Factors correlated with physical activity during pregnancy and associations of physical activity with spontaneous abortion, length of gestation, and birthweight

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ABSTRACT

Anne Marie Zaura Jukic: Factors correlated with physical activity during pregnancy and associations of physical activity with spontaneous abortion, length of gestation, and birthweight
(Under the direction of Julie Daniels)

The first study aim was to identify characteristics associated with self-reported physical activity at 17-22 and 27-30 weeks gestation using data from the Pregnancy, Infection, and Nutrition 3 Study. Correlates of low level recreational activity were mostly sociodemographic but most sociodemographics were not also correlated with higher level recreational activity. At 27-30 weeks, overweight/obese women were less likely to engage in recreational activity. At 17-22 weeks, women who began prenatal care later and women with a history of miscarriage were less likely to engage in recreational activity. Physical activity was positively associated with partner support and enjoyment of physical activity. This analysis is limited by self-reported physical activity measures and the performance of model selection based on a p-value. These associations may help target interventions to increase activity during pregnancy.

The second aim was to examine the association between vigorous physical activity and gestational age and birthweight (among term births). The third aim was to examine the association between vigorous physical activity and spontaneous abortion. Both aims used data from the Right From the Start Study, which measured vigorous physical activity at 13-16 weeks gestation. The association of total vigorous physical activity with preterm birth was U-shaped. However, vigorous recreational activity was associated with lower odds of preterm birth. Performing at least five sessions of vigorous recreational activity per week was associated with decreased odds of earlier birth (odds ratio (OR) (95% confidence interval, (CI)):0.66 (0.36, 1.21)). Women who reported starting exercise in preparation for pregnancy had lower odds of earlier birth OR(CI): 0.65 (0.45, 0.94), none gave birth preterm. Women who reported decreasing their vigorous activity from pre-pregnancy to interview had lower odds of spontaneous abortion, OR(CI): 0.44 (0.32, 0.61). We found no evidence that vigorous recreational activity was associated with adverse changes in pregnancy outcome. These analyses are limited by self-reported activity measures and low prevalence of vigorous activity. The spontaneous abortion analysis is susceptible to recall bias. Our analysis suggests that vigorous recreational activity during pregnancy may be safe. Future studies should examine the association of vigorous recreational activity with maternal injury and other perinatal outcomes.

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I. BACKGROUND

Introduction

As obesity continues to escalate in the United States[1], health care providers are becoming more committed to advocating regular recreational physical activity to their patients[2], however, when the patient is a pregnant woman the safety of this recommendation is less clear. The literature is inconclusive regarding the associations of physical activity and pregnancy outcomes. Therefore, to better inform clinicians and their patients in their decisions regarding physical activity during pregnancy, research should attempt to clarify the associations between physical activity and pregnancy outcome. The goals of the following project are to assess the associations of physical activity in early pregnancy with spontaneous abortion, length of gestation, and growth restriction, and to describe the maternal and pregnancy-related characteristics that are associated with women's physical activity across pregnancy.

Conceptual Framework

Introduction

In order to understand the implications of physical activity for pregnancy we must first review basic physiological responses to physical activity. Then these responses will be assessed in the context of pregnancy with a description of how they may antagonize or enhance the physiological changes necessary for a successful pregnancy.

Physiology of Physical Activity

When a bout of vigorous physical activity begins, the body is signaled to begin several physiologic adaptations. Some of the adaptations occur quickly, in a matter of seconds, while others take several minutes to induce. If the physical activity is continuous, all of the adaptations will be fully employed. If the activity is intermittent, some of the adaptations will be fully used while others will never begin.

When physical activity begins muscle tissue takes up more oxygen in order to produce more adenosine triphosphate (ATP) which is the compound necessary for muscle cells to perform work. This requirement for oxygen is immediate, but the physiologic responses that increase oxygen delivery are not, and thus a deficit is created in the amount of oxygen available to the working tissues[3]. The extent of this deficit is related to the intensity of the physical activity performed. It takes approximately 2 to 4 minutes for physiologic changes to meet the increased demand for oxygen, until the supply meets demand, energy is produced anaerobically[3].

In order to meet the demands of physical activity heart rate and respirations increase. Both the heart rate and the volume of blood pumped with each beat increase[3]. Breathing becomes deeper than at rest and this leads to greater expansion of the lung alveoli resulting in greater surface area for gas exchange to occur[4]. Additionally, blood circulation to the lungs is increased which causes more capillaries to open, increasing the rate of gas exchange[4].

In addition to the lungs, the amount of blood flow is altered for other organs (Table 1). A greater proportion of pumped blood is diverted to the organs that will support the increased activity (heart, skeletal muscle, skin) while less pertinent organs will have decreases in flow (digestive tract, kidneys, liver, bone, other)[4]. Blood flow to the skin is increased to dissipate the heat that is generated[4]. The rate of blood flow to the brain is unchanged, and remains constant regardless of the activity[4].

Table 1. Changes in blood flow in response to moderate exercise.*

Organ	Blood flow at rest (ml/min)	Blood flow during moderate exercise (ml/min)
Digestive tract, liver	1,350	600
Kidneys	1,000	550
Skeletal Muscle	750	8,000
Brain	650	650
Bone, other	650	450
Skin	450	1,700
Heart	150	550

*Adapted from L. Sherwood, age, weight, gender of population not specified[4]

Changes in glucose uptake also occur in response to physical activity. The contraction of skeletal muscles stimulates the insertion of glucose transporters into the plasma membrane of the working muscle cell[4]. In a resting state these transporters would only be inserted in response to insulin[4]. The increase in glucose transporters allows blood glucose to pass into the muscle cells, thereby lowering blood sugar. To keep the supply of glucose in the blood high, epinephrine is released which stimulates the liver to convert glycogen back into glucose[4]. Epinephrine also stimulates the skeletal muscle to break-down its glycogen[4]. Muscle tissue is unable to fully synthesize glucose from glycogen; instead, the muscle forms lactic acid and releases it into the blood stream so that it can be converted to glucose by the liver[4]. Finally, epinephrine inhibits the secretion of insulin, which allows the level of glucose in the blood to remain elevated and available to the muscles[4].

The increases in energy expenditure with physical activity also lead to increases in body temperature. As physical activity begins, body temperature rises until the mechanisms for dissipating heat have had adequate time to function[4]. Body temperature is then held constant, but at several degrees higher than in the resting state[4]. Temperature is held constant through vasodilation in the skin, as previously mentioned. Additionally, the elevation in body temperature stimulates the body to begin sweating[4]. Sweating leads to losses of water and minerals which can lead to dehydration.

How Physical Activity May Affect Pregnancy

The human body has many adaptations for meeting its increased needs for oxygen, glucose, and heat dissipation in response to physical activity. In addition, changes in epinephrine and other hormones induced by physical activity may have implications for pregnancy. The next section examines how these adaptations conflict with or support the needs of pregnancy.

