68] This agrees with an earlier study that found VPA can reversibly induce menstrual disorders in women, especially if compounded by weight loss.[70] The second prospective cohort study found no association between VPA and fecundability (≥5 vs. <1 hour/week: FR=1.11; 95% CI: 0.96, 1.28).[69] Similarly, a fertility study found time spent in VPA and total MET hours before in vitro fertilization (IVF) were not associated with probability of implantation, clinical pregnancy, or live birth.[71] Another IVF study showed that women who had successful implantation had significantly higher levels of self-reported physical activity combining multiple modes during the year before pregnancy than women who had unsuccessful implantations.[48]

Miscarriage

Miscarriage is defined as the loss of a clinically recognized pregnancy in the first 20 weeks after last menstrual period (LMP).[68] Among six studies that evaluated the association between physical activity during pregnancy and miscarriage,[72-77] only four had information on intensity or type of physical activity.[74-77] Among these studies, two suggested a protective effect from VPA,[74,75] while two found no association between VPA and miscarriage.[75,76] This inconsistency could be a result of incomplete evaluation of exposure; only one study evaluated multiple modes (recreational, occupational, outdoor/indoor household, child/adult care, or other activities) of VPA.[75] Additionally, no study controlled for potential confounding by nausea and vomiting. Since nausea is less common in pregnancies that end in miscarriage and is a common reason for women to stop or decrease being active during pregnancy, not adjusting for nausea and vomiting may result in potential bias.[78]

Birthweight

While some researchers report VPA is associated with having heavier infants,[59] some find VPA is associated with decreased birthweight, [8,9,51,60,79,91] other researchers observe no difference in mean birthweight between women engaging in VPA and those with no physical activity.[44,80] A meta-analysis of *moderate* physical activity with frequency ranging from 1 to 5 times per week, time per session ranging from 15 to 70 minutes, and duration ranging from 6 to 33 weeks of gestation, suggested no negative effect on fetal growth.[81] Whether more intense, frequent, prolonged sessions impair fetal growth is unknown. As a result of the small number of studies focusing on VPA, authors of another recent meta-analysis noted that they could not evaluate separate effects of moderate and vigorous intensity activities on birthweight.[82]

Challenges in current literature

The literature about the influence of VPA on pregnancy-related outcome is scant (Appendix 2). Selected study characteristics are summarized in Table 3 (page 17).

A major challenge in studying VPA in pregnancy is comparing across varied exposure definitions. For example, some studies defined VPA based on the type of activity,[68,69,71,83] some omitted their definition,[72,80] or used pre-determined cutoff points,[8,44,82] and some defined VPA based on the type of occupation (Table 3).[84] In addition, researches adopted different operational definitions of VPA. Traditionally, researchers focused on physical activity in bouts of at least 10 minutes in duration per guideline.[2] A recent study with accelerometer-based measures of physical activity and mortality outcome suggests that cumulative minutes per week of physical activity is associated with mortality benefits, regardless of length of individual bouts such as 10 minutes or 5 minutes, which are arbitrary.[85]

The literature also lacks community-recruited cohort studies; results from fertility clinic-based studies may not be generalizable to pregnant women in the general population.[48,71] Another challenge is residual confounding due to incomplete data on important covariates known to have potential to confound associations, such as race/ethnicity.[44,72] Race/ethnicity may distort the relationship between VPA and pregnancy-related outcomes since race is associated with pregnancy outcomes and may influence VPA through pathways such as the level of health consciousness.

Modes of VPA

In early studies of physical activity, researchers focused on physical exertion in recreational physical activity. In the 1980s, researchers began studying the subdivision of physical activity.[86,87] Using principle component analysis, researchers distinguished different modes of physical activity and found education, subjective experience of work load, and lean body mass varied by mode (occupational, recreational, and other physical activity).[87]

Researchers that only examined occupational physical activity found the effect of occupational VPA on lowering women's fecundability varied by working hours (day vs. night shift),[86] indicating the associations between pregnancy-related outcomes with recreational and occupational activities may be different and could be modified by circadian rhythms, sleep quality, and other factors.

Table 3. Summary of study characteristics of selected articles (2 per aim)

Author, year Setting, N	VPA Definition	Assessment Method/ Exposed Window	Outcome/ Comparator	Adjusted Estimate (95% CI) / Confounders
Wise, 2012[68] Denmark, 3,628	Running, fast cycling, aerobics, gymnastics, swimming	Self-reported online/ 6m prior to pregnancy	TTP/ No VPA	FR: 0.88 (0.77, 1.01) for <1 h/wk; 0.68 (0.54, 0.85) for 5+ h/wk / Cycle number, maternal/paternal age, BMI, alcohol, smoking, intercourse frequency, last method of contraception
McKinnon, 2016[69] North America, 2,062	Biking, jogging, swimming, racquetball, aerobic activities, weight/ resistance training	Self-reported online/ prior to pregnancy	TTP/ <1 h/wk VPA	FR: 1.04 (0.91, 1.20) 1-2 h/wk; 1.11 (0.96, 1.28) for 5+ h/wk / Age, parity, intercourse frequency, education, race, income, marital status, last method of contraception, alcohol, smoking, paternal BMI
Clapp, 1989[72] USA, 119	Undefined	Electrocardiogram/ 2m before pregnancy & during pregnancy	Miscarriage/ No exercise before pregnancy	Runners vs. aerobic dancers vs. controls: 8/49 vs. 7/39 vs. 7/28 (p>0.05)/ No adjustments
Madsen, 2008[83] Denmark, 92,671	Jogging, ball games, racket sports	Computer-assisted telephone interview/ 1st trimester	Miscarriage/ No exercise	HR: 3.6 (2.5, 5.2) for <11 wk; 4.2 (3.4, 5.2) for 11-14 wk; 2.1 (1.2, 3.5) for 15-18 wk; 1.2 (0.5,3.0) for 19-22 wk / Age, previous miscarriage, previous births
Sternfeld, 1995[44] USA, 388	>3 times/wk for >60 min/wk	In-person or phone interview/ 1st, 2nd, 3rd trimester	Birthweight/ No PA	Beta coefficient: -53g (-220, 114) / Gestational age, parity, BMI, infant sex
Bisson, 2017[8] Canada, 104	Mathews & Freedson cut points	Accelerometer/ At 17wk	Birthweight/ No VPA	Beta coefficient: -178g for 17wk (p=0.04) / Infant sex, gestational age, race, BMI, smoking, parity, daily energy intake & energy expenditure prior to pregnancy

Abbreviations: FR, fecundability ratio; HR, hazard ratio; h/wk, hour per week; m, month; BMI, body mass index; CI, confidence interval.

Most of the literature about physical activity during pregnancy measures recreational activity, neglecting other potentially more common forms of exertion, such as indoor/outdoor household activities.[69,71,72,88] Two studies collected occupational activities, in addition to recreational activities.[74,89] Only two studies collected data on multiple modes of physical activity (one included recreational, occupational, indoor household, and child care activities;[75] the other included household/caregiving, occupational, active living, and sports/exercise).[48] Their sample sizes of 346 and 141, respectively, were insufficient to evaluate the influence of VPA characteristics such as frequency, mode, or cumulative amount. Compared to previous studies, this work provides a more complete picture of the effect of VPA on pregnancy-related outcomes by assessing VPA combining all modes.

Clinical relevance and public health impact

VPA is a modifiable yet common exposure linked to pregnancy-related outcomes. The safety and benefits of VPA are not well-studied, leading some health care providers to discourage VPA in pregnancy. This work provides valuable information on the maximal threshold amount for safety for substantial numbers of women engaging in VPA regularly before pregnancy and those who may want to continue throughout pregnancy.

Results from this large observational analysis will also help determine whether frequency or amount of VPA combining multiple modes affect maternal and fetal outcomes, specifically for TTP, miscarriage, and birthweight. This work informs guideline developers, empowers women planning or carrying pregnancies, and raises public awareness on VPA that can promote behavioral changes and help avoid many current and future health problems and costs.

CHAPTER III.

VIGOROUS PHYSICAL ACTIVITY AND TIME TO PREGNANCY

Abstract

Background: VPA could influence TTP through modulating normal endocrine function and ovulation. The literature focusing primarily on recreational physical activity is incomplete in assessment of the relationship, ignoring all other modes of VPA such as outdoor/indoor household activities. I assessed whether cumulative VPA is associated with TTP among pregnant women who self-reported multiple modes of VPA.

Methods: *Right from the Start* (2000-2012) is a prospective cohort that enrolled women from the Southern US in early pregnancy. Frequency and amount of VPA and TTP were self-reported during first-trimester interviews. FRs and 95% CIs were estimated using discrete-time proportional hazards model adjusting for *a priori* confounders. Models with and without interaction between VPA and BMI were compared using likelihood ratio tests.

Results: Among 3,678 women intending to conceive, 35% (n=1,302) reported engaging in some form of VPA (recreational, occupational, outdoor/indoor household, child/adult care, or other activities) and 30% (n=1,095) achieved pregnancy during the first cycle of trying. Overall, engaging in any VPA was not associated with TTP (FR=1.02; 95% CI: 0.95, 1.10). Within BMI categories, neither amount nor frequency was associated with the probability of getting pregnant.

Conclusions: Neither the amount nor frequency of cumulative VPA substantively influenced TTP, regardless of women's BMI. This suggests women may continue levels of activity that are

vigorous and support general health and disease prevention while planning to conceive. Future studies may benefit from measuring VPA as a time-varying covariate.

Overview

VPA, in combination with nutritional and psychological factors, influences hypothalamic and pituitary function and consequently reproductive performance.[90] Current guidelines provide no definitive recommendation on the frequency or amount of physical activity for women attempting pregnancy. Combined with the lack of guidelines for VPA during pregnancy and relative lack of evidence, many health care providers and women planning for a pregnancy may be confused about the optimal VPA amount to minimize TTP. Research on the influence of cumulative VPA across various forms of physical activity in women of reproductive age is needed.

The objective of the study is to comprehensively evaluate the effect of VPA on TTP by assessing multiple modes of VPA that make up daily life, including recreational, occupational, indoor/outdoor household, child/adult care, or other activities, in a community-recruited pregnancy cohort.

Study population

This work used data from RFTS, a community-recruited cohort focused on better understanding early pregnancy health that enrolled over five thousand women from eight communities across the Southern United States from 2000 to 2012.[91] Women who were pregnant or trying to become pregnant, 18 years or older, spoke English, planned to carry to term, and did not use assisted reproductive technologies were eligible. Advertisement and community outreach efforts targeted women in their first trimester who were planning a pregnancy. Women planning to conceive, approximately 20% of the study population, received home pregnancy tests to aid early detection of pregnancy and were officially enrolled in the study after a first positive test.

All participants were asked to complete a brief intake interview during enrollment, a transvaginal research ultrasound with a target time of six weeks' gestation, a CATI with a target time of 13 weeks' gestation, and a pregnancy outcome form at the time of loss, live birth, or other pregnancy outcomes.

Population selection

To maintain independence between observations, this work only included information from the first study pregnancy if women participated in RFTS for more than one pregnancy (325 subsequent pregnancies were excluded). Among 5,780 enrolled participants, I also excluded women with unintended pregnancies (n=1,810) and those with no reported TTP (n=290) or VPA stats (n=2, Figure 3, page 22). Unintended pregnancies are excluded because they cannot contribute any cycles of trying to the analysis (see TTP definition, page 25). The resulting population of 3,678 women had uniform assessment of VPA from CATI during the first trimester. This study was approved by the Institutional Review Board (IRB) of Vanderbilt University Medical Center (070037).

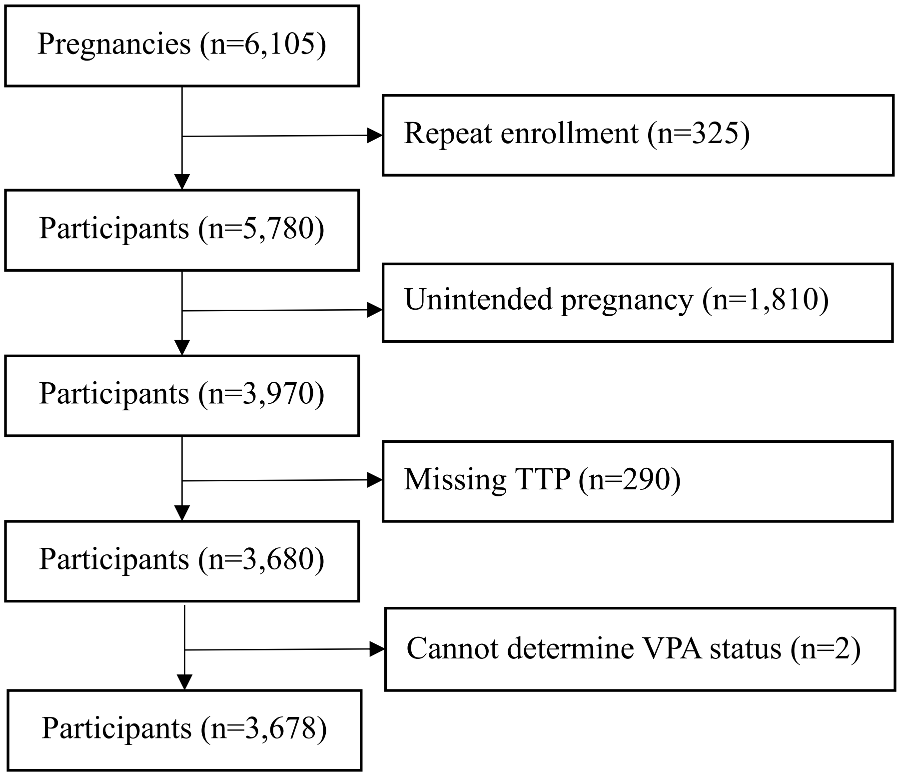

Figure 3. Flow chart of study subject exclusion criteria.

Abbreviations: TTP, time to pregnancy; VPA, vigorous physical activity.

Exposure assessment

Based on the Borg scale of perceived exertion, VPA was defined as any activity that women "feel hard or very hard, causing large increases in breathing and heart rate". Specifically, women were asked during the first trimester CATI if they currently engage in any of the following modes of VPA: recreational, occupational, outdoor/indoor household, child/adult care, or other activities. For each mode of physical activity, women could report the type, frequency (times/week), and amount (minutes/week) for up to three activities (Figure 4, page 23). Specific questions can be found in Appendix 1 (page 62).