Observed changes in blood flow associated with physical activity have led to the concern that the fetus will experience reduced blood flow. The potential reduction in blood flow to the fetus could result in hypoxia, nutrient deprivation, or increased exposure to the fetus's own metabolic wastes. Two questions are of interest; first, when pregnant, is the circulatory preference for the heart, lungs and skeletal muscle maintained, even at the expense of uterine or placental blood flow? And second, if blood flow is diverted from the uterus and fetal tissues during physical activity, is it detrimental?

These questions have been examined in several animal models. In pregnant sheep, physical activity for 40 minutes at 70% of maximal oxygen consumption led to a decrease in uterine blood flow[5]. In goats, even during brief (5-7 minute) bouts of activity, uterine blood flow was lower than at rest, with a greater decrease in myoendometrial blood flow compared to placental blood flow[6]. In rabbits, however, the response to physical activity is blunted during pregnancy with a smaller decrease in uterine artery blood flow during exercise compared to non-pregnant rabbits [7]. All of these animal studies were performed during the latter portion of the animals' pregnancies. Gestational age may drive differences in the effect of physical activity on uterine blood flow, for example in rabbits, the reduction in blood flow to the uterus in response to physical activity is confined to early gestation[8].

The literature regarding women is inconclusive. The challenge in studying women is in measuring uterine blood flow while they perform physical activity as the movement itself precludes the use of sensitive measurement tools. As a result, most studies of physical activity and blood flow rely on measurements made immediately after an activity session has been completed. However, the time between cessation of physical activity and measurement of blood flow patterns varies depending on the complexity of the measurement and instrumentation involved. One such study found that the average resistance to blood flow in the placental beds of the uterine arteries (as measured by Doppler pulsatile index) increased slightly after anaerobic physical activity was performed (high intensity, for as long as possible)[9]. Other Doppler studies have found similar results. In one study, five minutes of biking led to an increase in uteroplacental vascular resistance[10]. In another, strenuous biking led to a decrease in blood flow in the main uterine artery[11]. In other studies, however, there appeared to be no effect on uteroplacental blood flow of a 3 minute[12] or 6 minute[13] biking session. A 3 minute isometric handgrip exercise was not associated with an increase in placental vascular resistance as measured by a Simultaneous Multigate Spectral Doppler Imaging technique, which is thought to be more sensitive than a traditional Doppler scan[14]. The differences between studies could be due to the differing intensity and duration of physical activity in each study. Changes in blood flow may be related to the training status of the study population. A study of pregnant women at 36 weeks gestation found that portal vein blood flow, which may resemble uterine blood flow, is reduced during physical activity; however, this reduction is blunted in women who perform regular physical activity (40-60 minutes, 4-6 days per week). Thus a single exercise session in a pregnant woman who exercises regularly, does not elicit the same drop in portal vein blood flow seen in unconditioned pregnant women[15].

The previously described studies included healthy populations of women, and it is important to mention that women with certain pregnancy complications may be at higher risk for exercise induced vascular changes. For example, women with uteroplacental vascular insufficiency (defined as uterine artery mean pulsatility index >1.45 at 22-26 weeks of gestation) experienced a decrease in umbilical artery blood flow after submaximal exercise relative to women without this condition[16]. Women with pre-eclampsia or diabetes in the 32nd to 40th week of pregnancy showed a drop in placental blood flow 30 minutes after performing six minutes of bicycle activity. The control women did not show such a drop; the three groups had similar measures of placental flow before and 1 minute after activity[17].

Changes in uterine blood flow are one measure of the potential for fetal hypoxia. However, since changes in uterine blood flow may not be a direct measure of the fetal experience, fetal heart rate is also often examined. In general, studies have found some increase in fetal heart rate during or after maternal physical activity[9, 10, 18-20]. However, most of these studies also report average fetal heart rates that, while elevated from baseline, are still within the normal range (120-160 beats/minute)[9, 10, 18, 19]. In the one study in which the average was above this range, the heart rate returned to pre-activity levels within approximately 15 minutes of activity end[20]. Several authors have also made the point that changes in fetal heart rate may occur as a result of maternal epinephrine, and may not represent a decrease in oxygen availability[9, 18-20].

If physical activity does restrict fetal blood flow, it may not be harmful to the fetus. Blood flow to the uterus and placenta increases throughout pregnancy[21]. The fetus may have enough blood flow that the changes caused by physical activity are relatively insignificant[10]. Another mitigating factor is the decrease in plasma volume (~20%) that occurs during physical activity[5]. The resulting hemoconcentration may help to maintain adequate oxygen delivery to the fetus[5]. Oxygen saturation percentage may be slightly increased in pregnant women, which would maintain oxygen availability to the fetus. In one study, women biked at 85% of their predicted maximum heart rate at time points before and during pregnancy[22]. Their oxygen saturation during biking when performed before pregnancy, was approximately 98% while from 8 to approximately 29 weeks of gestation, their oxygen saturation was approximately 99%. In non-pregnant women oxygen saturation is either unaffected or slightly decreased during physical activity.

In spite of the mechanisms the body has for dissipating increased heat, some increase in body temperature can occur, particularly with physical activity of higher intensity and longer duration. The potential increase in maternal body temperature is of concern because hyperthermia has been associated with adverse pregnancy outcomes including birth defects and pregnancy loss[23]. The extent of damage caused by hyperthermia is related to the maximum temperature achieved, the duration of the temperature elevation, and the age of the embryo or fetus at exposure [23].

Few studies have examined the thermal response to physical activity in pregnant women. During pregnancy, body temperature may be less elevated in response to physical activity compared to preconception[24, 25]. This observation is consistent with the fact that during pregnancy the metabolic processes of the fetus generate heat that must be dissipated. Thus, pregnant women naturally adapt an increased ability to release heat (through vasodilation, increased skin circulation, and increased plasma volume). These physiological changes may also protect the fetus from increases in heat due to physical activity. These studies are limited, however, as they are based on small sample sizes (N=10 and 14), planned healthy pregnancies, and women who were physically active prior to pregnancy.

As described, physical activity increases the muscles' need for glucose. While mechanisms are in place for increasing blood glucose in response to the increased demand, these mechanisms may not be enough to fully maintain blood glucose at pre-activity levels. Glucose is the predominant energy source for the developing fetus, and is particularly important during the third trimester. Decrements in blood glucose during[26] or immediately post-physical activity[24, 27-29] have been observed in pregnant women. The decrease may depend on gestational age with a larger decrease in the third trimester compared with the first trimester[26], the second trimester[24, 27], or the first and second trimester[28]. The on blood glucose levels appears to be transient, with levels similar to pre-activity by 15[27], 20[26], or 45[28] minutes; although one study found no rebound by 20 minutes[29].

Similar to non-pregnant women, physical activity in pregnancy is associated with a decrease in insulin levels[27-29]. Pregnant women in these studies had higher insulin levels prior to activity compared to non-pregnant controls. Relative insulin resistance is a normal adaptation of pregnancy, and is thought to increase glucose availability to the fetus[21]. The decrease in insulin levels during activity may leave the fetus to compete with its mother for glucose[27]. A further concern is the potential for reduced norepinephrine response to physical activity in pregnant women[27, 28]. Since norepinephrine is involved in maintaining blood glucose levels, diminished response in pregnancy could further reduce the body's ability to maintain glucose availability.

Summary

Physical activity may overwhelm maternal mechanisms for heat dissipation or lead to competition between mother and fetus for oxygen and glucose. In theory, this could be detrimental to the pregnancy culminating in spontaneous abortion, growth restriction, or preterm birth. The scientific literature has not definitively affirmed or discredited the existence of this maternal-fetal competition, nor has it fully investigated the mechanisms by which physical activity may support pregnancy. For example, in non-pregnant individuals, physical activity increases blood volume, heart size, and stroke volume, quickens the skin's sweat response, and increases fat metabolism during rest[30]. These changes may be beneficial for a developing pregnancy. However, in total, we cannot rule out the possibility that physical activity is detrimental to pregnancy.

Review of the Literature

Introduction

Given the potential for competition between mother and fetus and the inconclusive nature of the physiological literature, it is important to examine the human epidemiological evidence for an association of physical activity with pregnancy outcome. First, we review the risk factors for, and potential mechanisms of, miscarriage, preterm birth, and growth restriction. Second, we review the literature investigating the associations between physical activity and these three pregnancy outcomes.

Spontaneous Abortion

The medical definition of spontaneous abortion is, "the termination of pregnancy by any means before the fetus is sufficiently developed to survive…without medical or mechanical means to empty the uterus"[21]. Epidemiological studies have used several definitions of spontaneous abortion. In some cases, spontaneous abortion is defined as an intrauterine pregnancy loss prior to 20 weeks of gestation and in others 22 weeks or 28 weeks. Hospital-based studies of spontaneous abortion include only losses that involved hospital admittance while other studies are based on participant self-report. Some studies required a chromosomal assessment of the aborted tissue and compared chromosomally normal with chromosomally abnormal spontaneous abortions.

The rate of pregnancy loss after implantation has been estimated at 30%[31]. Of recognized pregnancies with a gestational sac, the subsequent probability of loss has been estimated at 11.5%[32]. Approximately 50-60% of first trimester miscarriages are associated with a chromosomal defect of the embryo; the remainder are largely unexplained [33]. Studies investigating risk factors for pregnancy loss have not had great success, with many studies finding no characteristics associated with increased risks and some finding very small increases in risk. (For an informal comparison of these studies see Appendix A.)

Older women have been shown to have a higher risk of spontaneous abortion[32, 34-40]. The age range included in each study varies, but one study found increased odds of spontaneous abortion as early as age 30 (relative to age 25-29)[37]. Another study has suggested that the proportion of pregnancies spontaneously aborted increases monotonically with maternal age[41]. Warburton and Fraser, in one of the earliest studies of this subject[39], suggested that the increase in risk associated with maternal age may be an artifact caused by women with a history of spontaneous abortion being successively older at each pregnancy attempt. However, when they looked at women with no history of abortion, the risk still increased with age. In total, it seems that spontaneous abortion increases with age with women aged 35-39 having approximately twice the risk of spontaneous abortion as women aged 25-29, and women over 40 having 2-3 times the risk (Figure 1).

Similarly, increasing paternal age has been related to spontaneous abortion[35, 39, 42]. The associations are weaker for paternal age compared with maternal age with men over 40 having approximately 1.5 times the risk of men aged 25-29. For both men and women, increasing age may be associated with an increase in chromosomal abnormalities which then leads to spontaneous abortion[36]. In a study of women undergoing assisted reproductive technologies, the association of spontaneous abortion with maternal age was only observed among women who conceived using their own oocytes[43]. Women who conceived using donor oocytes showed a consistent proportion of spontaneous abortion across all ages. The authors suggest that increasing age is associated with decreasing oocyte quality which then leads to an increasing proportion of spontaneous abortions.

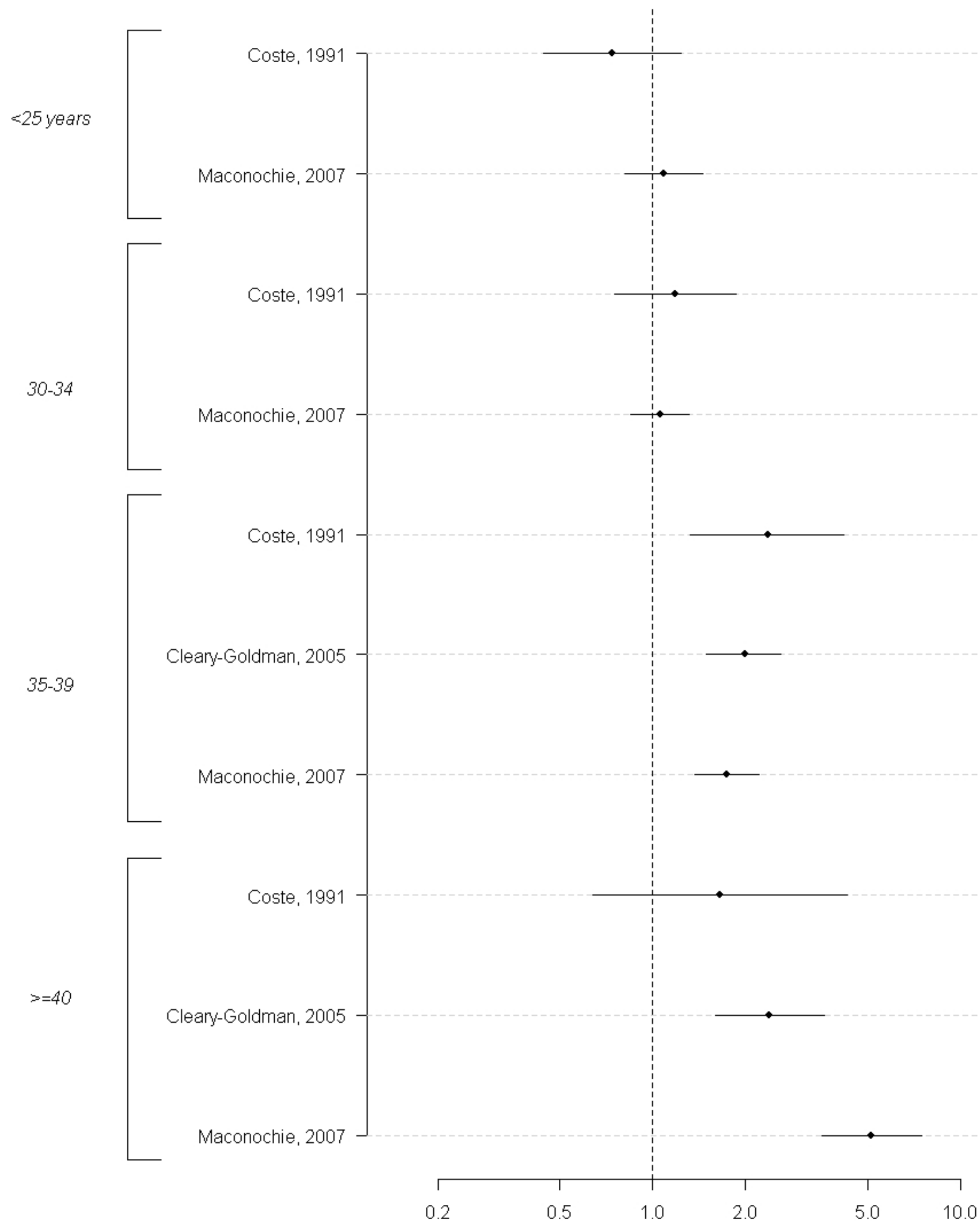

Figure 1. Point estimates (odds ratios or risk ratios) from studies of maternal age and spontaneous abortion (referent category is age 25-29 years).