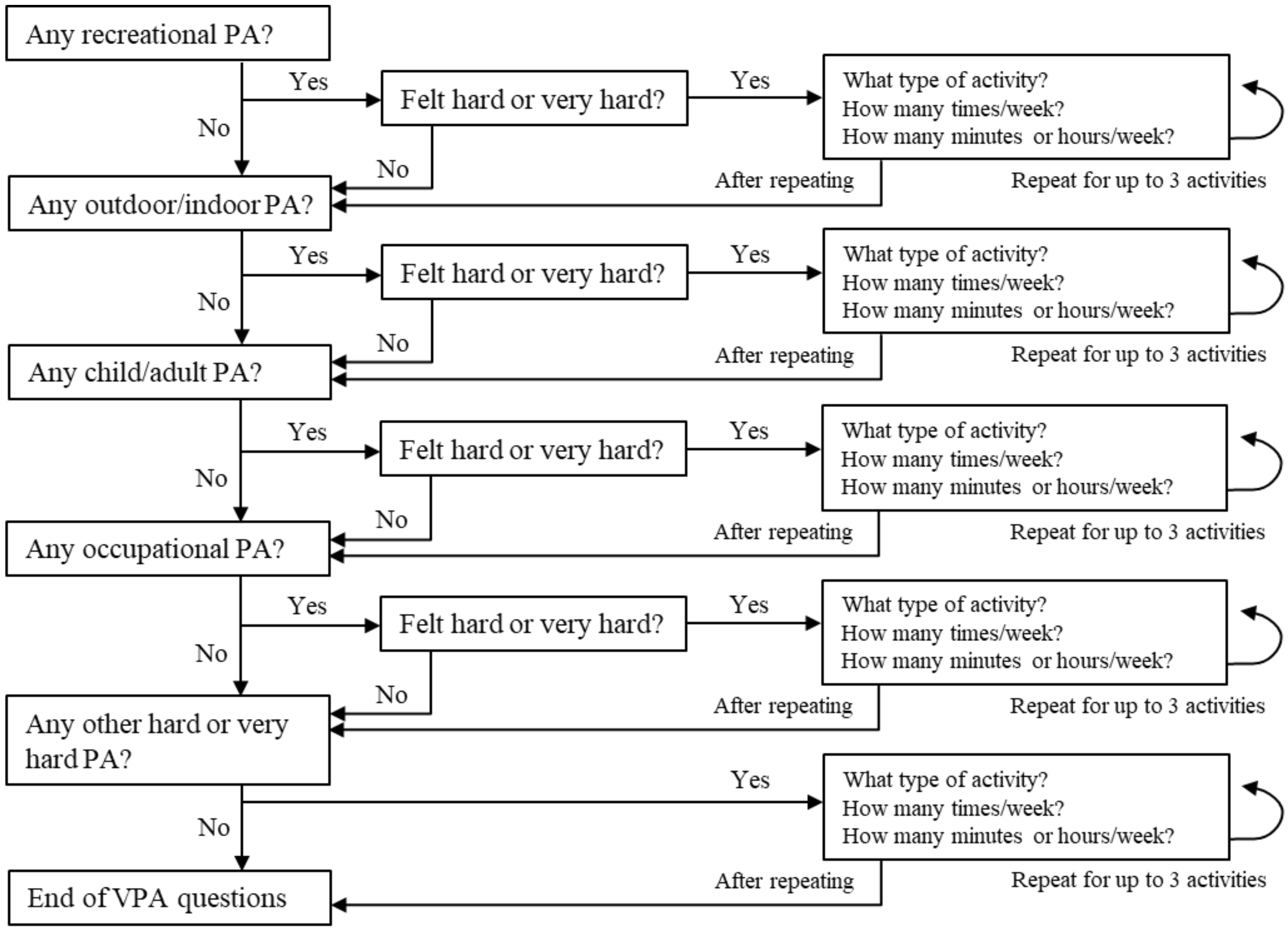

Figure 4. Structure recall for assessing VPA, RFTS, 2000-2012

Abbreviation: PA, physical activity

Short descriptions with examples of each mode of VPA were provided to help women recall and categorize activities engaged in (Table 4, page 24).

The frequency (times/week) for each activity was summed to obtain the total times per week of each mode of VPA and then summed across modes to obtain the total frequency of VPA engaged in. Similarly, the total amount of VPA can be calculated as the sum of minutes per week of each activity across modes. Cumulative frequency and amount of VPA were winsorized respectively at the 99th percentile to limit extreme values and reduce the effect of possibly spurious outliers.

Current guidelines only provide recommendations on the amount of VPA per week. I chose to examine both frequency and amount of VPA because they reflect different aspects of VPA patterns. A recent study found that cumulative amount of physical activity is associated with lower mortality, regardless of how the activity is accumulated.[85] Whether the association between cumulative amount of VPA and pregnancy-related outcomes is independent of frequency deserves exploration. If an optimal amount of VPA is identified, whether to perform either single long or multiple shorter bouts of activity would be informative.

Table 4. Modes of physical activity queried, RFTS, 2000-2012

Modes	Examples
Recreational activity	Brisk walking, jogging, swimming, biking, tennis, soccer, dancing
Occupational activity	Lifting or carrying heavy objects
Indoor/outdoor household activity	Working in the yard or mopping or vacuuming
Child/adult care activity	Playing with children, pushing a stroller/wheelchair, carrying/lifting a child/adult
Other activity	Any other activity that meets the definition (activities that "felt hard or very hard, meaning that the activity caused large increases in breathing and heart rate")

Out of 13 sections in the interview, VPA assessment was nested in the third section. Questionnaire fatigue was unlikely to occur early. VPA assessment followed questions about caffeine and fish consumption and proceeded questions about hobbies/exposure to toxins, tobacco use, and alcohol/drug consumption. VPA questions were phrased in a neutral way, without notions implying benefits or harm (Appendix 1, page 62). Women were not prompted to perceive VPA as risk or benefit; hence, social desirability bias is of minimal concern.

Outcome assessment

TTP is defined as the number of menstrual cycles of trying before achieving pregnancy.[61] During the first-trimester telephone interview, women with intended pregnancies were asked if they became pregnant during the 1st, 2nd, or 3rd cycle of trying. If a woman did not become pregnant within the first three cycles of trying, she was asked to estimate the number of cycles of unprotected intercourse before she became pregnant.

For women who could not recall the number of cycles but reported how many months or years of trying, their TTP was adjusted based on their self-reported cycle length (defined as the first day of bleeding in one period to the first day of bleeding in the next period). In this analysis, the average cycle length was 28 days with interquartile range from 28 to 30. If a woman reported trying 4 months before becoming pregnant and her cycle length was 25 days, her TTP was calculated as 4*(365.25/12)/25=4.87 cycles. Adjusting for cycle length often led to a fractional number of cycles; I rounded the number of cycles down to the nearest integer since ovulation and TTP are inherently discrete measures. Cycles beyond 11 months were censored.

Covariates

Information on key covariates including sociodemographic characteristics, reproductive history, and behavioral and lifestyle factors was collected using CATI. Domains represented are listed below (

Table 5, page 26). Details of variable construction, as required, is provided in Appendix 3 (Table 20, page 84).

Table 5. Key covariates and their operationalization

Covariates	**Operationalization**
Maternal age	Continuous, years
Maternal race/ethnicity	Non-Hispanic white, non-Hispanic black, Hispanic, other
Maternal BMI*	Continuous, kg/m^2
Maternal education level	High school or less, some college, and college or more
Marital status	Married, other
Household income	≤$40,000; $40,001-80,000; ≥$80,001
Parity	Nulliparous, 1, ≥2
Frequency of intercourse	0-1, 2, 3, >4 times/week
Maternal smoking status	Never, distant quit (>4 months), current or recent quit (≤4 months)
Maternal alcohol use	Never, distant quit (>4 months), current or recent quit (≤4 months)
Prior miscarriage	0, 1, ≥2
Menstrual cycle regularity	Regular, irregular (having >2 months without a cycle since ceasing hormonal contraceptives or having >2 months without a cycle in the past 12 months while using non-hormonal contraceptives)
Maternal caffeine intake	None, any
Maternal vitamin use	None, any
Maternal folic acid use	None, any

** Maternal BMI was calculated using standardized measures of height and weight obtained at the first-trimester ultrasound visits. If unavailable, self-reported height and weight was used.*

Distribution of self-reported BMI was compared to that of measured BMI to ensure consistency. The two distributions did not differ significantly.

To better understand the relationships among covariates with exposure and outcome, the following directed acyclic graph (DAG) was constructed.[92] Assuming correct specification, adjusting for maternal age, race/ethnicity, BMI, education level, alcohol use, smoking status, household income, and intercourse frequency are sufficient to address confounding in the association of VPA and TTP (Figure 5).

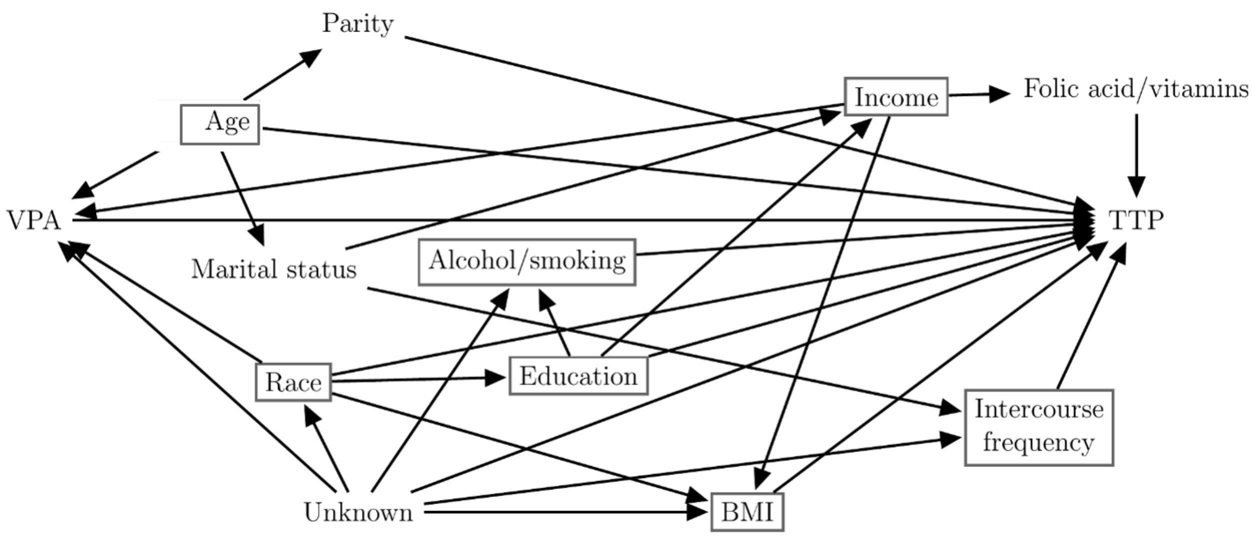

Figure 5. DAG representing the relationship among covariates with VPA and TTP
Abbreviations: TTP, time to pregnancy; VPA, vigorous physical activity; BMI, body mass index. Boxed covariates are a priori confounders adjusted for in models.

Missing data

The proportion of missing data is presented below (Table 6). Menstrual cycle regularity is the only covariate missing more than 5%. It did not enter models and was only used to conduct sensitivity analysis. Given low amounts of missing for all other covariates, the potential impact of multiple imputation would be minimal. Thus, I conducted complete case analyses.

Table 6. Proportion of missing data for key covariates

Covariates	Aim 1 (N=3,678)	
	n	%
Maternal age	0	0
Maternal race/ethnicity	0	0
Maternal BMI	33	0.9
Maternal education level	0	0
Marital status	0	0
Household income	75	2.0
Parity	27	0.7
Frequency of intercourse	24	0.7
Maternal smoking status	1	<0.1
Maternal alcohol use	0	0
Prior miscarriage	27	0.7
Menstrual cycle regularity	248	6.7
Maternal caffeine intake	0	0
Maternal vitamin use	5	0.1
Maternal folic acid use	22	0.6

Abbreviation: BMI, body mass index.

Analysis

Univariate and bivariate analyses

For direct comparisons of continuous measures between two groups, unpaired t-test was used for normally distributed measures and the Wilcoxon rank-sum test was used for non-parametric measures. For comparisons of categorical measures, the Pearson chi-squared test was used (Table 8, page 34).

Outliers and influence points

Outliers and influence points for all variables were assessed. The distribution of VPA frequency, as well as the text description for frequencies greater than 99^{th} percentile, was inspected. Extreme observations that are not logically possible were recoded to missing; extreme observations that are logically possible were transformed to reduce the influence of the outlier. Similar inspection was conducted for VPA amount. Consistency validations were conducted between related variables. This included checking if minutes of VPA is only reported for women engaging in VPA.

Statistical model

To estimate the association between VPA and TTP, a discrete-time proportional hazard model was used to estimate FR, 95% CI, and predicted probabilities. I tested if the proportional hazard assumption was violated by plotting the log-log survivor function for women engaging in any VPA vs. none, where parallel log-log survivor curves indicated proportional hazards. Stratified proportional hazard models were not necessary since the proportional hazard assumption holds; only one proportional hazard model and one set of coefficients are presented. Survival time was defined as cycles of trying prior to LMP.

VPA frequency (times/week) was analyzed in two ways. First, I allowed for the possibility of a non-linear relation between total frequency of VPA and TTP by using a restricted cubic spline (RCS) fitting approach. For large sample sizes, the placement of knots are not as important as the number of knots; I chose to place knots at the recommended 5^{th}, 27.5^{th}, 50^{th}, 75.5^{th}, and 95^{th} percentiles (Figure 7, page 37).[93] Modelling VPA frequency continuously is the most flexible method with the least assumptions and the most power. Modelling VPA frequency as a categorical variable (quantiles) may increase interpretability when comparing women participating in the highest category of VPA frequency to those in the lowest category. This would inevitably decrease the power to detect a difference if it exists. VPA amount (minutes/week) was analyzed in a similar fashion, both as a continuous variable and a categorical variable (Table 9, page 36). When examining the effect of VPA frequency, I also adjusted for VPA amount (continuous) since women with the same frequency yet different VPA amount may have different biological responses. I also adjusted for VPA frequency (continuous) when examining the effect of VPA amount.

VPA was also analyzed as a dichotomous variable (any vs. none), assuming women who engage in VPA have different TTP from those who do not. Dichotomizing VPA leaves out important information but remains the most common method in the literature; dichotomizing VPA allows my results to be more comparable to other studies.

As a secondary analysis, I also stratified the association between VPA frequency and TTP by VPA mode. The same was conducted for the association between VPA amount and TTP. These stratified analyses compare the effect of VPA among different modes.

Confounding

Maternal age, race/ethnicity, BMI, education level, alcohol use, smoking status, household income, and intercourse frequency entered all adjusted models as *a priori* confounders based on DAG and the literature (Figure 5, page 27). Among *a priori* confounders, age and BMI were modelled using RCS with knots placed at 5^{th}, 27.5^{th}, 50^{th}, 75.5^{th}, and 95^{th} percentiles.

Effect measure modification

Women's BMI might affect the association between VPA and TTP. Biological evidence supports that BMI may play an important role in the relationship between VPA and TTP as obesity is found to delay TTP for women with regular menstrual cycles.[24] I test if BMI interacts with frequency or amount of VPA using likelihood ratio tests by comparing models with and without interaction terms. I also stratified by BMI category since lean vs. normal vs. obese women may have a biologically different response to VPA.[52]

Sensitivity analysis

Several sensitivity analyses were conducted. The first sensitivity analysis addresses concerns about VPA status during first trimester not representing VPA status prior to pregnancy. I used self-reported data on the change in overall typical VPA since becoming pregnant to estimate VPA status prior to pregnancy (see Appendix 1 for exact questions, page 64). For women who were participating in VPA in the first trimester and reported their VPA decreased or stayed the same after getting pregnant, I can infer they were engaged in VPA prior to pregnancy. I excluded women for whom I cannot infer VPA status prior to pregnancy (n= 1,359, see Table 7, page 32). Women who reported increasing (n=63) or decreasing (n=776) VPA after getting pregnant were only included when VPA is modelled as a dichotomized variable since data on their VPA measures (frequency and amount) was not collected prior to pregnancy.

Table 7. VPA status prior to pregnancy based on self-reported change in VPA during first trimester

First-trimester VPA	Change in VPA	VPA prior to pregnancy	N (%)
Yes	Increased	Unknown	46 (1.3)
Yes	Decreased	Yes	776 (21.1)
Yes	Stayed the same	Yes	480 (13.1)
None	Increased	None	63 (1.7)
None	Decreased	Unknown	1,313 (35.7)
None	Stayed the same	None	1,000 (27.2)

Secondly, I repeated the analysis excluding women who engaged in no physical activity across modes. Women reporting no physical activity at all may have different preexisting medical conditions from women reporting non-VPA, which prevents them from engaging in any physical activity, vigorous or not. Only 2% of women reported no physical activity across all mode of physical activity but combining them with women engaging in non-VPA may introduce bias.

Since TTP for women with irregular cycles could be less accurate, I repeated the analysis excluding women reporting irregular periods, defined as having more than two months without a cycle since they stopped using hormonal contraceptives or having more than two months without a cycle in the past 12 months while using non-hormonal contraceptives. Lastly, I restricted the analysis to women who were interested in participating in the study before achieving pregnancy. Women planning a pregnancy received home pregnancy tests to aid early detection of pregnancy and may have more accurate self-reported measures of VPA and TTP.

All statistical analyses were conducted at a 2-sided significance level of 0.05 using Stata 14.2 (StataCorp, Texas, United States).[94] Code is available on request.

Power calculation

Since the discrete-time proportional hazard model is a discrete analogue of the Cox proportional hazards model,[95] HRs are used for convenience in power estimation. Assuming the median TTP among participants engaging in non-VPA is 2 cycles, this analysis has 90% power to detect a true HR less than 0.89 or greater than 1.12 among participants engaging in VPA (n=1, 302) and those who do not (n=2,376) at alpha=0.05 (Figure 6).[96]

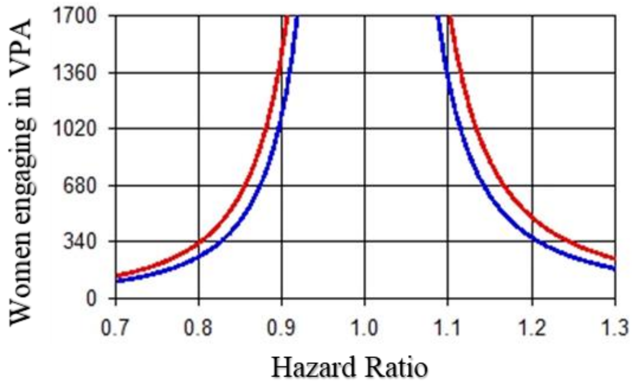

Figure 6. Power curve for test of median TTP

**Upper curve (red) represents 90% power, lower curve (blue) represents 80% power.*

Results

Among 3,678 women, 1,302 (35%) reported engaging in some mode of VPA. The most common mode of VPA was recreational VPA (n=713; 19%), followed by indoor/outdoor household activities (n=307; 9%), child/adult care activities (n=326; 9%), other activities (n=180; 5%), and occupational activities (n=102; 3%). I compared maternal characteristics among women engaging in any VPA vs. none (Table 8, page 34). Among women engaging in VPA, a third (n=378; 29%) engaged in more than one mode of VPA. Women engaged in any VPA were less likely to take vitamins (p=0.02), more likely to be multiparous (p<0.01), and more likely to have higher numbers of prior miscarriages (p<0.01) or irregular cycles (p=0.01).

Table 8. Maternal characteristics by VPA status: *RFTS*, 2000-2012 (n=3,678)

Characteristic	Any VPA N=1,302 (35%)[a]	No VPA N=2,376 (65%)[a]
Maternal age, years		
<25	150 (11.5)	274 (11.5)
25-29	433 (33.3)	923 (38.9)
30-34	509 (39.1)	852 (35.9)
≥35	210 (16.1)	327 (13.8)
Race/ethnicity		
White non-Hispanic	1,032 (79.3)	1,845 (77.7)
Black non-Hispanic	150 (11.5)	275 (11.6)
Hispanic	71 (5.5)	146 (6.2)
Other non-Hispanic	49 (3.8)	109 (4.6)
Missing	0	1
Body mass index		
Underweight	23 (1.8)	61 (2.6)
Normal weight	754 (58.3)	1,342 (57.1)
Overweight	288 (22.3)	559 (23.8)
Obese	229 (17.7)	389 (16.6)
Missing	8	25
Education level		
High school or less	144 (11.1)	276 (11.6)
Some college	189 (14.5)	323 (13.6)
College or more	969 (74.4)	1,777 (75.8)
Marital status		
Married	1,263 (97.0)	2,285 (96.2)
Other	39 (3.0)	91 (3.8)
Household income		
≤$40,000	268 (21.1)	482 (20.7)
$40,001-80,000	506 (39.8)	969 (41.6)
≥$80,001	497 (39.1)	881 (37.8)
Missing	31	44
Parity		
0	557 (43.0)	1,266 (53.7)
1	529 (40.9)	805 (34.2)
≥2	208 (16.1)	286 (12.1)
Missing	8	19
Intercourse frequency (times/week)		
≤1	311 (24.1)	458 (19.4)
2	316 (24.5)	639 (27.0)
3	338 (26.2)	714 (30.2)
≥4	324 (25.1)	554 (23.4)
Missing	13	11

(continued)	**Any VPA N=1, 302 (35%)[a]**	**No VPA N=2,376 (65%)[a]**
Smoking		
Never	973 (74.7)	1,832 (77.1)
Current/recent quit	111 (8.5)	179 (7.5)
Distant quit[c]	218 (16.7)	364 (15.3)
Missing	0	1
Alcohol		
Never	162 (12.4)	326 (13.7)
Current/recent quit	758 (58.2)	1,288 (54.2)
Distant quit[c]	382 (29.3)	762 (32.1)
Prior miscarriage		
0	977 (75.5)	1,873 (79.5)
1	247 (19.1)	392 (16.6)
≥2	70 (5.4)	92 (3.9)
Missing	8	19
Menstrual cycle regularity[d]		
Irregular	169 (13.9)	240 (10.8)
Regular	1,047 (86.1)	1,974 (89.2)
Missing	86	162
Caffeine intake		
None	411 (31.6)	801 (33.7)
Any	891 (68.4)	1,575 (66.3)
Prenatal vitamins		
None	30 (2.3)	30 (1.3)
Any	1,270 (97.7)	2,343 (98.8)
Missing	2	3
Folic acid		
None	21 (1.6)	23 (1.0)
Any	1,270 (98.4)	2,342 (99.0)
Missing	11	11
Study site		
North Carolina	739 (56.8)	1,418 (59.7)
Tennessee	497 (38.2)	830 (34.9)
Texas	66 (5.1)	128 (5.4)

Abbreviation: VPA, vigorous physical activity.

[a] *Data are counts and column percentages for each characteristic. Percentages exclude missing data and may not add up to 100% due to rounding.*

[b] *Body mass index was calculated as weight (kg)/height (m)^2 and was categorized as underweight: <18.5; normal weight: 18.5–24.9; overweight: 25.0–29.9; or obese: ≥30.*

[c] *Distant quit defined as cessation prior to four months before first-trimester interview.*

[d] *Irregular menstrual cycle defined as having >2 months without a cycle since they stopped using hormonal contraceptives or having >2 months without a cycle in the past 12 months while using non-hormonal contraceptives.*

Thirty percent of couples (n=1,095; 29.8%) achieved pregnancy during the first cycle of trying. After three cycles, 65% of couples reported becoming pregnant. Overall, engaging in any VPA was not associated with TTP (FR=1.02; 95% CI: 0.95, 1.10). This was also true when I compared quartiles of cumulative amount per week and quartiles of cumulative frequency per week to no VPA (Table 9, page 36). When VPA amount and frequency were modelled continuously using RCS, the probability of getting pregnant in a given cycle did not vary by VPA amount or frequency (Figure 7, page 37).

Table 9. Association of VPA and time to pregnancy: *RFTS*, 2000-2012 (n=3,678)

VPA Characteristics	No. of pregnancy[a]	No. of cycles	Crude		Adjusted[b]	
			FR	95% CI	FR	95% CI
Any VPA						
No	2,199	11,179	1.00	Reference	1.00	Reference
Yes	1,197	5,846	1.01	(0.94, 1.08)	1.02	(0.95, 1.10)
VPA amount (minutes/week)[c,d]						
Q1: 1-30	288	1,426	0.98	(0.86, 1.10)	1.00	(0.88, 1.13)
Q2: 31-75	273	1,469	0.96	(0.85, 1.09)	0.96	(0.85, 1.10)
Q3: 76-180	363	1,553	1.04	(0.93, 1.17)	1.06	(0.94, 1.19)
Q4: 181-1630	263	1,301	1.07	(0.95, 1.22)	1.10	(0.96, 1.25)
Missing	10	97				
VPA frequency (times/week)[c,d]						
Q1: 1-2	282	1,436	0.97	(0.86, 1.10)	1.00	(0.88, 1.14)
Q2: 3-4	295	1,547	0.97	(0.86, 1.10)	0.97	(0.86, 1.10)
Q3: 5-11	352	1,517	1.10	(0.98, 1.22)	1.10	(0.98, 1.23)
Q4: 12-120	262	1,268	1.02	(0.89, 1.16)	1.05	(0.92, 1.19)
Missing	6	78				

Abbreviations: VPA, vigorous physical activity; FR, fecundability ratio; CI, confidence interval; Q, quartile.

[a] *Number of pregnancies do not add up to 3,678 due to censoring (282 pregnancies were achieved beyond 11 months of trying).*

[b] *Adjusting for a priori confounders age, race/ethnicity, body mass index, education level, alcohol use, smoking, income, and intercourse frequency.*

[c] *VPA amount and VPA frequency were mutually adjusted as continuous variables.*

[d] *Only available for women engaging in any VPA. Categories based on quartiles.*

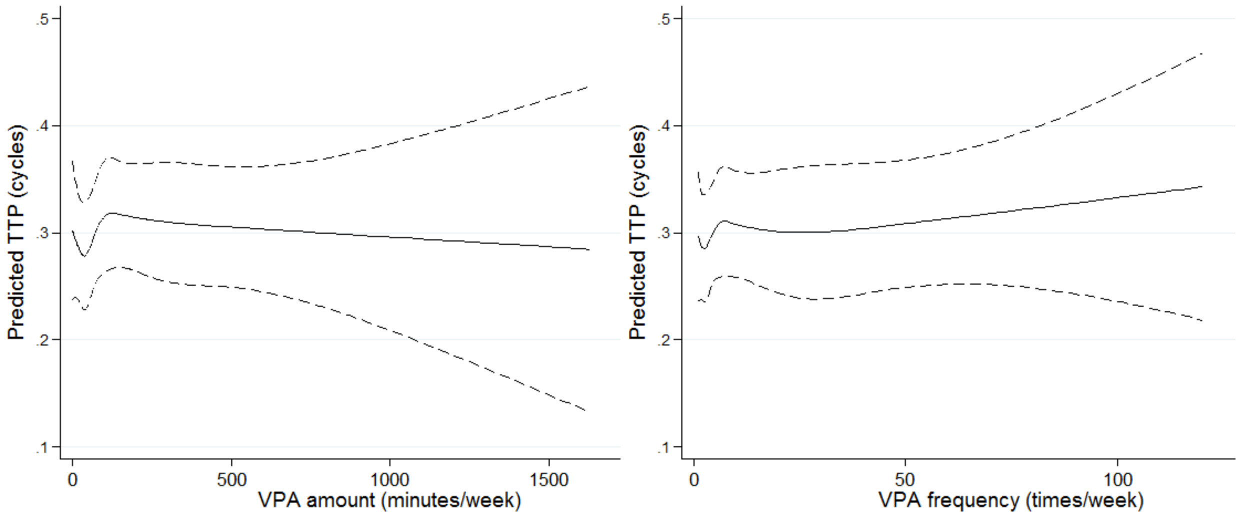

Figure 7. Association of vigorous physical activity (VPA) and time to pregnancy (TTP)
Abbreviations: TTP, time to pregnancy; VPA, vigorous physical activity. Adjusted for age (RCS), race/ethnicity, BMI (RCS), education level, alcohol use, smoking, income, and intercourse frequency. RCS with knot placement at 5, 40, 75, 150, and 480 minutes/week, corresponding to 5th, 27.5th, 50th, 72.5, and 95th percentiles for those engaging in VPA.

I stratified the analysis by BMI categories in Table 10. Most women were normal weight (n=2,096; 58%), with few women underweight (n=84; 2%) and a meaningful number overweight (n=847; 23%) or obese (n=618; 17%). While estimates for underweight women are imprecise to due small numbers, VPA did not seem to be associated with probability of getting pregnant regardless of BMI category (Table 10, page 38). Results were similar when I excluded women with irregular periods (n=409; 11%), when I excluded women engaging in no physical activity (n=83; 2%), and when I restricted to women who were given pregnancy tests before achieving pregnancy (n=1,301; 35%).

Table 10. Association of VPA and time to pregnancy stratified by BMI: *RFTS*, 2000-2012 (n=3,645)[a]

VPA Characteristics	Underweight N=84 FR (95% CI)[b]	Normal N=2,096 FR (95% CI)[c]	Overweight N=847 FR (95% CI)[c]	Obese N=618 FR (95% CI)[c]
Any VPA				
No	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Yes	1.01 (0.57, 1.78)	0.99 (0.90, 1.09)	1.05 (0.90, 1.22)	1.05 (0.87, 1.26)
VPA amount (minutes/week)[d,e]				
Q1: 1-30	0.70 (0.30, 1.64)	0.99 (0.83, 1.18)	1.05 (0.80, 1.37)	0.97 (0.72, 1.32)
Q2: 31-75	0.98 (0.30, 3.21)	0.87 (0.73, 1.03)	0.97 (0.74, 1.28)	1.37 (0.97, 1.94)
Q3: 76-180	0.74 (0.21, 2.57)	0.96 (0.82, 1.12)	1.21 (0.93, 1.57)	1.19 (0.87, 1.62)
Q4: 181-1630	1.03 (0.29, 3.67)	1.08 (0.90, 1.30)	1.14 (0.80, 1.62)	0.88 (0.58, 1.32)
VPA frequency (times/week)[d,e]				
Q1: 1-2	0.68 (0.23, 2.10)	0.95 (0.79, 1.13)	1.04 (0.80, 1.36)	1.24 (0.90, 1.71)
Q2: 3-4	0.69 (0.27, 1.75)	0.93 (0.78, 1.09)	1.04 (0.79, 1.36)	0.98 (0.69, 1.38)
Q3: 5-11	1.11 (0.42, 2.91)	1.10 (0.93, 1.29)	0.97 (0.71, 1.32)	1.26 (0.90, 1.76)
Q4: 12-120	0.74 (0.15, 3.74)	1.03 (0.84, 1.26)	0.99 (0.73, 1.35)	0.98 (0.67, 1.44)

Abbreviations: VPA, vigorous physical activity; FR, fecundability ratio; CI, confidence interval; Q, quartile.

[a] *Thirty-three participants missing body mass index were excluded. BMI was calculated as weight (kg)/height (m)2 and was categorized as underweight: <18.5; normal weight: 18.5 – 24.9; overweight: 25.0 – 29.9; or obese: ≥30.*

[b] *Adjusted for only age (continuous) and race/ethnicity to avoid overfitting.*

[c] *Adjusted for a priori confounders age (RCS), race/ethnicity, education level, alcohol use, smoking, income, and intercourse frequency.*

[d] *VPA amount and VPA frequency were mutually adjusted as continuous variables.*

[e] *Only available for women engaging in any VPA. Categories based on quartiles.*

Discussion

Overall, I found neither the amount nor frequency of cumulative VPA substantively influenced TTP in our community-based pregnancy cohort. While multiple studies have suggested that competitive female athletes have increased risks of oligomenorrhea and amenorrhea and thus delayed TTP,[64-67] few studies evaluated the association between VPA and TTP in the general population. Our results agree with an earlier online study of women enrolled prior to conception that found no association between VPA and fecundability (≥5 vs. <1 hour/week: FR=1.11; 95% CI: 0.96, 1.28).[69] Further, this is not affected by women's BMI.

Strengths of our study include capturing women engaging in all modes of VPA and limiting bias in the process. Among women engaging in VPA (n=1,302), half reported engaging in recreational activities (n=713). The other half would have been miscategorized as engaging in no VPA if only asked to report recreational activities. A second strength is an interview designed to reduce bias. Questionnaire fatigue was unlikely to occur early since VPA questions were nested in the third section out of thirteen in the interview. VPA assessment followed questions about caffeine and fish consumption and preceded questions about hobbies/exposure to toxins, tobacco use, and alcohol/drug consumption. Moreover, VPA questions were phrased in a neutral way so women were not prompted to perceive VPA as a risk or benefit; hence social desirability bias is of minimal concern.