While many studies adjust for parity in their multivariable analyses, few studies have reported an association of parity with spontaneous abortion. One author that found an association between higher parity and spontaneous abortion attributed the observation to confounding by maternal age (older women are at higher risk of spontaneous abortion and are more likely to be parous)[32]. The potential association between parity and spontaneous abortion is further complicated by the association of history of spontaneous abortion with increased risk of spontaneous abortion[44-46]. Women with a history of spontaneous abortion will likely also be of lower parity. In this case, higher parity would appear protective. Lower odds of spontaneous abortion has been reported for women with a previous live birth, even after adjustment for both age and previous miscarriage (OR: 0.63 (0.48, 0.84)), suggesting an independent association of parity with spontaneous abortion[35]. In total, it is unclear if the reported associations for age, history of miscarriage and parity are independent.

Recently, vitamin use has been associated with lower risk of spontaneous abortion (OR (CI): ~0.5 (~0.3-0.6)[35, 47]. The association of vitamin use with spontaneous abortion has been inconsistent and even controversial. Repeated miscarriage has been associated with higher levels of plasma folate (9.0-13.9 nmol/L: OR (CI): 2.3 (1.1, 4.6) and >14.0 nmol/L: OR (CI): 2.2 (1.0, 4.9))[46]. However, higher levels of plasma folate have also been associated with lower risk of any spontaneous abortion (not only repeated) with estimates for the same categories of folate of, OR (CI): 0.84 (0.59, 1.20) and 0.74 (0.47, 1.16), respectively[48]. A Cochrane review of randomized trials found no association of any vitamin use compared with no or minimal vitamin use, and spontaneous abortion (OR (CI): 1.08 (0.95, 1.24))[49]. While overall no association was detected, attention has been focused on one larger trial (N = 5502) that reported a slightly increased risk of spontaneous abortion with vitamin use (RR (CI): 1.14 (0.97, 1.34))[50]. A subsequent analysis of data from a Californian Health Maintenance Organization supported an association between multivitamin use and spontaneous abortion (RR (CI): 1.14 (0.96, 1.35)). Explanations of these findings included a true abortifacient effect[51, 52], random error[53], survival bias[51, 52, 54], and effects on menstrual cycle function[55]. A later study of almost 24,000 women found no increase in spontaneous abortion with folic acid supplementation (OR (CI): 0.97 (0.84, 1.12))[56]. While this seemingly exonerates folic acid, the studies reporting increased spontaneous abortion incidence included multivitamins. Thus the association of multivitamins with spontaneous abortion remains unclear.

Surprisingly, few studies have examined the association of maternal body mass and spontaneous abortion. One early study reported reduced risk of spontaneous abortion with obesity (OR (CI): 0.80 (0.56, 1.16)[57]. The data for this analysis were obtained from control women in case-control studies of cancer and reproductive histories were recalled (average age ~50). Additionally, the authors did not specify how “obesity” was defined in terms of measure (body mass index or body weight) or cutpoint. A subsequent study of primiparous women suggested higher risk of early miscarriage (OR (CI): 1.2 (1.1-1.5)) and repeat miscarriage (OR (CI): 3.5 (1.0, 12.0) for women with body mass index greater than 30 kg/m^2 (N=1644) (compared with 19-24.9 kg/m^2 (N=3288))[58]. This association was not solidly confirmed subsequently, although this study had a smaller number of obese women (N=390) and their confidence interval is not incompatible with a small increase in risk (OR (CI): 0.92 (0.65, 1.31))[35]. Finally, an analysis from the Danish National Birth Cohort suggested risks of fetal death for obese (body mass index >30 kg/m^2) women that were higher than normal weight women (18.5-24.9 kg/m^2) and increased over gestation from 14-19 gestational weeks (HR (CI): 1.6 (1.0, 2.5)) to >40 weeks (HR (CI): 4.6 (1.6, 13.4))[59]. Thus, while few studies exist, an association of pre-pregnancy body mass index with spontaneous abortion appears likely.

Several studies report a significant positive association of smoking with spontaneous abortion with odds ratios ranging from 1.2 to 3.3[38, 60-65]. Other studies have found non-significant increases in spontaneous abortion with cigarette smoking[35, 66-71], or no association at all[37, 72] (Figure 2). Differences between studies may be due to varying measures of smoking (cigarettes or cotinine), categories of smoking, the time frame the smoking exposure reflects (preconception, first trimester, second trimester) or the gestational ages of the spontaneous abortions. Current smoking has also been associated with recurrent miscarriage (at least two)[73, 74]; in one case the risk increased with increasing number of cigarettes smoked[74]. Maternal exposure to environmental tobacco smoke may also be associated with higher risk of spontaneous abortion[61, 75]. Paternal smoking may be associated with spontaneous abortion either directly or through environmental tobacco smoke[76].