In the literature, between 25 and 33% of couples in the general population are estimated to achieve pregnancy after one cycle of trying.[97-99] RFTS consisted of couples aware of their fertility and similar to the general population (30% achieved pregnancy after one cycle). Our study did not take into consideration some factors that influence fecundability, such as stress and anxiety level, paternal VPA pattern, and prior fitness levels.[88,100] Our study also did not collect information on nutrition. However, our cohort consists of participants with primarily medium to high socioeconomic status (SES), evidenced by income/education level/insurance status, suggesting malnutrition is highly unlikely. In addition, almost all women took prenatal vitamins and folate supplements (Table 8, page 34).

An optimal frequency and/or amount of VPA to achieve pregnancy TTP was not identified. This may be due to considerable individual variation in contributing physiological and psychological factors. Researchers have found TTP to be a more sensitive parameter for biological changes induced by VPA than menstrual function.[86] In addition, overall correct dating in cohort suggests LMP report is accurate and those who say they have regular cycles do.[101] Another possible explanation is that the comparison group used in our analyses, consisting of both women engaging in non-VPA and women engaging in no physical activity, is not homogenous. In a sensitivity analysis where I excluded those engaging in no physical activity from our relatively selective group of volunteers with similar SES, results were similar. Our study did not estimate the amount of non-VPA women engaged in since our primary focus is assessing VPA.

Another consideration is that I assumed that first-trimester VPA reflects VPA levels prior to pregnancy. Although most women decrease physical activity after getting pregnant, those who were highly active before getting pregnant are more likely to remain active during pregnancy.[102] A recent review found higher activity levels during pregnancy are predicted by several demographic factors such as education and income,[103] which are unlikely to change in a short amount of time. One-week recall may not reflect long-term VPA patterns, but VPA in a typical week in first trimester may be sufficient to retain the order of pre-pregnancy VPA from higher to lower levels in the cohort. This may be less true for women who had longer TTP (35% of women did not achieve pregnancy in the first three cycles of trying).

Conclusion

Current knowledge is limited in terms of thoroughly measuring multiple modes of VPA in community-based studies. Our study indicates that VPA has no effect on TTP, regardless of women's BMI. Our results advance understanding of physical exertion around conception and inform individual women and health care providers about the risks and benefits of engaging in VPA while planning a pregnancy. This work also has important public health implications since it suggests women may continue levels of activity that are vigorous and supports general health and disease prevention while planning to conceive. Considering individual VPA may vary across time, future studies may benefit from measuring VPA as a time-varying covariate. Additional data about body composition and ovulatory function would also enhance our understanding of VPA and fecundability.

CHAPTER IV

VIGOROUS PHYSICAL ACTIVITY DURING FIRST TRIMESTER OF PREGNANCY AND MISCARRIAGE

Abstract

Background: VPA can influence quality of implantation and miscarriage risk in early pregnancy through modulating endometrial receptivity. However, the association has been inconclusive. Prior studies primarily focused on recreational physical activity, neglecting potentially more common modes of VPA. I evaluated the association between VPA combining modes and miscarriage.

Methods: *Right from the Start* (2000-2012) is a community-based cohort of women in early pregnancy from Southern US. Cumulative VPA was obtained by summing self-reported frequency and amount of activities and across modes during the first trimester. Survival time was calculated using self-reported LMP and timing of loss, which was determined through self-report or obtained from medical records. HRs and 95% CIs were estimate using marginal structural Cox models, adjusting for *a priori* confounders.

Results: Among 5,424 women, 1,978 (36%) reported engaging in some form of VPA and 645 (11.9%) experienced miscarriage. Overall, engaging in any VPA seemed to be associated with a slight increase in miscarriage risk (HR=1.20; 95% CI: 0.99, 1.45). However, this relationship does not hold when restricting to women who reported their VPA status prior to miscarriage (HR=1.11; 95% CI: 0.80, 1.54).

Conclusions: Neither the amount nor the frequency of cumulative VPA was associated with miscarriage risk in our population-recruited cohort. Since VPA may vary within individuals across time, future study may benefit from measuring VPA as a time-varying covariate.

Overview

Prospective studies have shown light to moderate recreational physical activity has no impact on miscarriage.[73,104-106] The relationship between VPA and miscarriage is not clear. Fear of risk of miscarriage may be a barrier for pregnant women to engage in VPA. Research on the influence of VPA is also needed for women of reproductive age since approximately half of all pregnancies in the United States are unplanned or unintended.[107]

Current literature has not addressed potential bias from symptoms like nausea and vomiting that are biologically associated with pregnancy well-being and can influence exercise patterns.[78] If women with these symptoms engage in VPA less often in early pregnancy compared to women without symptoms, this would incorrectly suggest miscarriage is less likely among women engaged in non-VPA since women with nausea and vomiting symptoms are known to have decreased risk of miscarriage. In a large prospective cohort of women enrolled in early pregnancy, this study evaluated the cumulative effect of VPA on miscarriage while assessing for confounding by nausea and vomiting using self-reported information on severity of symptoms.

Study population

Briefly, I used data from RFTS, a community-based pregnancy cohort that enrolled women in early pregnancy from North Carolina, Tennessee, and Texas (2000-2012).[91] Refer to Aim 1 (page 20) for details on eligibility criteria and study events.

Population selection

Women could enroll in RFTS for more than one pregnancy. Only the first study pregnancy is included to ensure independence among observations (325 subsequent pregnancies were excluded). I also excluded women with missing VPA status, other pregnancy loss, or missing gestational age at enrollment, resulting in a population of 5,424 women (Figure 8). Among these study participants, 645 (11.9%) experienced miscarriages.

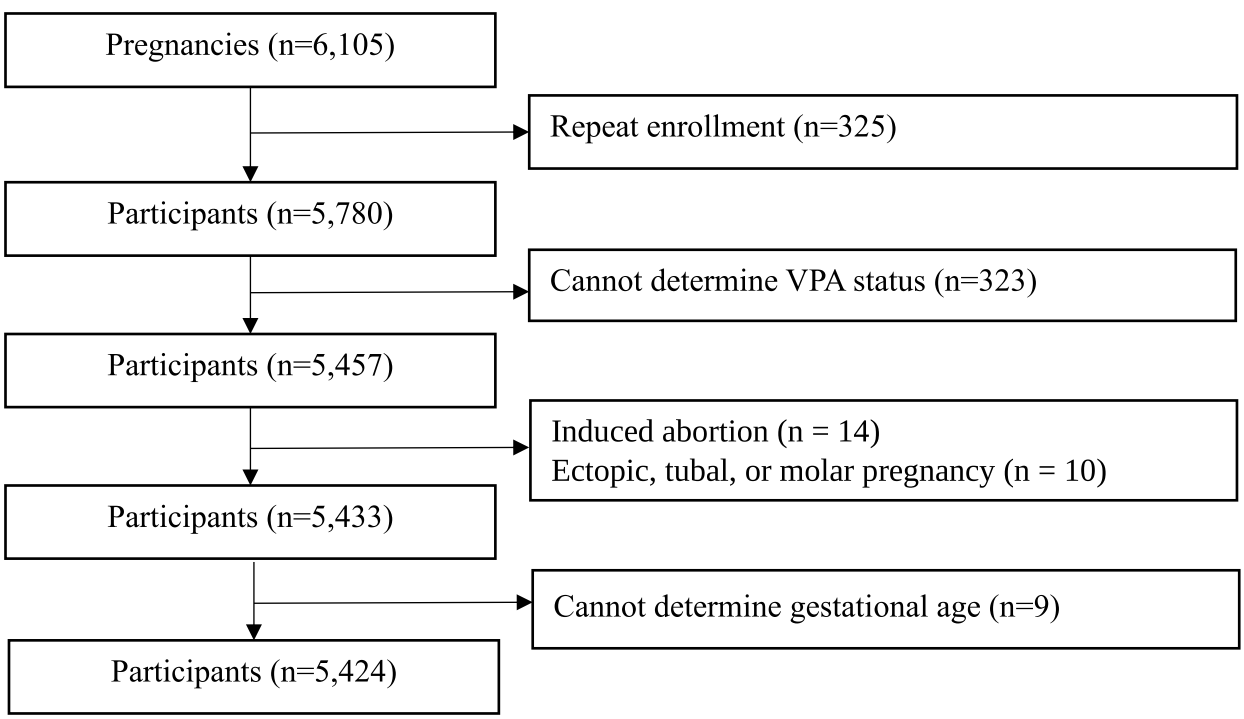

Figure 8. Flow chart of study subject exclusion criteria

Abbreviation: VPA, vigorous physical activity.

A small proportion of women did not provide frequency or amount of VPA. Women with incomplete VPA measures (n=37) were excluded when VPA is modelled as continuous or categorical.

Exposure assessment

My exposure of interest is the frequency and amount of VPA per week pregnant women engaged in during first trimester. VPA was defined as physical activity that felt “hard or very hard, meaning that the activity caused large increases in breathing and heart rate” in a typical week. During CATI, women were asked if they engaged in any of the following modes of VPA: recreational, occupational, outdoor/indoor household, child/adult care, or other activities. Refer to Aim 1 (page 22) for details on recall structure and exposure operationalization.

Outcome assessment

Miscarriage is defined as pregnancy loss in the first 20 weeks after LMP.[68] Researchers often adjust estimated date of delivery for the pregnancy using ultrasound adjusted LMP if ultrasound LMP differed from self-reported LMP by more than 7 days. Pregnancies that end in miscarriage may show signs of delayed fetal growth at the time of ultrasound, resulting in systematically smaller gestational age estimates compared to self-reported LMP.[108] To avoid this misclassification of gestational dating for miscarriages, I used self-reported LMP, which has been shown to be accurate in this cohort.[101] Survival time was calculated using self-reported LMP and timing of loss. Timing of loss was self-reported (n=470) or obtained from medical records (n=170). When timing of loss is unavailable, censoring date was used to calculate time at risk (n=5).

The comparison group included live births (n=4,600), still births (n=27), and those with unknown pregnancy outcomes (n=152). Live births and still births are known to survive past 20 weeks of gestation and were censored at 140 days gestation (regardless of they were loss to follow up). Pregnancies with unknown outcome were censored at censoring date or 140 days, whichever came first. In addition, I also censored gestation days prior to enrollment for all pregnancy outcomes since pregnancies need to survive past enrollment date to be included in our study. This is also known as "left truncation" or "ragged study entry."[109]

Covariates

Information was collected on key covariates including sociodemographic characteristics, reproductive history, and behavioral and lifestyle factors using CATI. Domains represented are listed below (Table 11). Details of variable construction, as required, is provided in Appendix 3 (Table 20, page 84).

Table 11. Key covariates and their operationalization

Covariates	**Operationalization**
Maternal age	Continuous, years
Maternal race/ethnicity	Non-Hispanic white, non-Hispanic black, Hispanic, other
Maternal BMI*	Continuous, kg/m^2
Maternal education level	High school or less, some college, and college or more
Marital status	Married, other
Household income	≤$40,000; $40,001-80,000; ≥$80,001
Parity	Nulliparous, 1, ≥2
Nausea/vomiting symptoms	No symptoms, nausea only, nausea and vomiting symptoms
Pregnancy intention	Unintended (not trying), intended (trying)
Maternal smoking status	Never, distant quit (>4 months), current or recent quit (≤4 months)

Maternal alcohol use	Never, distant quit (>4 months), current or recent quit (≤4 months)
Maternal diabetes	None, any (type I, type II, gestational diabetes, multiple types)
Prior miscarriage	0, 1, ≥2
Maternal caffeine intake	None, any
Maternal vitamin use	None, any
Maternal folic acid use	None, any

** Maternal BMI was calculated using standardized measures of height and weight obtained at the first-trimester ultrasound visits. If unavailable (n=385, 7%), self-reported height and weight was used. Distribution of self-reported BMI was compared to that of measured BMI to ensure consistency. The two distributions did not differ significantly.*

To explicitly state my understanding of the relationships between covariates with the exposure and outcome, I present the following DAG.[92] If the DAG is correctly specified, adjusting for nausea/vomiting symptoms, maternal age, race/ethnicity, BMI, education level, alcohol use, smoking status, pregnancy intention, and household income should produce the least biased estimate possible (Figure 9).

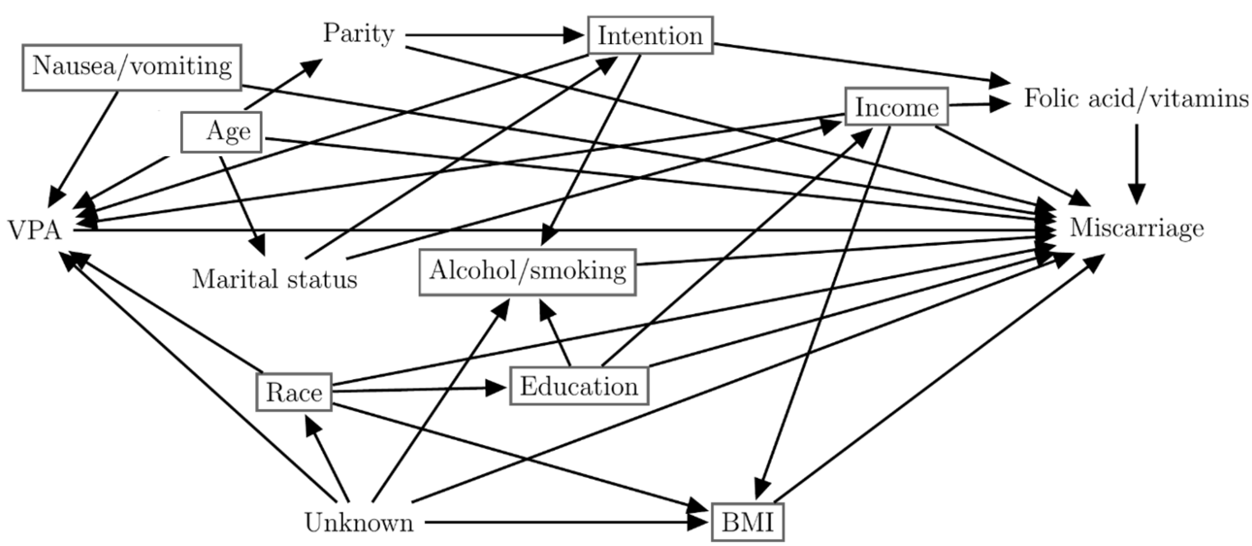

Figure 9. DAG representing the relationship among covariates with VPA and miscarriage

Abbreviations: VPA, vigorous physical activity; BMI, body mass index. Boxed covariates are a priori confounders adjusted for in models.

Missing data

Given low amounts of missing data presented below, the potential impact of missingness is minimal. Thus, I conducted complete case analyses (Table 12, page 48).

Table 12. Proportion of missing data for key covariates

Covariates	**Aim 2 (N=5,424)**	
	n	%
Maternal age	0	0
Maternal race/ethnicity	3	0.1
Maternal BMI	64	1.2
Maternal education level	1	<0.1
Marital status	0	0
Household income	186	3.4
Parity	79	1.5
Nausea/vomiting symptoms	297	5.1
Pregnancy intention	11	0.2
Maternal smoking status	1	<0.1
Maternal alcohol use	1	<0.1
Maternal diabetes	9	0.2
Prior miscarriage	69	1.3
Maternal caffeine intake	0	0
Maternal vitamin use	10	0.2
Maternal folic acid use	0	0

Abbreviation: BMI, body mass index.

Analysis

I conducted univariate and bivariate analyses to compare maternal characteristics among women engaging in any VPA vs. none (

Table 13, page 53). I also examined outliers and influence points for all variables and conducted logic checks for extreme observations. Refer to Aim 1 for details (page 28).

Confounding

Maternal age, race, BMI, education level, alcohol use, smoking status, pregnancy intention, nausea/vomiting symptoms, and household income were identified as *a priori* confounders based on DAG and the literature (Figure 9, page 47). VPA frequency per week (continuous) and amount per week (continuous) were mutually adjusted for when any VPA is performed. Age and BMI were modelled using RCS with knots placed at 5th, 27.5th, 50th, 75.5th, and 95th percentiles.