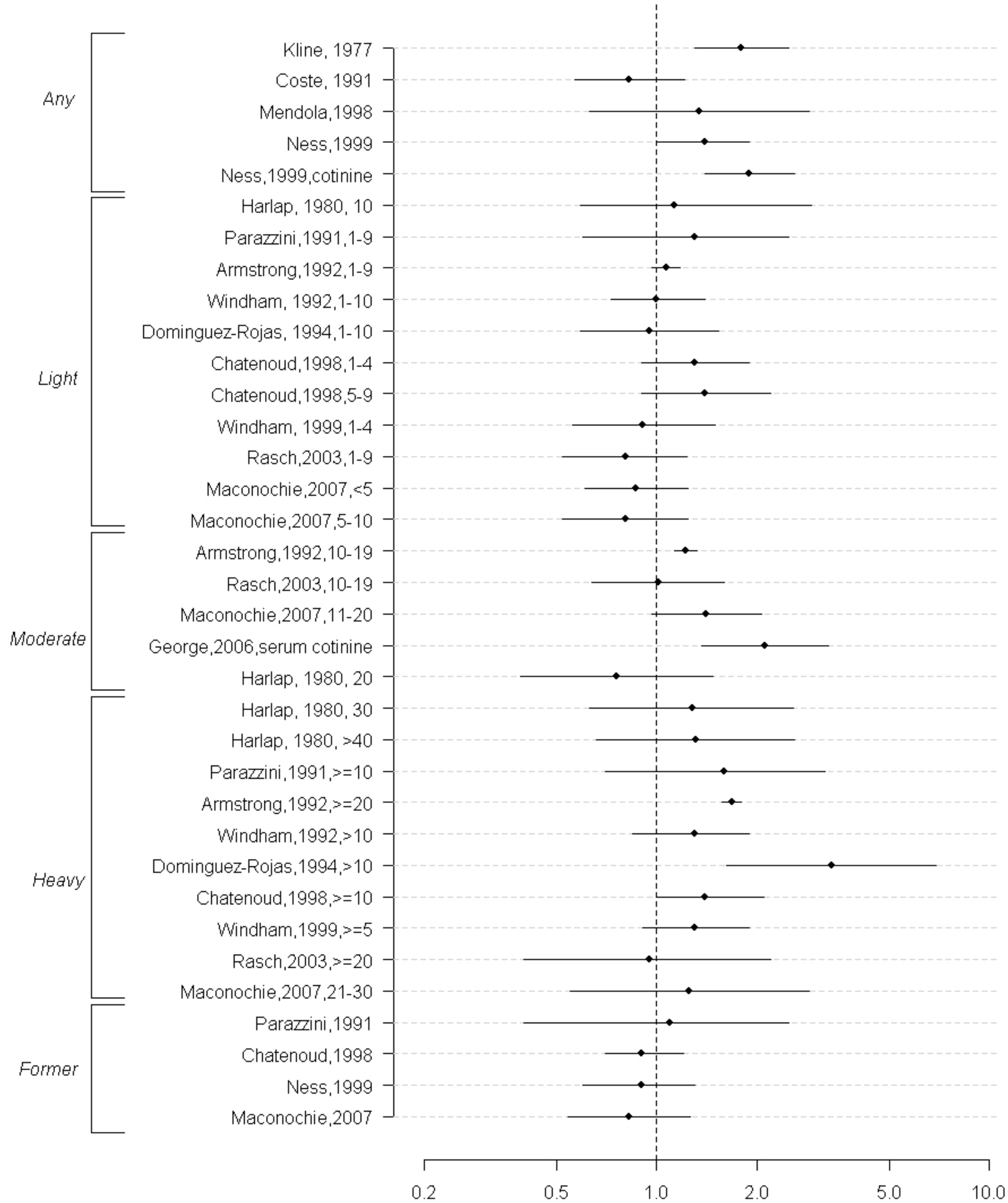

Figure 2. Summary of effect estimates (odds ratios and risk ratios) from studies investigating maternal cigarette smoking and spontaneous abortion. (The numbers following the reference are cigarettes/day.)

Coffee consumption of at least eight cups per day has been associated with late (at least 20 weeks completed gestation) fetal death[77]. Coffee intake in the first trimester has also been statistically significantly[60, 66] and non-significantly[74] associated with spontaneous abortion, with one study finding a dose-response association of cups of coffee per day and the odds of spontaneous abortion[60]. The association of coffee with spontaneous abortion is thought to be related to caffeine. The odds of spontaneous abortion may be increased in women who consume as little as 141 mg of caffeine per day[38] (one cup of drip coffee contains approximately 100 mg of caffeine). Other studies have reported an odds ratio for spontaneous abortion of at least 1.4 for caffeine levels of over 163 mg/day[78] and at least 301 mg/day[71, 79], although one study reported a "non-significant" association for as much as 300 mg/day (a point estimate was not reported)[80]. None of the caffeine studies adjusted for nausea, a potential confounder. However, in studies that have accounted for nausea, the association of spontaneous abortion with caffeine is still unclear. In some cases caffeine has been associated with spontaneous abortion even after adjustment for nausea with reported odds ratios of approximately 2 relating caffeine intake of 301-500 mg/day and >500 mg/day[81] or with increasing levels of caffeine (p for trend =0.05)[82]. The latter study further reported a significant interaction between smoking and caffeine intake; the odds of spontaneous abortion increased for increasing levels caffeine intake among non-smokers only. In contrast to these analyses, after accounting for nausea, caffeine was not associated with spontaneous abortion, even at levels above 300[83] and 500 mg/day[35].

Nausea may be an modifier of the association between caffeine and spontaneous abortion with associations between caffeine (>300 mg/day[84] or ≥100 mg/day[85]) and spontaneous abortion only among women who experience nausea. The hypothesis is that the absence of nausea signals a pregnancy destined for termination, regardless of caffeine exposure.

More specific investigations of the association of caffeine with spontaneous abortion have focused on genotypic and phenotypic information. Both CYP1B1[86] and CYP1A2[87] may modify the association between caffeine and spontaneous abortion. These enzymes are involved in the metabolism of several substrates including hormones, drugs, and notably, caffeine.

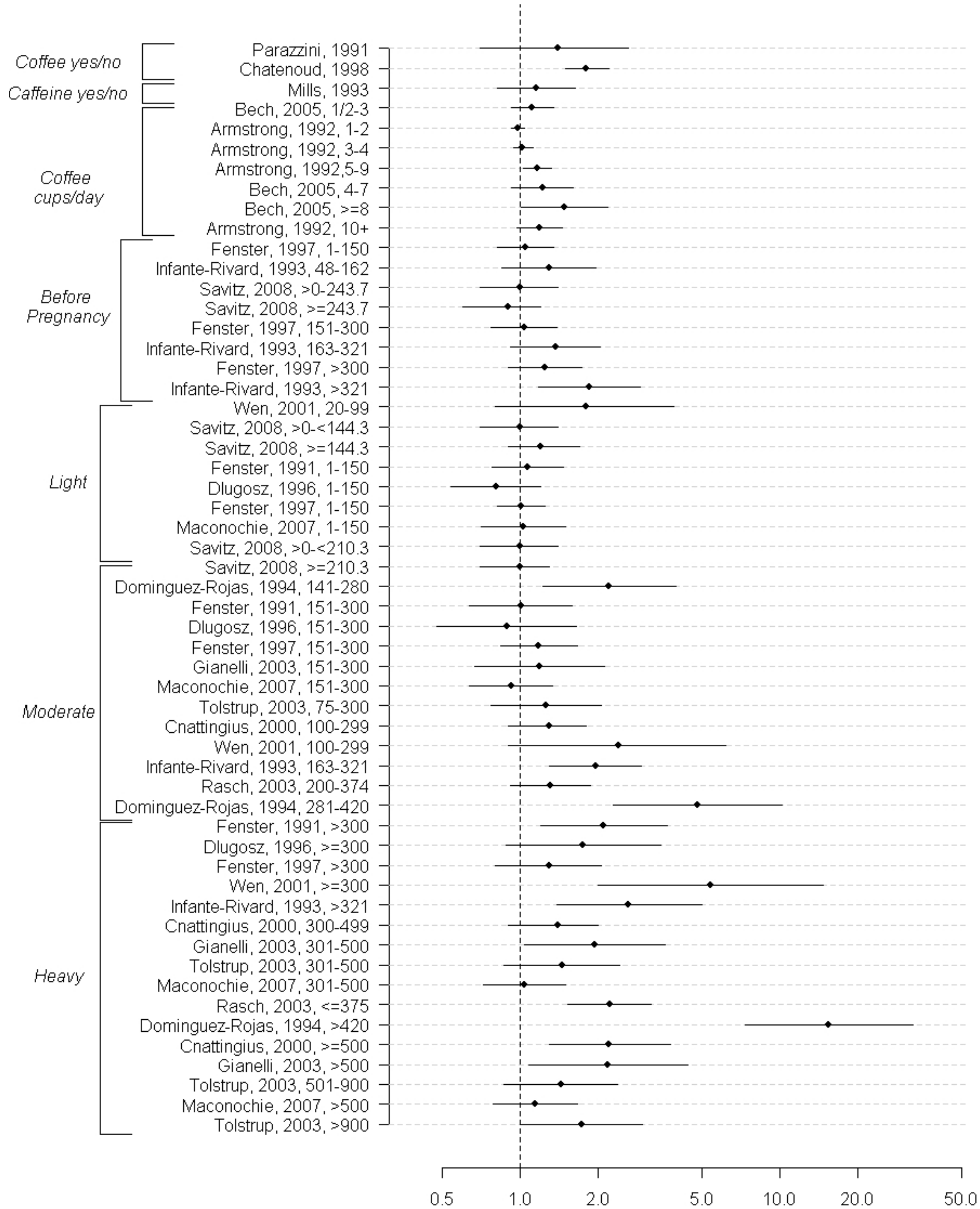

Figure 3. Graphical summary of the studies investigating caffeine (in mg/day) and spontaneous abortion (genetic studies are not included).

Alcohol intake has also been inconsistently associated with spontaneous abortion. Studies of any versus no alcohol consumption tend to find null (RR (CI): 0.9 (0.6, 1.5))[74] or small associations (OR (CI): 1.2 (1.0, 1.4)[66]). Some strong associations of moderate to heavy drinking have been reported, with risk ratios or odds ratios ranging from 2 to 4 for daily alcohol consumption in the first trimester[35, 88] or for one drink or more per day "during pregnancy"[70]. However, other studies report much smaller odds ratios (1.3[79] and 1.8[60]) for high levels of intake (more than 13 and 21 or more drinks per week, respectively), and one study has found no association of alcohol consumption even when stratified by frequency[89]. Two studies that assess the amount of alcohol consumed (in units per week) reported conflicting results, one suggesting a strong association of 5 or more units of alcohol per week (OR = 4.8)[72] and one suggesting a small association (OR = 1.4) for a larger amount of alcohol intake (more than 14 units/week)[35]. However, only three of these studies have adjusted for nausea which may be a confounder[35, 66, 88]. In two of the studies[35, 88], adjustment for nausea did not substantially alter the point estimates (although confidence intervals widened); the third study adjusted for nausea, but does not indicate its importance as a confounder. It is possible that the timing of the alcohol exposure is important to its pathology since one study found a positive association of alcohol (in drinks per day) with spontaneous abortion in the second trimester, but not the first trimester[70] (this study did not adjust for nausea). Another difficulty in interpreting the alcohol literature is the possibility of biased reporting by the mother, as many of the studies collected alcohol intake information retrospectively and heavy consumption of alcohol is likely to be stigmatized. Additionally, alcohol consumption and smoking may interact[66], thus estimates of associations with alcohol will be dependent on the smoking profile of the participants.

Non-steroidal anti-inflammatory drugs (NSAIDs) or aspirin around the time of conception (HR (CI): 5.6 (2.3, 13.7), 4.3 (1.3, 14.2), respectively) or for more than one week (HR (CI): 8.1 (2.8, 23.4), 3.0 (0.7, 12.9)) have been associated with a higher rate of miscarriage[90]. Paracetamol (acetaminophen products) which may be prescribed for similar indications as NSAIDs or aspirin, showed no association although confidence intervals were wide (HR (CI): 0.8 (0.2, 3.3), 0.7 (0.2, 2.9)). This suggests that the association is for the drug itself and not the indication. Similarly, in a Danish study women who filled prescriptions for NSAIDs seven to nine weeks before their miscarriage had almost 3 times the odds of spontaneous abortion compared to filling a prescription at any time in the first trimester (CI: 1.8, 4.0)r[91]. The authors of the Danish study updated their results adjusting for gestational age, and still found a positive, although weaker, association (OR (CI): 1.59 (0.93, 2.7))[92]. The Danish study suggests that risk of spontaneous abortion is higher if the prescription is filled earlier. It is unclear, however, if this is influenced by reverse causality, symptoms of miscarriage prompt pain medication use. Decreased risk of spontaneous abortion with aspirin use during pregnancy (first through fourth month) was reported in another study, with estimates ranging from 0.73 to 0.92[93]. The association for any aspirin use during pregnancy was OR (CI): 0.79 (0.62, 1.01). Exposure ascertainment is challenging as it is difficult to capture infrequent or inconsistent NSAID use.

Feeling “stressed, anxious, depressed, out of control or overwhelmed” during the first 12 weeks of pregnancy was associated with three times the odds of spontaneous abortion as women who were “happy, relaxed or in control” (CI: 2.5, 3.8)[35]. In the same study, an increasing number of reported stressful or traumatic life events were also associated with increasing odds of spontaneous abortion with odds ratios from approximately 1.5 to 3. This is consistent with another study which found increased odds of chromosomally normal spontaneous abortion among women with at least one reported recent negative life event compared to women who did not report any (OR (CI): 2.6 (1.3, 5.2))[94]. Maternal work-related stress was not strongly related to spontaneous abortion as an independent predictor (OR (CI): 1.2 (0.8, 1.7)), however, the association between work stress and spontaneous abortion was higher among older women, smokers and primigravid women (odds ratios from 1.4 to 1.8)[95]. The association of spontaneous abortion with stress may be more pronounced in early gestation, thus timing of stress measurement during pregnancy in a given study will affect the observed association[96].

In addition to maternal and paternal behaviors and characteristics, physiological mechanisms have been implicated in spontaneous abortion. These mechanisms may be hormonal, as in endocrine disorders, or immune, as in lupus, or mechanical, as in placental defects. Discussion of these mechanisms follows.

Endocrine disorders such as luteal phase defect and polycystic ovary disease have been implicated in pregnancy loss[97]. Luteal phase defect may result in poor progesterone production which is not sufficient to maintain a pregnancy. However, progesterone treatment has not been clearly beneficial in women with recurrent pregnancy loss. Thus it is unclear if low progesterone is a biological mechanism responsible for pregnancy loss. An association between polycystic ovary disease and pregnancy loss is hypothesized because women with recurrent pregnancy loss have a high prevalence of polycystic ovary syndrome. Polycystic ovary syndrome is associated with hormonal imbalances including insulin resistance and high androgen levels which may interfere with the normal hormones of pregnancy. In diabetic women poor glycemic control has been associated with spontaneous abortion[98].

One additional hypothesized mechanism for pregnancy loss is a placental defect. About two-thirds of first trimester pregnancy losses exhibit evidence of defective placentation [33]. The process of embryonic implantation and placental growth is complicated and involves decidualization of the uterine lining and remodeling of the maternal vasculature. In a healthy early pregnancy the maternal spiral arteries in the uterus are blocked resulting in low oxygen tension; if this blockage is incomplete the onset of placental circulation is premature and disorganized exposing the fetal and placental tissues to relatively high levels of oxygen[99]. Abnormally high oxygen concentrations cause oxidative stress and are damaging to both fetal tissues and the placenta, potentially leading to the expulsion of the embryo[100].