Statistical model

Stabilized inverse probability weights (IPWs) were calculated to account for confounding.[110] IPW effectively creates a pseudo-population where associational differences are unbiased estimators for the causal difference in the observed study population. In the non-stabilized case with a binary exposure, the weights simulate a pseudo-population where each member of the study population is cloned, and one copy is assigned to each exposure group. Thus, IPW is intuitively appealing in that it simulates a randomized controlled trial using non-randomized data. IPW readily generalizes to multicategory and continuous exposures, and stabilized weights reduce the variance of estimates.

Stabilized IPWs were computed as follows. For binary VPA, the non-stabilized weight is the inverse of the probability of engaging (or not engaging) in VPA conditioned on covariates (identified using DAG). These probabilities were obtained using logistic regression. The weights were then stabilized by multiplying by the unconditional probability of engaging (or not engaging) in VPA. In general, the stabilized weights are of the form

$$SW_{VPA} = \frac{f(VPA)}{f(VPA \mid Cov)}$$

where $f(\cdot)$ represents the probability mass function (pmf) for categorical VPA and the probability density function (pdf) for continuous VPA. When VPA amount and VPA frequency are modelled categorically, $f(VPA \mid Cov)$ is obtained using multinomial logistic regression. When VPA is modelled continuously using RCS, I assumed the densities are lognormal distributions, with means and variances estimated by linear regression. The positivity assumption holds for all models.

IPWs estimated above were respectively applied to marginal structural Cox models where VPA is modelled as binary, categorical, and continuous (Table 14, page 55). HRs and 95% CIs were estimated for the associations between VPA and miscarriage risk. No departure from the proportional hazard assumption was detected. Weighted models were compared using the Wald test.

Sensitivity analysis

Evaluation of the effect of VPA on miscarriage did not always take place before miscarriage occurrence. As a sensitivity analysis to assess recall bias, I repeated the analysis excluding women whose VPA was recalled because her CATI was conducted after miscarriage (n=424,

Table 15, page 56). A second sensitivity analysis excluded women engaging in no physical activity across all modes since they may have different risk compared to women engaging in non-VPA.

All statistical analyses were conducted at a 2-sided significance level of 0.05 using Stata 14.2 (StataCorp, Texas, United States).[94] Code is available on request.

Power calculation

Assuming the median time to miscarriage among participants engaging in non-VPA is 140 days, this work had 90% power to detect a true HR less than 0.88 or greater than 1.14 among participants engaging in VPA (n=1,978) and those who do not (n=3,446) at alpha=0.05 (Figure 9, following page).[33]

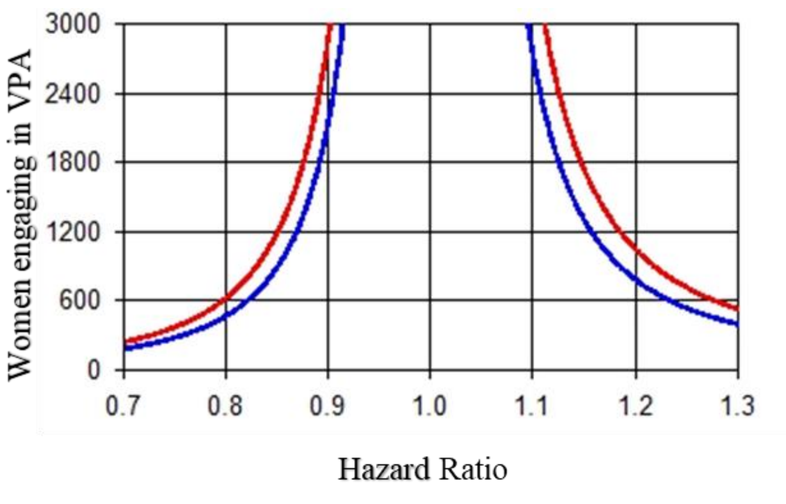

Figure 10. Power curve for median survival time

**Upper curve (red) represents 90% power, lower curve (blue) represents 80% power.*

Results

Among 5,424 women, 1,978 (36%) reported engaging in some mode of VPA. The most common mode of VPA was recreational (n=980, 18%), followed by indoor/outdoor household (n=591, 11%), child/adult care (n=539, 10%), other (n=289, 5%), and occupational activities (n=194, 4%). Among women engaging in VPA, a third (n=615, 31%) engaged in more than one mode of VPA. Women engaged in any VPA were less likely to have prenatal ($p=0.01$) and folic acid ($p=0.01$), were more likely to be multiparous ($p<0.01$), and more likely to have: higher BMI ($p=0.01$), nausea/vomiting symptoms ($p<0.01$), an unintended pregnancy ($p=0.02$), numbers of prior miscarriages ($p<0.01$), and caffeine intake ($p<0.01$,

Table 13).

Six hundred and forty-five (11.9%) pregnancies ended in miscarriage, half of which occurred prior to 9 weeks gestation. Among miscarriages, the median survival time from enrollment is 22 days (interquartile range [IQR]: 12, 36). For pregnancies that did not end in miscarriage, the median follow-up time from enrollment is 95 days (IQR: 84, 104). Overall, engaging in any VPA seemed to be associated with a slight increase in miscarriage risk in the adjusted model (HR=1.20; 95% CI: 0.99, 1.45, Table 14). However, this relationship does not hold when the analysis is restricted to women who reported their VPA status prior to experiencing miscarriage (HR=1.11; 95% CI: 0.80, 1.54,

Table 15).

Compared to women performing less than 30 minutes of VPA, women performing higher amounts of VPA are not at increased risk of miscarriage (Table 14). While a statistically significant HR is observed in

Table 15, this is likely an unstable estimate based on small subsamples (only 6 miscarriages occurred in the highest category of VPA amount). When VPA amount and frequency are modelled continuously, the relationships do not change meaningfully relative to CI widths (Figure 11, page 57). Please note that the seemingly different patterns of effect estimates between modelling VPA categorically (

Table 15) and continuously (Figure 11) are due to tails of the VPA distribution forced to be linear in RCS models.

Table 13. **Maternal characteristics by VPA status: *RFTS*, 2000-2012 (n=5,424)**

Characteristic	Any VPA N=1,978 (36%)[a]	No VPA N=3,446 (64%)[a]
Maternal age, years		
<25	407 (20.6)	669 (19.4)
25-29	615 (31.1)	1,243 (36.1)
30-34	668 (33.8)	1,062 (30.8)
≥35	288 (14.6)	472 (13.7)
Race/ethnicity		
White non-Hispanic	1,398 (70.8)	2,393 (69.5)
Black non-Hispanic	374 (18.9)	654 (19.0)
Hispanic	123 (6.2)	241 (7.0)
Other non-Hispanic	81 (4.1)	157 (4.6)
Missing	2	1
Body mass index[b]		
Underweight	38 (2.0)	97 (2.9)
Normal weight	1,041 (53.2)	1,822 (53.5)
Overweight	450 (23.0)	822 (24.2)
Obese	428 (21.9)	662 (19.5)
Missing	21	43
Education level		
High school or less	358 (18.1)	611 (17.7)
Some college	380 (19.2)	596 (17.3)
College or more	1,239 (62.7)	2,239 (65.0)
Missing	1	0
Marital status		
Married	1,761 (89.0)	3,078 (89.3)
Other	217 (11.0)	368 (10.7)
Household income		
≤$40,000	641 (33.4)	1,013 (30.5)
$40,001-80,000	677 (35.3)	1,271 (38.3)
≥$80,001	599 (31.3)	1,037 (31.2)
Missing	61	125
Parity		
0	805 (41.3)	1,754 (51.6)
1	742 (38.1)	1,111 (32.7)
≥2	401 (20.6)	532 (15.7)
Missing	30	49
Nausea and vomiting		
Neither	224 (12.0)	517 (15.8)
Nausea only	833 (44.7)	1,426 (43.7)
Nausea and vomiting	807 (43.3)	1,320 (40.5)
Missing	114	183

(continued)	**Any VPA N=1,978 (36%)[a]**	**No VPA N=3,446 (64%)[a]**
Pregnancy intention		
Intended	1,409 (71.5)	2,536 (73.7)
Not intended	563 (28.6)	905 (26.3)
Missing	6	5
Smoking		
Never	1,416 (71.6)	2,560 (74.3)
Current/recent quit	257 (13.0)	394 (11.4)
Distant quit[c]	305 (15.4)	491 (14.3)
Missing	0	1
Alcohol		
Never	259 (13.1)	508 (14.7)
Current/recent quit	1,131 (57.2)	1,874 (54.4)
Distant quit[c]	587 (29.7)	1,064 (31.9)
Missing	1	0
Diabetes[d]		
None	1,911 (96.8)	3,348 (97.3)
Any	63 (3.2)	93 (2.7)
Missing	4	5
Prior miscarriage		
0	1,463 (75.1)	2,673 (78.7)
1	372 (19.2)	583 (17.2)
≥2	113 (5.8)	141 (4.2)
Missing	20	49
Caffeine intake		
None	558 (28.2)	1,114 (32.3)
Any	1,420 (71.8)	2,332 (67.7)
Prenatal vitamins		
None	83 (4.2)	100 (2.9)
Any	1,888 (95.8)	3,340 (97.1)
Missing	7	6
Folic acid		
None	74 (3.8)	87 (2.5)
Any	1,887 (96.2)	3,339 (97.5)
Missing	17	20
Study site		
North Carolina	1,091 (55.2)	1,979 (57.4)
Tennessee	739 (37.4)	1,209 (35.1)
Texas	148 (7.5)	258 (7.5)

Abbreviation: VPA, vigorous physical activity.

[a] Data are counts and column percentages for each characteristic. Percentages exclude missing data and may not add up to 100% due to rounding.

[b] *Body mass index was calculated as weight (kg)/height (m)^2 and was categorized as underweight: <18.5; normal weight: 18.5–24.9; overweight: 25.0–29.9; or obese: ≥30.*

[c] *Distant quit defined as cessation prior to four months before first trimester interview.*

[d] *Type I (n=18), type II (n=18), gestational (n=119), and multiple types (n=1) were combined.*

Table 14. Association of VPA and miscarriage: *RFTS*, 2000-2012 (n=5,424)

VPA Characteristics	Births (n=5,424)	Miscarriage (n=645)	Crude		IPW Adjusted[a]	
			HR	95% CI	HR	95% CI
Any VPA						
No	3,446	399	1.00	(Reference)	1.00	(Reference)
Yes	1,978	246	1.09	(0.93, 1.27)	1.20	(0.99, 1.45)
VPA amount (minutes/week)[b,c]						
Q1: 1-30	530	57	1.00	(Reference)	1.00	(Reference)
Q2: 31-75	467	65	1.31	(0.92, 1.87)	1.03	(0.64, 1.65)
Q3: 76-180	538	75	1.31	(0.92, 1.84)	1.10	(0.71, 1.71)
Q4: 181-1630	419	47	1.03	(0.70, 1.52)	0.75	(0.41, 1.36)
Missing	24	2				
VPA frequency (times/week)[b,c]						
Q1: 1-2	435	56	1.00	(Reference)	1.00	(Reference)
Q2: 3-4	454	65	1.13	(0.79, 1.61)	1.07	(0.63, 1.84)
Q3: 5-11	571	80	1.10	(0.97, 1.54)	1.21	(0.72, 2.02)
Q4: 12-120	498	41	0.63	(0.50, 0.94)	0.74	(0.41, 1.34)
Missing	20	4				

Abbreviations: VPA, vigorous physical activity; HR, hazard ratio; CI, confidence interval; IPW, inverse probability weighting; Q. quartile.

[a] *Adjusting for a priori confounders age, race/ethnicity, body mass index, education level, alcohol use, smoking, pregnancy intention, nausea/vomiting symptoms, and household income.*

[b] *VPA amount and VPA frequency were mutually adjusted as categorical variables.*

[c] *Only available for women engaging in any VPA. Categories based on quartiles.*

Table 15. **Association of VPA and miscarriage excluding women with recalled VPA:** ***RFTS*****, 2000-2012 (n=5,221)**

VPA Characteristics	**Births (n=5,000)[a]**	**Miscarriage (n=221)**	**Crude**		**IPW Adjusted[a]**	
			HR	**95% CI**	**HR**	**95% CI**
Any VPA						
No	3,189	142	1.00	(Reference)	1.00	(Reference)
Yes	1,811	79	0.99	(0.75, 1.30)	1.11	(0.80, 1.54)
VPA amount (minutes/week)[b,c]						
Q1: 1-30	500	27	1.00	(Reference)	1.00	(Reference)
Q2: 31-75	429	27	1.17	(0.69, 2.00)	0.83	(0.41, 1.67)
Q3: 76-180	482	19	0.71	(0.39, 1.28)	0.56	(0.28, 1.12)
Q4: 181-1630	378	6	0.28	(0.12, 0.68)	0.10	(0.02, 0.50)
Missing	22	2				
VPA frequency (times/week)[b,c]						
Q1: 1-2	392	13	1.00	(Reference)	1.00	(Reference)
Q2: 3-4	411	22	1.65	(0.83, 3.27)	1.60	(0.69, 3.73)
Q3: 5-11	518	27	1.60	(0.83, 3.10)	1.96	(0.89, 4.32)
Q4: 12-120	472	15	0.97	(0.46, 2.03)	1.22	(0.49, 3.05)
Missing	18	2				

Abbreviations: VPA, vigorous physical activity; HR, hazard ratio; CI, confidence interval; IPW, inverse probability weighting; Q. quartile.

[a] *Adjusting for a priori confounders age, race/ethnicity, body mass index, education level, alcohol use, smoking, pregnancy intention, nausea/vomiting symptoms, and household income.*

[b] *VPA amount and VPA frequency were mutually adjusted as categorical variables.*

[c] *Only available for women engaging in any VPA. Categories based on quartiles.*

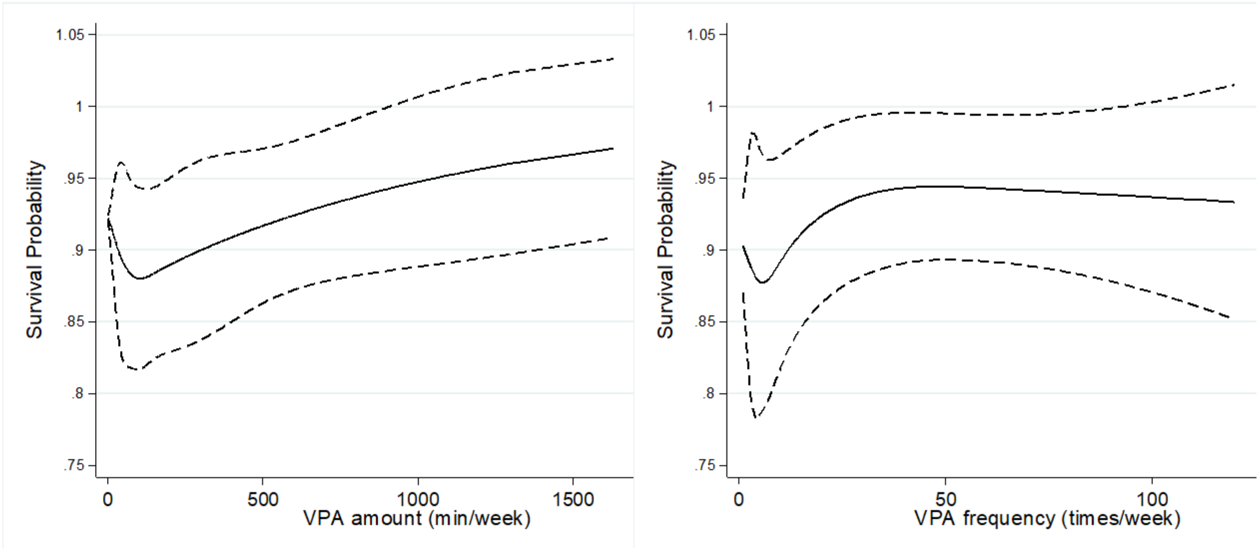

Figure 11. Association between VPA and miscarriage risk

Abbreviations: TTP, time to pregnancy; VPA, vigorous physical activity. Adjusted for age (RCS), race/ethnicity, BMI (RCS), education level alcohol use, smoking, pregnancy intention, nausea/vomiting symptoms, and household income. RCS with knot placement at 5, 40, 75, 150, and 480 minutes/week, corresponding to 5th, 27.5th, 50th, 72.5, and 95th percentiles for those engaging in VPA.