Placental damage may also be the mechanism for pregnancy loss in women with antiphospholipid antibodies[101]. Antiphospholipid antibodies are found in both young women and young men at a prevalence of 1 to 5%; the prevalence increases with age[102]. The presence of the antibodies is associated with other conditions such as systemic lupus erythrematosis or vascular thrombosis[102]. The antiphospholipid antibodies may be associated with pregnancy loss by causing placental infarctions through thrombosis[101]. It is also possible that the antiphospholipid antibodies bind to beta2-glycoprotein binding proteins that are expressed in the embryonic trophoblast[101]. The trophoblast is an important component of the placenta and the binding of these antibodies may prohibit the healthy development of the placenta.

Maternal smoking has been hypothesized to influence arteriole remodeling and placental development which may explain any association with pregnancy loss[103]. Further support for a connection between uterine function and smoking is found in a recent study of in vitro fertilization through oocyte donation that reported a lower pregnancy rate among recipients who are heavy smokers[104].

In summary, other than age, history of spontaneous abortion and possibly obesity, there do not appear to be many strong predictors of miscarriage. Some studies have found suggestive associations for smoking, alcohol and caffeine use, but the results are not consistent and adjustment for confounding factors, such as nausea, is not always complete. Additionally, many studies use a retrospective study design in which participants are asked after the end of a pregnancy to recall exposures in the first trimester. This leaves the study susceptible to recall bias or misclassification since it may be difficult to remember exposures early in pregnancy. Control women defined as those with live births may also have to remember back over a longer period of time than the cases, as cases are interviewed proximal to the loss, and controls must remember the first trimester after giving birth at >28 weeks gestation. Many studies of spontaneous abortion are limited by small sample size leading to wide confidence intervals and unstable estimates. Exposure assessments lack uniformity in terms of measurement timing during pregnancy. Embryological development is rapid in early pregnancy and certain exposures may have very specific time windows of effect, yet most studies of spontaneous abortion do not assess the precise timing of the exposures of interest, or they characterize the timing generally as “first trimester” or “before pregnancy”. Studies include differing definitions of “spontaneous abortion” with some studies including terminations at <20 weeks and others at <28 weeks. Losses that occur later in gestation may be etiologically distinct from earlier losses, especially if the exposure has a particular time window of effect. Thus, further studies of spontaneous abortion can be informative.

Physical Activity and Spontaneous Abortion

This section first provides an overview of the literature investigating recreational physical activity and spontaneous abortion. This is followed by a review of the literature involving other modes of physical activity and spontaneous abortion. Finally a summary of this work is presented.

Knowledge of the early pregnancy events that may lead to miscarriage is limited. Physical activity has been hypothesized to lead to pregnancy loss through affects on reproductive hormone levels[105], thermoregulation[24], blood flow to the uterus[30], and related increases in muscular oxygen consumption[30].

1. Recreational physical activity

Three previous studies suggest a lower risk of miscarriage for women who perform recreational physical activity in pregnancy[106-108], and four suggest a higher risk[34, 109-111]. The estimates from the former three studies were around 0.6 with confidence intervals from approximately 0.3 to 1.0. The first study suggesting lower risk found a reduced proportion of pregnancy loss in women who continued to perform recreational physical activity during pregnancy (compared to those who discontinued early in pregnancy), although the sample size was small and the differences were not statistically significant[106]. Additionally, this study focused on very physically active women with an exposed group who had participated in regular exercise for at least two years and an 'unexposed' group matched to the exercising group for age, weight, percent body fat, and other lifestyle characteristics. Thus, it may be true that regular recreational physical activity among women who are in the habit of exercising is not detrimental, but this does not mean that it is beneficial if it is begun during pregnancy or if the woman is not very physically fit. Alternatively, it may be detrimental for a woman who is very physically fit to discontinue exercising altogether, but this type of woman is less prevalent in the population at large. The second study found a lower proportion of chromosomally normal pregnancy losses among women who performed recreational physical activity compared to women who did not perform recreational physical activity[107]. This comparison between chromosomally normal and abnormal losses is predicated on the idea that recreational activity cannot cause chromosomal abnormalities; this assumption is untested. Moreover, this is a case-control study, which does not account for potential differences in the gestational age of spontaneous abortions. The third study is an analysis of several Swedish birth cohorts followed for the occurrence of clinical miscarriage[108]. The authors do not describe their “exercise” measurement, but show a decreased risk of spontaneous abortion for women who exercise that is not statistically significant.

Risk estimates from the four studies that reported increased risk of spontaneous abortion with recreational activity ranged from 1.3 to 3.7. The width of this range may be attributed to differing exposure measures and study populations. Two of the studies suggest that recreational activity may be detrimental to implantation. In a study from an in vitro fertilization population[110], the authors found that women who exercised 4 or more hours per week for 1 to 9 years had twice the odds of pregnancy loss, and twice the odds of implantation failure compared to those who did not exercise. The authors suggest that because fertilization is performed in vitro, the increase in pregnancy failure in this group may be due to an alteration in hormonal milieu or the uterine environment. One further study measured daily intensity of “physical strain” which incorporated any physical activity including tennis, running, and heavy lifting. Their results suggested that high levels of physical strain around the time of implantation were associated with approximately twice the risk pregnancy loss[109]. They did not find any association with monthly average leisure activity. We were unable to assess physical activity at the time of implantation since pre-pregnancy activity was not ascertained in our study.

Of the remaining two studies implicating recreational activity, one reported an increased prevalence of spontaneous abortion among anaesthesiologists who exercised during pregnancy (OR: 1.6 (CI: 1.2, 2.1))[34]. However, this study did not describe the exercise exposure, mentioning only that it was performed more than one time per week. Finally, a large study from the Danish National Birth Cohort reported increasing risk of spontaneous abortion with increasing exercise (in hours per week) (HR: 3-4, depending on gestational age of the loss) and with high-impact exercise (HR: 2-4)[111]. However, their assessment of exercise occurred after the pregnancy loss in some cases and data from prospective exposure ascertainment suggested a much weaker and inconsistent association. Further, this analysis was not adjusted for pregnancy symptoms such as nausea/vomiting and vaginal bleeding.

In total, evidence that recreational activity is associated with spontaneous abortion is not convincing. The limitations of the previous studies that find detrimental associations include: a unique study population[110], an exposure that combines recreational with other modes of physical activity[109], lack of detail in the description of their exercise measurement[34], or potential recall bias[111].