Discussion

While some researchers suggest a protective effect from VPA,[8,10] some found no association between VPA and risk of miscarriage,[72,36,37] and others found a harmful effect from VPA.[83] Levels of safe physical activity frequency and amount in pregnancy have not been established. Overall, I found neither the amount nor the frequency of cumulative VPA was associated with miscarriage risk in our population-recruited cohort.

When comparing women engaged in any VPA with women engaged in none, results were attenuated when restricting to women who reported their VPA measures prior to experiencing miscarriage. Similar attenuation of results were observed in a large Danish prospectively recruited cohort where some exposure assessment was conducted after the miscarriage (HR=2.9;

95% CI: 2.4-3.5 vs. HR=1.8; 95% CI: 1.0-2.9 when comparing women engaged in 270-419 min/week of recreational physical activity vs. non-exercisers).[78]

One possible explanation for our attenuated results is that I adjusted for nausea and vomiting symptoms. Since nausea is less common in pregnancies that end in miscarriage and is a common reason for women to stop or decrease physical activity during pregnancy, not adjusting for nausea and vomiting may bias results. Compared to women experiencing neither nausea or vomiting symptoms, women experiencing nausea (HR=0.46; 95% CI: 0.37-0.56) and women experiencing both nausea and vomiting (HR=0.17; 95% CI: 0.13-0.22) were less likely to have pregnancies that ended in miscarriage. To the author's knowledge, this is the first study adjusting for nausea and vomiting symptoms while assessing the relationship between VPA and miscarriage, which may have contributed to our overall null results.

Another difference is that our study captured higher proportions of early miscarriages; 80% of women in our study had miscarriages prior to 11 weeks gestation while only 20% of the Danish cohort had miscarriages prior to 11 weeks. While little can be done to fix under-reporting due to unrecognized very early losses,[111] efforts were made to recruit women prior to conception (n=1,400, 26%) and women early in pregnancy (median days of gestation at enrollment is 53 days for RFTS1, 41 days for RFTS2, and 34 days for RFTS3). Enrolling women early in pregnancy increases the likelihood of detecting early miscarriage via ultrasound. In addition, establishing a relationship with women early and providing free pregnancy tests improves pregnancy detection.

Other considerations include that our study used a slightly different definition for miscarriage (pregnancy loss prior to 20 weeks vs. 22 weeks gestation) and that we did not estimate the amount of non-VPA since our primary focus was assessing the relationship between

VPA and miscarriage. Results from the Danish study included both moderate and vigorous recreational physical activity.

Conclusion

Pregnancy is an ideal time for positive lifestyle modifications, including sustaining physical activity behavior. In an early pregnancy cohort, this work contributes data on the safe upper limit for frequency and amount of physical activity during early pregnancy while addressing the potential confounding influence of nausea and vomiting symptoms. This work helps providers to facilitate, counsel, and support VPA in pregnancy. Future direction may benefit from modelling nausea and vomiting as time-varying covariates since symptoms may vary across time and influence miscarriage risk.

CHAPTER V

FIRST TRIMESTER VIGOROUS PHYSICAL ACTIVITY AND BIRTHWEIGHT

Abstract

Background: VPA can influence birthweight through affecting optimal perfusion and placental growth, as well as modulating energy excess. Prior studies focused on recreational physical activity and neglected potentially more common modes of VPA. I aimed to evaluate if cumulative frequency and amount of VPA during first trimester are associated with birthweight.

Methods: *Right from the Start* (2000-2012) is a prospective cohort that enrolled pregnant women from the southeastern US. During first-trimester interview, women recalled the type, frequency, and duration of up to three activities for each mode of VPA (recreational, outdoor/indoor household, occupational, child/adult care, and other activities). Date of birth and birthweight were obtained from vital or medical records. Stabilized IPWs were used in marginal structural mean models to estimate the effect of VPA on birthweight to account for confounding and selection bias.

Results: Among 5,020 women, 36% (n=1,816) reported performing some type of VPA. While VPA frequency does not have substantial impact on birthweight, compared to the lowest quartile of VPA amount, engaging in VPA in the highest quartile may be associated with having a heavier infant birthweight (on average 146.1 grams, 95% CI: 54.4, 237.8).

Conclusions: While VPA frequency was not associated with infant birthweight, VPA amount may be associated with a moderate increase in birthweight. This suggests women may continue

levels of activity that are vigorous. Future research powered to detect an optimal amount per week is needed.

Overview

Infant birthweight is a strong predictor for infant health. As birthweight decreases, an infant's risk of mortality increases.[112] Low birthweight (< 2,500 grams) constitutes 8% of all births in the United States.[113] Reduced birthweight may lead to poor growth in childhood and higher incidence of metabolic and cardiovascular diseases in adulthood.[114,115] On the other side of the birthweight spectrum, macrosomia (> 4,000 grams) increases the risk of birth complications and metabolic syndrome for the infant.[116,117] As the prevalence of overweight and obesity increases in the United States, the proportion of macrosomic infants is increasing as well.[118] Established risk factors for low birthweight and high birthweight include maternal race, maternal BMI, gestational age, and socioeconomic status [119-121]. However, the influence of lifestyle factors such as nutrition and VPA on birthweight is less clear.

This study aims to better understand the influence of multiple modes of VPA on infant birthweight. Specifically, I evaluated whether frequency and amount of VPA characterized during the first trimester are associated with infant birthweight

Study population

I used RFTS, a community-based cohort of early pregnancies in the Southern US (2000-2012), to achieve this aim.[91] Refer to Aim 1 (page 20) for eligibility criteria and study events.

Population selection

For women who enrolled in RFTS for more than one pregnancy (n=325), only their first study pregnancy is included to maintain independence of observations. I also excluded women with multiple gestation (n=455) and those with missing VPA status (n=305), which resulted in a population of 5,020 women (Figure 12).

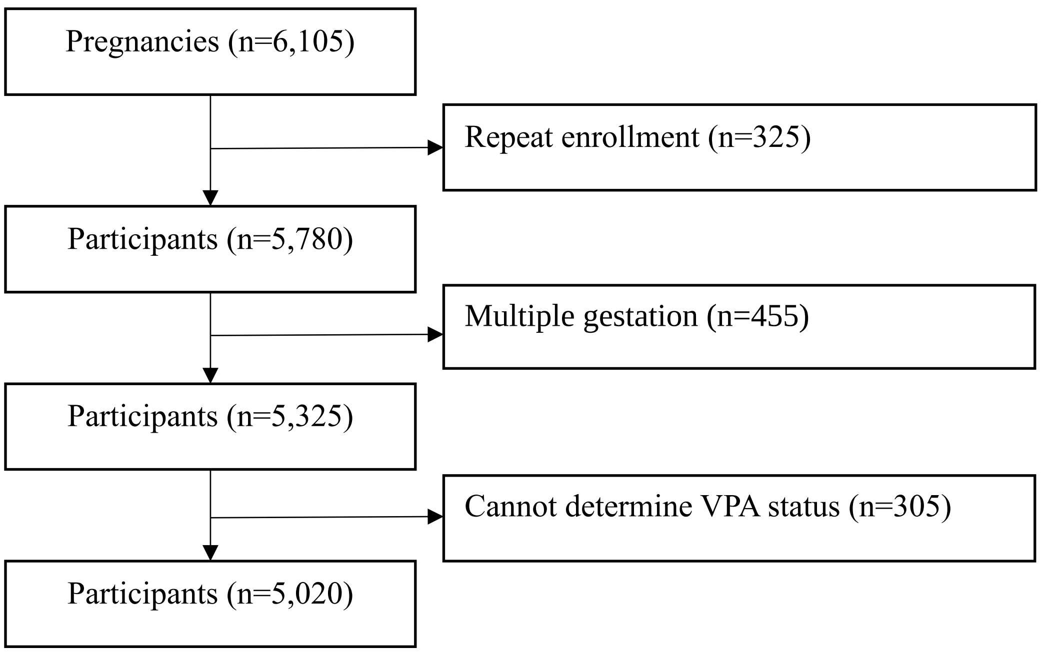

Figure 12. Flow chart of study subject exclusion criteria
Abbreviations: VPA, vigorous physical activity.

A small number of women (n=24) did not provide frequency or amount of VPA. Women with incomplete VPA measures were further excluded when modeling VPA as continuous or categorical.

Exposure assessment

VPA was defined as physical activity in any mode (recreational, occupational, outdoor/indoor household, child/adult care, or other activities) that “feel hard or very hard, meaning that the activity caused large increases in breathing and heart rate” in a typical week. Refer to Aim 1 (page 22) for details on recall structure and exposure operationalization.

Outcome assessment

Birthweight at delivery was obtained from medical or vital records. The hierarchy of sources was hospital discharge summaries and prenatal care records (22%), birth and fetal death records (35%), and participant self-report of pregnancy outcome forms (43%). Gestational age at birth was calculated using date of birth from medical or vital records and ultrasound-confirmed LMP. When ultrasound LMP differed from self-reported LMP by more than 7 days, adjusted LMP was used based on the first-trimester study ultrasound which was typically the participants' earliest. The distribution of birthweight by week of gestation is comparable to that based on data from the 2009-2010 US Natality Report (comparison not shown).[122]

Covariates

Information was collected on key covariates including sociodemographic characteristics, reproductive history, and behavioral and lifestyle factors using CATI. Domains represented are listed below (

Table 16). Details of variable construction, as required, is provided in Appendix 3 (Table 20, page 84).

Table 16. Key covariates and their operationalization

Covariates	**Operationalization**
Maternal age	Continuous, years
Maternal race/ethnicity	Non-Hispanic white, non-Hispanic black, Hispanic, other
Maternal BMI*	Continuous, kg/m^2
Maternal education level	High school or less, some college, and college or more
Marital status	Married, other
Household income	≤$40,000; $40,001-80,000; ≥$80,001
Parity	Nulliparous, 1, ≥2
Prior preterm birth	None, any
Pregnancy intention	Unintended (not trying), intended (trying)
Maternal smoking status	Never, distant quit (>4 months), current or recent quit (≤4 months)
Maternal alcohol use	Never, distant quit (>4 months), current or recent quit (≤4 months)
Maternal diabetes	None, any (type I, type II, gestational diabetes, multiple types)
Maternal caffeine intake	None, any
Maternal vitamin use	None, any
Maternal folic acid use	None, any
Infant sex	Male, female

** Maternal BMI was calculated using standardized measures of height and weight obtained at the first-trimester ultrasound visits. If unavailable (n=137, 4%), self-reported height and weight* *was used. Distribution of self-reported BMI was compared to that of measured BMI to ensure consistency. The two distributions did not differ significantly.*

I visualized my understanding of the relationships between covariates with the exposure and outcome in the following DAG.[92] If correct specification, adjusting for maternal age, race, BMI, education level, alcohol use, smoking status, pregnancy intention, gestational age, and household income should give us the least biased estimate of the association between VPA and birthweight (Figure 13). Gestational weight gain is likely an intermediate on the pathway from VPA to birthweight and was not adjusted for.

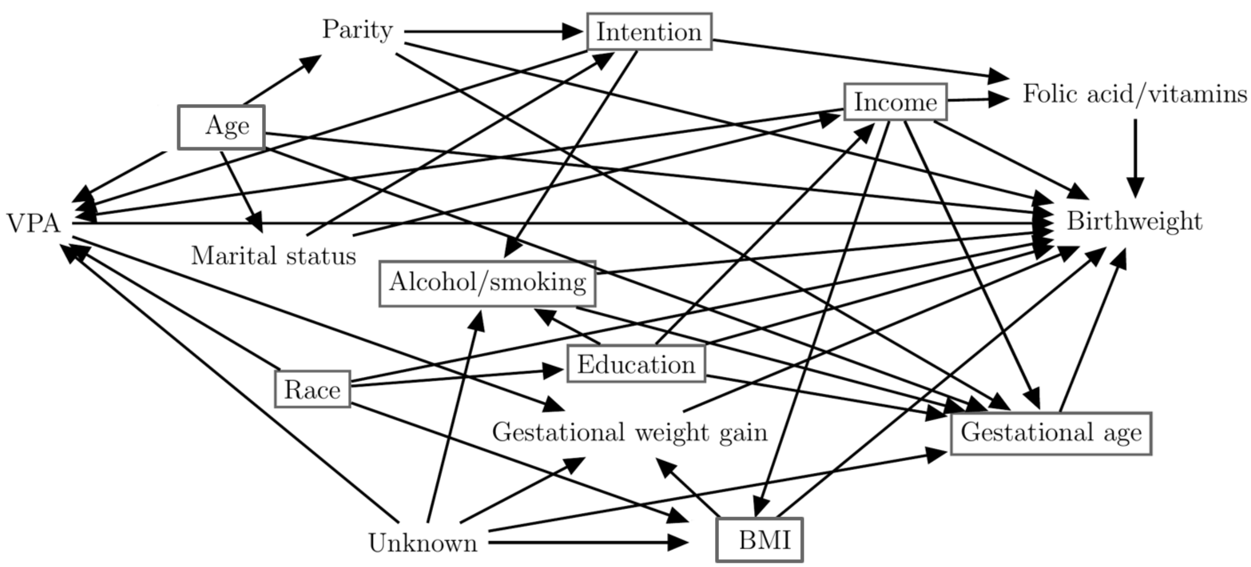

Figure 13. DAG representing the relationship among covariates with VPA and birthweight
Abbreviations: VPA, vigorous physical activity; BMI, body mass index. Boxed covariates are a priori confounders adjusted for in models.

Missing data

The proportion of missing data for key covariates is presented below (Table 17). Given low amounts of missing for all other covariates, the potential impact of multiple imputation would be minimal. Thus, I conducted complete case analyses.

Table 17. Proportion of missing data for key covariates

Covariates	Aim 3 (N=5,020)	
	n	%
Maternal age	1	<0.1
Maternal race/ethnicity	3	0.1
Maternal BMI	49	1.0
Maternal education level	1	0
Marital status	0	0
Household income	174	3.5
Parity	65	1.3
Prior preterm birth	65	1.3
Pregnancy intention	10	0.2
Maternal smoking status	1	<0.1
Maternal alcohol use	1	<0.1
Maternal diabetes	6	0.1
Maternal caffeine intake	0	0
Maternal vitamin use	13	0.3
Maternal folic acid use	27	0.5

Abbreviation: BMI, body mass index.

Analysis

Univariate and bivariate analyses

Among women engaging in any VPA vs. none, maternal and infant characteristics were compared using Student t-test for continuous covariates and Pearson chi-squared test for categorical covariates (

Table 18, page 71). See Aim 1 (page 28) for details on logic and quality checks for extreme observations.

Confounding

Maternal age, race, BMI, education level, alcohol use, smoking status, pregnancy intention, gestational age, and household income entered all adjusted models as *a priori* confounders based on DAG and the literature (Figure 13, page 65). VPA frequency per week (continuous) and amount per week (continuous) were mutually adjusted for when any VPA is performed. Age and BMI were modelled using RCS with knots placed at 5th, 27.5th, 50th, 75.5th, and 95th percentiles.

Statistical model

Stabilized IPWs were calculated to account for confounding (similar to Aim 2, page 48), as well as selection bias.[110] If VPA influenced fetal survival and measured covariates confounded the relationship between VPA and fetal survival, restricting our analysis to live birth is effectively conditioning on a collider, giving rise to selection bias.

IPW accounts for selection bias by introducing a new set of censoring weights which create a pseudo-population where no one is censored. Let C be a censoring indicator equal to 1 if censored and 0 if uncensored. Since I am interested in estimating the causal effect among uncensored individuals, the pdf and pmf are in the form of

$$f(VPA, C = 0 \mid Cov) = f(VPA \mid Cov) \times f(C = 0 \mid Cov, VPA).$$

Stabilizing by $f(VPA, C = 0) = f(VPA) \times f(C = 0 \mid VPA)$ yields overall weight

$$SW = \frac{f(VPA, C = 0)}{f(VPA, C = 0 \mid Cov)} = \frac{f(VPA)}{f(VPA \mid Cov)} \times \frac{f(C = 0 \mid VPA)}{f(C = 0 \mid Cov, VPA)}.$$

(Censored individuals have weight $SW = 0$.) The first factor is the same as stabilized weight SW_{VPA} in Aim 2 (page 48) and the second factor is the censoring stabilized weight, say SW_C. The probabilities in the censoring weights were calculated using logistic regression. The positivity assumption holds for all models.

Once weights were calculated, I used them in marginal structural mean models to estimate the effect of VPA on birthweight where VPA can be dichotomous, categorical, or continuous (RCS). Refer to Aim 1 (page 28) for details on different approaches for modelling frequency and amount of VPA. When possible, I conducted stratified analyses by VPA mode (recreational, occupational, indoor/outdoor household, child/adult care, or other activities) for the associations mention above.

Effect measure modification

First, I tested if maternal BMI interacts with frequency or amount of VPA. If the interaction term is significant, I stratified models by BMI category. Maternal BMI might alter physiological characteristics that affect their ability to perform VPA and lean vs. normal vs. obese women may have a biologically different response to VPA.[52] I also tested if frequency and amount of VPA interacts with infant sex as fetal response to maternal VPA may differ by sex.

Sensitivity analysis

The first sensitivity analysis excludes women who reported no physical activity since they may be at higher risk of miscarriage and were instructed not to engage in VPA. Only 2% of women reported no physical activity across all modes but combining them with women performing non-vigorous physical activity may introduce bias. The second sensitivity analysis excludes women with prior pre-/post-term births since history of pre-/post-term births may be caused by unknown underlying medical reasons and thus influence medical care and pregnancy outcome for the current study pregnancy. In addition, I repeated the analysis excluding women who had preterm births due to medical indications including induction of labor for maternal fetal indications or placental abruption, previa, and bleeding. This was performed since the influence of VPA on birthweight may be different for preterm births due to medical indications vs. spontaneous preterm births.

All statistical analyses were conducted at a 2-sided significance level of 0.05 using Stata 14.2 (StataCorp, Texas, United States).[94] Code is available on request.

Power calculation

Assuming birthweight is normally distributed with a standard deviation of 558 grams, this work would have 90% power to detect a true difference in mean birthweight of 53 grams among participants engaging in VPA (n=1,816) and those who do not (n=3,204) at alpha=0.05.[33]

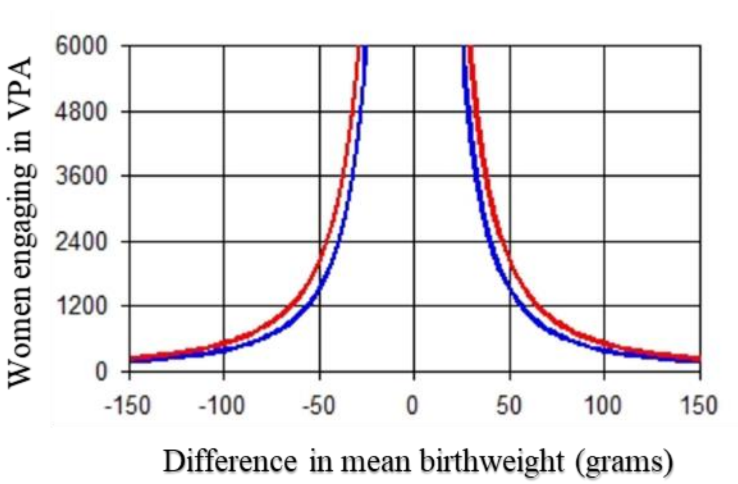

Figure 14. Power curve for test of mean birthweight

*Upper curve (red) represents 90% power, lower curve (blue) represents 80% power.

Results

Similar to previous work from our group, 36% of women in this analysis reported performing some type of VPA.[3] Compared to women not engaged in VPA, women engaged in any VPA are more likely to be multiparous ($p<0.01$), have history of preterm birth ($p<0.01$), have caffeine intake ($p=0.01$), have no vitamins/folic acid supplements ($p=0.02$). Other maternal and infant characteristics are similar (

Table 18, page 71).

Overall, engaging in any VPA is not associated with change in infant birthweight. When adjusting for *a priori* confounders using IPW, VPA frequency does not have substantial impact on birthweight. However, compared to the lowest quartile of VPA amount, engaging in VPA in the highest quartile may be associated with having a heavier infant birthweight (on average 146.1 grams, 95% CI: 54.4, 237.8, Table 19, page 73). A closer examination of the relationship between VPA amount and birthweight is presented in Figure 15 where VPA amount is modelled continuously (Wald test p=0.04, page 74).

The first sensitivity analysis excludes women who reported no physical activity since they may be at higher risk of miscarriage and were instructed not to engage in VPA. Only 2% of women reported no physical activity across all modes but combining them with women performing non-vigorous physical activity may introduce bias. Results are very similar to the full dataset, with a few minor ordering changes. The second sensitivity analysis restricted to women with previous term birth since history of pre/post-term births may be due to underlying medical reasons and lead to modified care for the current pregnancy. One noticeable difference is that effect size of gestational week is smaller as extreme birthweights are less common in this dataset. Results were also similar when I repeated the analysis excluding women who had preterm births due to medical indications (n=65).

Table 18. Maternal and infant characteristics by VPA status: *RFTS*, 2000-2012 (n=5,020)

Characteristic	Any VPA N=1,816 (36%)[a]	No VPA N=3,204 (64%)[a]
Maternal age, years		
mean (sd)	29 (5.1)	29 (5.2)
18-24	374 (20.6)	625 (19.5)
25-29	577 (31.8)	1,175 (36.7)
30-34	620 (34.2)	987 (30.8)
≥35	244 (13.4)	417 (13.0)
Missing	1	0
Race/ethnicity		
White non-Hispanic	1,289 (71.1)	2,243 (70.0)
Black non-Hispanic	330 (18.2)	582 (18.2)
Hispanic	119 (6.6)	230 (7.2)
Other non-Hispanic	76 (4.2)	148 (4.6)
Missing	2	1
Body mass index[b]		
mean (sd)	26.1 (6.6)	25.7 (6.1)
Underweight	37 (2.1)	90 (2.9)
Normal weight	963 (53.5)	1,712 (54.0)
Overweight	408 (22.7)	756 (23.8)
Obese	392 (21.8)	613 (19.3)
Missing	16	33
Education level		
High school or less	323 (17.8)	558 (17.4)
Some college	352 (19.4)	550 (17.2)
College or more	1,140 (62.8)	2,096 (65.4)
Missing	1	0
Marital status		
Married	1,621 (89.3)	2,875 (89.7)
Other	195 (10.7)	329 (10.3)
Household income		
≤$40,000	586 (33.3)	934 (30.3)
$40,001-80,000	635 (36.1)	1,189 (38.5)
≥$80,001	538 (30.6)	964 (31.2)
Missing	57	117
Parity		
0	744 (41.6)	1,647 (52.0)
1	679 (38.0)	1,035 (32.7)
≥2	366 (20.5)	484 (15.3)
Missing	27	38
Prior preterm birth		
None	1,611 (90.1)	2,936 (92.7)
Any	178 (10.0)	230 (7.3)

(continued)	**Any VPA N=1,816 (36%)[a]**	**No VPA N=3,204 (64%)[a]**
Missing	27	38
Intended pregnancy		
No	515 (28.4)	836 (26.1)
Yes	1,296 (71.6)	2.363 (73.9)
Missing	5	5
Smoking		
Never	1,302 (71.7)	2,383 (74.4)
Current/recent quit	238 (13.1)	364 (11.4)
Distant quit[c]	276 (15.2)	456 (14.2)
Missing	0	1
Alcohol		
Never	245 (13.5)	478 (14.9)
Current/recent quit	1,029 (56.7)	1,743 (54.4)
Distant quit[c]	541 (29.8)	983 (30.7)
Missing	1	0
Diabetes[d]		
None	1,756 (96.9)	3,115 (97.3)
Any	57 (3.1)	86 (2.7)
Missing	3	3
Caffeine consumption		
None	518 (28.5)	1,028 (32.1)
Any	1,298 (71.5)	2,176 (68.0)
Prenatal vitamins		
None	70 (3.9)	85 (2.7)
Any	1,739 (96.1)	3,113 (97.3)
Missing	7	6
Folic acid		
None	65 (3.6)	78 (2.5)
Any	1,738 (96.4)	3,112 (97.6)
Missing	13	14
Infant sex		
Male	572 (52.2)	1,066 (52.1)
Female	523 (47.8)	979 (47.9)
Missing	721	1,159
Study site		
North Carolina	1,006 (55.4)	1,845 (57.6)
Tennessee	684 (37.7)	1,129 (35.2)
Texas	126 (6.9)	230 (7.2)

Abbreviation: VPA, vigorous physical activity.

[a] *Data are counts and column percentages for each characteristic. Percentages exclude missing data and may not add up to 100% due to rounding.*

[b] *Body mass index was calculated as weight (kg)/height (m)^2 and was categorized as underweight: <18.5; normal weight: 18.5–24.9; overweight: 25.0–29.9; or obese: ≥30.*

[c] *Distant quit defined as cessation prior to four months before first trimester interview.*

[d] *Type I (n=11), Type II (n=11), gestational diabetes (n=78), and multiple types (n=1) were combined due to small numbers.*

Table 19. Association of VPA and birthweight: *RFTS*, 2000-2012 (n=5,020)

VPA Characteristics	n (%)[a]	Crude		IPW Adjusted[b]	
		Coefficient	95% CI	Coefficient	95% CI
Any VPA					
No	3,204 (63.8)	0.00 (Ref)	0.00 (Ref)	0.00 (Ref)	0.00 (Ref)
Yes	1,816 (36.2)	30.5	(-6.4, 67.4)	25.0	(-12.5, 62.5)
VPA minutes[c]					
Q1: 1-30	484 (9.7)	0.00 (Ref)	0.00 (Ref)	0.00 (Ref)	0.00 (Ref)
Q2: 31-75	421 (8.4)	**125.4**	**(44.7, 206.2)**	**117.6**	**(26.4, 208.9)**
Q3: 76-180	493 (9.9)	**95.9**	**(18.9, 172.9)**	74.3	(-18.7, 167.2)
Q4: 181-1630	394 (7.9)	**160.7**	**(79.4, 242.0)**	**146.1**	**(54.4, 237.8)**
Missing	24				
VPA frequency[c]					
Q1: 1-2	398 (8.0)	0.00 (Ref)	0.00 (Ref)	0.00 (Ref)	0.00 (Ref)
Q2: 3-4	418 (8.4)	39.9	(-45.0, 124.7)	69.1	(-48.4, 186.6)
Q3: 5-11	520 (10.4)	20.6	(-59.7, 100.9)	18.2	(-97.7, 134.2)
Q4: 12-120	464 (9.3)	34.9	(-46.3, 116.1)	43.0	(-71.6, 157.5)
Missing	16				

Abbreviations: BMI for body mass index; CI for confidence interval.

[a] *Data are counts and column percentages for each characteristic. Percentages exclude missing data and may not add up to 100% due to rounding.*

[b] *Adjusting for a priori age, race/ethnicity, body mass index, education level, alcohol use, smoking, income, gestational age, and pregnancy intention*

[c] *Only available for women performing VPA. Categories based on quartiles.*

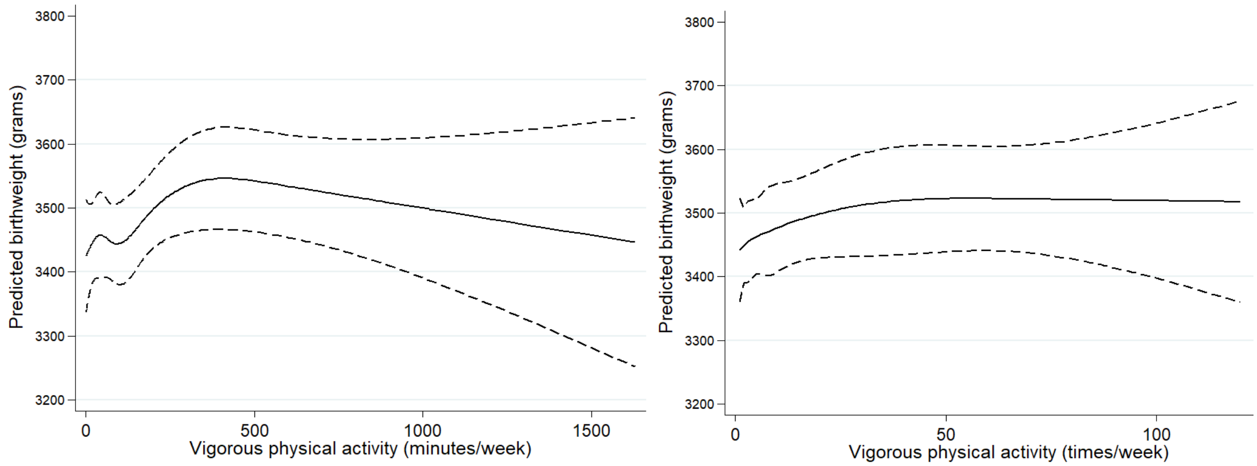

Figure 15. Association of vigorous physical activity (VPA) and birthweight among subgroup performing VPA

Abbreviation: VPA, vigorous physical activity. Adjusted for age (RCS), race/ethnicity, BMI (RCS), education level, alcohol use, smoking, income, pregnancy intention, and gestational age. VPA amount and VPA frequency were mutually adjusted as continuous variables. RCS with knot placement at 10, 35, 80, 170, and 540 minutes/week, and knots at 1, 3, 5, 11, and 65 times/week, corresponding to 5th, 27.5th, 50th, 72.5, and 95th percentile for those performing VPA.

Discussion

VPA frequency was not associated with infant birthweight, but we found birthweight to vary based on VPA amount per week. While the CIs are wide and we cannot conclude an optimal amount per week, the shape of the relationship deserves further research. If an optimal amount truly exists, physical activity interventions targeted towards pregnant women during the first trimester will have the potential to improve birth outcomes on a population level. This is especially exciting since women tend to be highly motivated to make lifestyle behavioral changes and interact with their providers early in pregnancy.

A major strength of this study is that birthweight was examined as a continuous outcome among women engaging in non-VPA and VPA, which has more statistical power than evaluating mean birthweight[80] or proportion of preterm birth (delivery before 37 weeks gestation).[8,44] Compared to previous studies, this work also provides a more comprehensive understanding of the effect of VPA on birthweight by assessing VPA combining all modes. Our study will contribute data to the small number of studies focusing on VPA and birthweight.[82]

While I did not observe any associations between the frequency and amount of cumulative VPA with miscarriage risk in Aim 2, our study may not have captured very early pregnancy losses. For the current aim, selection bias can arise because our study only observes birthweight for those who survived and traditional outcome regression effectively conditions on a collider (fetal survival) in the causal pathway. Selection bias can also arise from having a considerable amount of birthweight missing (n=714, 19%) due to women delivering in nearby states or other unknown reasons. Assuming birthweight is missing at random, complete case analysis with covariate adjustment should provide unbiased results with similar precision compared to imputing the outcome.[123] Our statistical approach using IPW makes our study less susceptible to both potential sources of selection bias, should they exist.

Our study has several limitations to consider. First, information on strong determinants of birth weight were not collected, such as gestational weight gain, pre-pregnancy weight, and nutritional and environmental exposures during pregnancy.[21,60,124] The homogeneity of the study population, evidenced by similar household income, as well as the adjustment for gestational age, may decrease the impact of maternal nutrition on birthweight. Second, the study did not measure sedentary behaviors, which may affect intrauterine environment and fetal development. However, one study showed that early pregnancy sedentary time was not associated with mean birthweight.[80] Third, we did not have information on parental and grandparental birth weight. In a recent study of grandmother-mother-child triads, birthweight and fetal growth showed intergenerational continuity.[125] Lastly, since VPA was assessed during the first trimester interview around 12 weeks gestation, reporting of activity frequency and amount in "a typical week" reflects that during the periconception period. While we do not know if women continued their activity frequency and amount throughout pregnancy, the literature suggest women with the highest level of recreational activity before pregnancy reduce their activity level, but remained the most active during pregnancy, compared to women with low-intensity.[102]

Conclusion

In summary, this unique longitudinal study is appropriate for examining the association between maternal VPA during the first trimester and infant birthweight. These results advance knowledge about the potential relationship between VPA amount and birthweight. Since the gestational period is a special opportunity to promote the adoption of physically active lifestyles, this work on VPA, a potentially modifiable risk factor, may lead to higher probability of delivering normal weight infants.

CHAPTER VI

CONCLUSION AND FUTURE DIRECTIONS

Although current guidelines are limited, a large proportion of women engage in VPA. Close to 50% of women of reproductive age reported engaging in recreational VPA for at least once a week, according to the National Health Examination Survey.[4] As opposed to volitional physical activities typically known as recreational activity or exercise, VPA can span all areas of our daily responsibilities. Ways that VPA may influence pregnancy-related outcomes are not restricted to any specific mode of VPA; the literature focusing primarily on recreational physical activity is incomplete in assessment of the relationship between VPA and pregnancy-related outcomes because it neglects all other modes of VPA, such as outdoor/indoor household activities.

A recent systematic review found that fear of adverse effects was the most common barrier to physical activity among pregnant women (20 out of 27 studies identified concerns about safety of physical activity).[127] This barrier to physical activity may be further exemplified for women planning or carrying a pregnancy who want or are currently engaging in VPA. Leveraging a large prospective pregnancy cohort, this work shows that cumulative VPA frequency and amount across modes have no effect on TTP (Aim 1), regardless of women's BMI. I also found that neither cumulative VPA amount nor frequency was associated with miscarriage risk (Aim 2). While VPA frequency was no predictive of infant birthweight, higher VPA amount may be associated with a moderate increase in birthweight (Aim 3). These results suggest women may continue levels of activity that are vigorous prior to and during pregnancy. This work contributes data on the safe upper limit for physical activity prior to and during early pregnancy and supports general health and disease prevention while planning and carrying a pregnancy.

Pregnancy is an ideal time for positive lifestyle modifications, including sustaining physical activity behavior. These studies help advance our understanding of physical exertion around conception and during pregnancy, which will inform individual women about the risks and benefits of engaging in VPA immediately prior to and during pregnancy. This work will also help health care providers to facilitate, counsel, and support women who wish to continue engaging in VPA while planning or carrying a pregnancy. Since VPA may vary within individuals over time, further research is needed, especially measuring VPA as a time-varying covariate. Additional data about body composition, ovulatory function, nutritional status would also enhance our understanding of VPA and pregnancy-related outcomes.

CHAPTER VII

APPENDICES

Appendix 1. First-trimester interview questions assessing vigorous physical activity

For the next few questions think about physical activities you now do in a typical week.

C9a. At this time, do you do any <u>recreational</u> physical activity or exercise, like brisk walking, jogging, swimming, biking, tennis, soccer, or dancing?
Yes No → *C10a.* Don't know → *C10a.* Refused → *C10a.*

C9b. Do any of these recreational activities feel hard or very hard, meaning that the activity caused large increases in breathing and heart rate? *[currently]*
Yes → *fill in table* No Don't know Refused

C10a. At this time, do you do any <u>outdoor household activities</u>, like working in the yard or <u>indoor household activities</u>, like mopping or vacuuming?
Yes No → *C11a.* Don't know → *C11a.* Refused → *C11a.*

C10b. Do any of these household activities feel hard or very hard, meaning that the activity caused large increases in breathing and heart rate? *[currently]*
Yes → *fill in table* No Don't know Refused

C11a. At this time, do you do any <u>child or adult care</u> activities that are not part of your work, like playing with children, pushing a stroller or wheelchair, or carrying or lifting a child or adult *[don't include these activities if part of your work responsibilities]***?**
Yes No → *C12a.* Don't know → *C12a.* Refused → *C12a.*

C11b. Do any of these child or adult care activities feel hard or very hard, meaning that the activity caused large increases in breathing and heart rate? *[currently]*
Yes → *fill in table*
No
Don't know
Refused

C12a. *[if B1. = No or if B2. = 0, then skip to C13a]* **At this time, do you do any <u>work activities</u> like lifting or carrying heavy objects?**
Yes No → *C13a.* Don't know → *C13a.* Refused → *C13a.*

C12b. Do any of these work activities feel hard or very hard, meaning that the activity caused large increases in breathing and heart rate? *[currently]*
Yes → *fill in table* No Don't know Refused

C13a. At this time, do you do any <u>other activities</u> that feel hard or very hard meaning that the activity causes large increases in breathing and heart rate?

Yes → *fill in table* No → *C29.* Don't know→ *C29.* Refused→ *C29.*

[for C14. to C28. complete the table below by asking the following questions]

a. What type of hard or very hard activities do you do during a typical week?

b. How many times in a typical week do you do *[activity]***?**
[If respondent is having difficulties estimating how often she does a particular activity: first ask how many days a week she does X. Then ask, on a typical day, how many times she does X. The interviewer can then help calculate # times a week. Then ask, for average length of time she does X each time and calculate for each week.]

c. On average, for how many minutes or hours do you usually do *[activity]* each week**?**
[If respondent is having difficulties estimating how often she does a particular activity: first ask how many days a week she does X. Then ask, on a typical day, how many times she does X. The interviewer can then help calculate # times a week. Then ask, for average length of time she does X each time and calculate for each week.]
new act: Do you do any other type of hard or very hard ______ activity?

Interviewer: note if this activity is recreational, household, child / adult care, work, or other.	a. What type of hard or very hard activities do you do during a typical week?	b. How many times in a typical week do you do(activity)?	c. On average, for how many minutes or hours do you usually do (activity) each week?
14. R, H, C, W, O	____ □ don't know □ refused	# times, □dk □refused	Hours, minutes, dk, ref
15. R, H, C, W, O	____ □ don't know □ refused	# times, □dk □refused	Hours, minutes, dk, ref
16. R, H, C, W, O	____ □ don't know □ refused	# times, □dk □refused	Hours, minutes, dk, ref
17. R, H, C, W, O	____ □ don't know □ refused	# times, □dk □refused	Hours, minutes, dk, ref
18. R, H, C, W, O	____ □ don't know □ refused	# times, □dk □refused	Hours, minutes, dk, ref
19. R, H, C, W, O	____ □ don't know □ refused	# times, □dk □refused	Hours, minutes, dk, ref
20. R, H, C, W, O	____ □ don't know □ refused	# times, □dk □refused	Hours, minutes, dk, ref
21. R, H, C, W, O	____ □ don't know □ refused	# times, □dk □refused	Hours, minutes, dk, ref
22. R, H, C, W, O	____ □ don't know □ refused	# times, □dk □refused	Hours, minutes, dk, ref
23. R, H, C, W, O	____ □ don't know □ refused	# times, □dk □refused	Hours, minutes, dk, ref
24. R, H, C, W, O	____ □ don't know □ refused	# times, □dk □refused	Hours, minutes, dk, ref
25. R, H, C, W, O	____ □ don't know □ refused	# times, □dk □refused	Hours, minutes, dk, ref
26. R, H, C, W, O	____ □ don't know □ refused	# times, □dk □refused	Hours, minutes, dk, ref

27. R, H, C, W, O	____ □ don't know □ refused	# times, □dk □refused	Hours, minutes, dk, ref
28. R, H, C, W, O	____ □ don't know □ refused	# times, □dk □refused	Hours, minutes, dk, ref

[C29. ask of all respondents]

C29. Think about your overall typical vigorous physical activity since you became pregnant. Compared to before you became pregnant, has your vigorous activity increased, decreased or stayed the same? *[Vigorous activity means that the activity caused a large increase in breathing and heart rate. We want to know whether overall, she does more, less, or the same amount of vigorous activity before and after getting pregnant. She can change the number of times/hours she does vigorous exercise and/or activities that she used to do before getting pregnant may feel different now that she's pregnant.]*

- ❑ Increased
- ❑ Decreased
- ❑ Stayed the same
- ❑ Don't know
- ❑ Refused

Appendix 2. Literature search on VPA and pregnancy-related outcomes

A preliminary PubMed search using terms "(physical activity OR physical strain OR physical stress OR exercise OR fitness OR metabolic equivalents OR exertion OR expenditure) AND (vigorous OR rigorous OR intense OR high impact OR high intensity OR high-intensity OR high fatigue OR strenuous OR heavy) AND (pregnant OR pregnancy)" resulted in 1105 articles (Figure 3). When I included search terms for my outcomes of interest (Aim 1: "(Time to pregnancy OR time to conception OR fertile OR fertility OR fecundability)"; Aim 2: "(spontaneous abortion OR miscarriage OR loss)"; Aim 3: "(birthweight OR birth weight OR infant weight)") and required all search terms to appear in the title or abstract, only 20, 31, and 57 articles remained, respectively. Excluding review articles and articles not focused on adult women engaging in VPA during pregnancy, 11, 9, and 38 articles remained. Search was conducted August 7th, 2018 with no restriction on publication year.

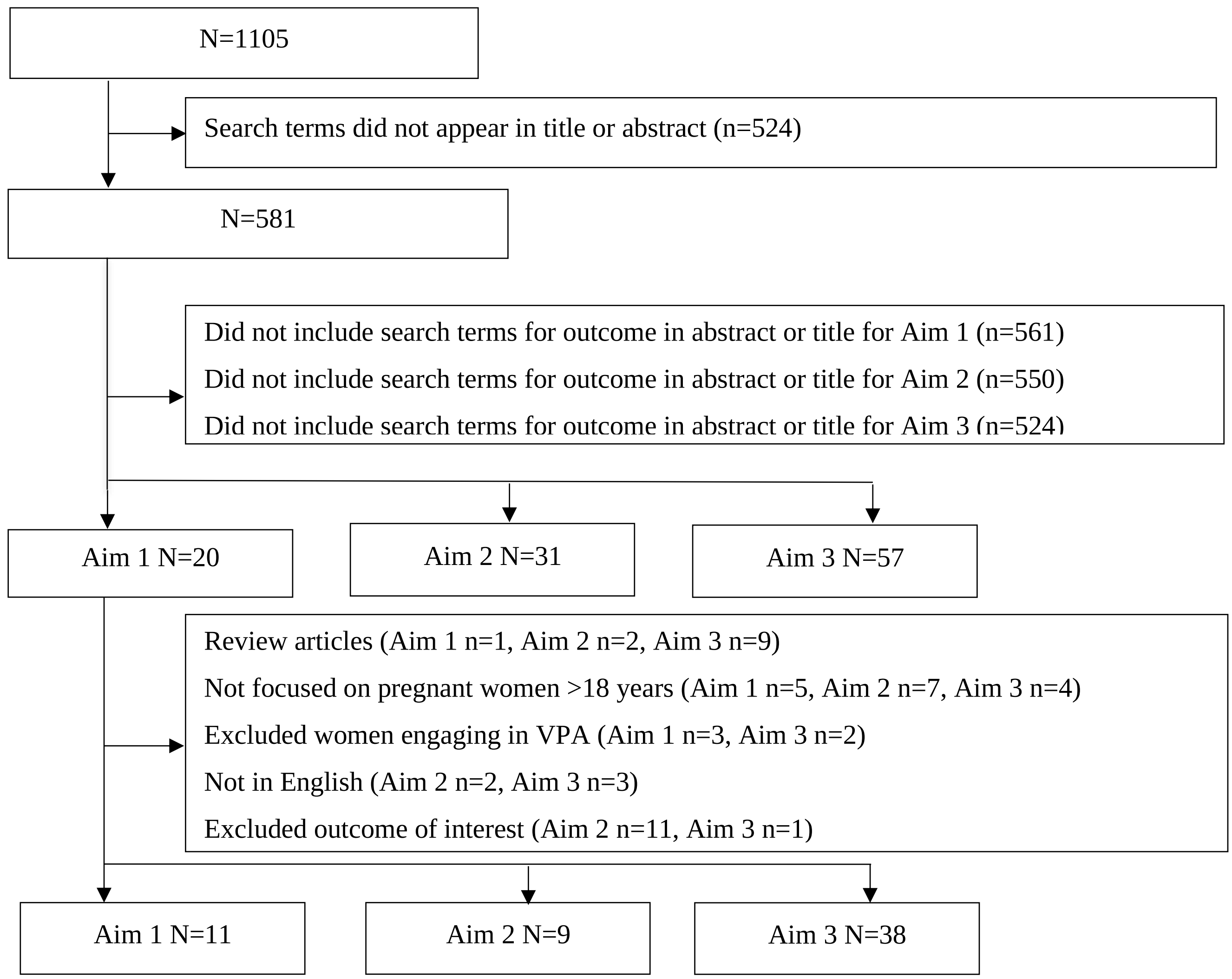

Figure 16. Flow diagram of preliminary literature search

Appendix 3. Details on the collection and construction of key covariates

Table 20. Data collection and variable construction

Covariates	**Source**	**Construction (operationalization)**
Maternal age	First-trimester interview	Difference between date of birth and LMP (years)
Maternal BMI	Ultrasound visit; First-trimester interview	Height/weight measured at ultrasound visit; self-reported height/weight was used when measurements not available (kg/m^2)
Maternal race/ethnicity	First-trimester interview	Self-reported race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other)
Maternal education level	First-trimester interview	Highest level of education completed (High school or less, some college, and college or more)
Parity	First-trimester interview	Total number of prior deliveries after 20 weeks' gestation (nulliparous, 1, 2+)
Household income	First-trimester interview	Monthly household income (≤$40,000; $40,001-80,000; ≥$80,001)
Marital status	First-trimester interview	Single/never married, married, separated, divorced, widowed (married vs. other)
Maternal smoking status	First-trimester interview	Smoking status at time of interview (never, distant quit [>4 months], current or recent quit [≤4 months])
Maternal alcohol use	First-trimester interview	Drinking status at time of interview (never, distant quit [>4 months], current or recent quit [≤4 months])
Maternal vitamin use	First-trimester interview	Take prenatal vitamins (no vs. yes)
Maternal folic acid use	First-trimester interview	Take vitamins or supplements with folic acid (no vs. yes)

Pregnancy intent	First-trimester interview	Intent to get pregnant (unintended/not trying vs. intended/trying)
Frequency of intercourse	First-trimester interview	Frequency of intercourse (times/week)
Last method of contraception	First-trimester interview	Last method of contraception (hormonal vs. non-hormonal)
Maternal diabetes	First-trimester interview	Gestational and pre-gestational diabetes status (None, type I, type II, gestational diabetes, multiple types)
Nausea	First-trimester interview	Difference between the start date and end date of nausea (days)
Vomiting	First-trimester interview	Difference between the start date and end date of vomiting (days)
Infant sex	Hospital discharge summaries and prenatal care records; birth and fetal death records; participant self-report of pregnancy outcome form	Infant sex (male vs. female)
Gestational weight gain	First-trimester interview; vital records	Difference between self-reported weight at deliver on the birth certificate and first-trimester weight measured at ultrasound visit

CHAPTER VIII

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