2. Other modes of physical activity

Physiologically, it seems plausible that any physical stress could be considered 'physical activity,' including long hours of standing, lifting heavy loads, housework and childcare, in addition to exercises such as running, swimming, and biking. However, the associations between these different types of activities and miscarriage have varied among studies. Several previous studies have examined occupational physical exertion and spontaneous abortion. Increased risk for spontaneous abortion has been reported for women who stand for long hours (OR: 1.3 (CI: 1.1, 3.5)[112], 1.6 (1.1, 2.3)[113]), lift heavy loads (RR: 2.0 (CI:1.5, 2.5)[113], OR: 2.0 (1.7, 2.5)[114]), or spend longer amounts of time in postures that increase intra-abdominal pressure (i.e. bending versus standing) (with estimates from 1.3 to 3.2 depending on the exposure measure used[114, 115]). In contrast, two studies suggest no association of standing with spontaneous abortion (OR: 0.9 (0.6, 1.6)[107], 1.0 (0.7, 1.5)[116]), one reported no association with bending (OR: 1.1 (0.63, 2.0)[116]), and three find no of lifting during pregnancy (odds ratios of approximately 1)[112, 115, 117]. One study reported a tendency toward decreased risk with more frequent lifting (OR: 0.40 (0.16, 1.0))[116]. Two studies have suggested associations between occupational fatigue and intensity scores and spontaneous abortion, with odds ratio estimates of 1.2 to 3.3[114, 115]. Physical effort has been associated with spontaneous abortion (RR 1.9 (90% CI: 1.4, 2.3)[113]) while activity level at work[118] and intensity of occupational activity[116] have not. Although there may be some physiological similarities between occupational physical activity and recreational physical activity, it is not clear that their associations with spontaneous abortion are analogous.

Only a handful of studies have reported associations for other modes of physical activity and spontaneous abortion. Caring for young children more than 50 hours per week and cleaning house for more than 7 hours per week have been associated with decreased risk of spontaneous abortion (OR: 0.8 (CI: 0.6, 1.0) and OR: 0.6 (CI: 0.5, 0.9), respectively)[112]. However, chromosomally normal (versus aberrant) pregnancy loss was not associated with housework (more than 10 hours/week, OR: 1.2 (CI: 0.5, 2.9)), or childcare ("all day", OR: 1.2 (CI: 0.7, 2.0))[107]. A hospital-based study found higher hours of housework among women who experienced spontaneous abortion in an unadjusted analysis (no estimates presented)[114]. The association between housework and spontaneous abortion may be confined to women with a history of spontaneous abortion (OR: 2.3 (1.5, 3.5))[116]. The inconsistencies in these results may suggest that further investigation of household and child/adult care activities should be more specific, obtaining information regarding how the activities are performed or any chemicals used.

3. Summary

In total, very little research has examined the association of physical activity with spontaneous abortion. (For an informal comparison of these studies see Appendix B.) The literature represents several definitions of physical activity, with some addressing physically stressful occupational physical activities, and others focusing on various recreational physical activities. In some studies, what specific activities are measured is vague and it is unknown whether all types of activities have been identified for each participant. In some cases activities of different kinds are combined, so that the exposure represents a mixture of, for example, recreational activity, exercise, and/or household activities. Additionally, in some studies all four characteristics of physical activity (frequency, intensity of each session, duration of each session, and the type performed) were not assessed, leading to a general, dichotomous measure of “exercise in pregnancy”. Failure to measure all four categories may lead to misclassification. For example, if the frequency of physical activity is the only measurement obtained in a study, then there may be residual differences between the ‘exercise’ and ‘non-exercise’ groups of women with respect to the intensity, duration, or type. These differences may be related to the risk of miscarriage (or other pregnancy outcomes) (Figure 4).

The inconsistencies in both the methodology and results of the physical activity/spontaneous abortion literature suggest that further research that includes detailed physical activity assessments would be informative.

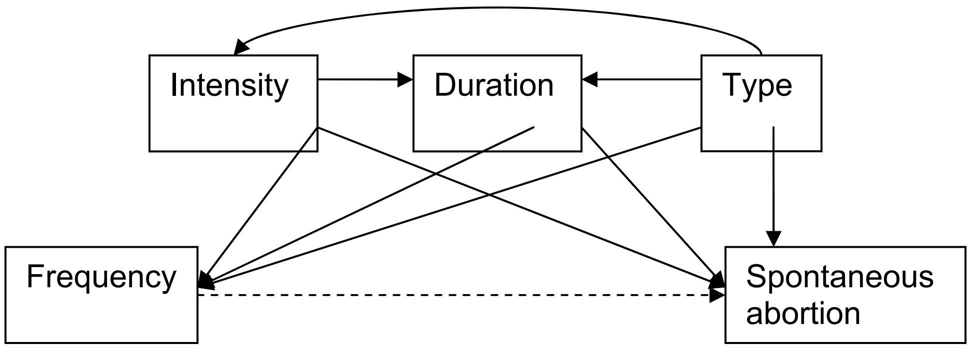

Figure 4. Simplified directed acyclic graph depicting the dimensions of physical activity and their hypothesized associations with spontaneous abortion, as an example of the potential for misclassification.

Preterm Birth, Birthweight, and Growth Restriction

In the United States, preterm birth has been rising steadily over the last two decades ("preterm" defined as birth <37 weeks gestation)[119]. This increase is likely related to concomitant increases in the rate of multiple gestations and obstetric intervention in high-risk pregnancies. However, some evidence exists of small left-ward shifts in the distribution of gestational age at birth for both spontaneous births (no evidence of medical intervention or premature rupture of membranes) and births with premature rupture of membranes (with no evidence of induction)[120]. This is of public health concern because preterm delivery is associated with morbidity and mortality in infants[121-123]. Fetal growth restriction is a term that refers to suboptimal growth in the fetus[21]. This is often operationalized as birthweight below some cutpoint for a given gestational age. Birthweight as a continuous variable is also a common descriptor of size at birth. While these are technically distinct endpoints, hypothesized biological mechanisms for these measures overlap and are thus presented simultaneously in this section.

Inflammation has been suggested as a mechanism for preterm birth partially due to its association with bacterial vaginosis[124, 125]. An infection could lead to inflammation of the placenta, or chorioamnionitis, which could predispose the membranes to rupture. Alternatively, the inflammation in the placenta could interrupt gas exchange and blood flow causing hypoxia, or it could cause a maternal fever[126, 127]. While the evidence has been conflicting, chorioamnionitis has also been associated with fetal growth restriction, possibly through the mechanism of altered blood flow[128]. Other placental features that may be related to inflammation or infection, and therefore preterm birth, have also been associated with small-for-gestational-age births. These features include placental infarction and ischemic change[129].

Another hypothesized mechanism for preterm birth is a maternal genetic or heritable factor that not only affects a given pregnancy, but can be passed to a daughter and her future pregnancies. For example, in a study from Utah, 42% of women who delivered prior to 35 weeks gestation reported that their mothers also had one or more preterm births[130]. Further support for the heritability of preterm birth can be found in a large registry study of Norway[131]. In this study, mothers born preterm were at increased risk of preterm birth (RR (CI): 1.5 (1.4, 1.7)). The association for fathers was weaker (RR (CI): 1.1 (1.0, 1.2)). Other studies have found a correlation between mother's birthweight, and other maternal genetic factors, with infant birthweight[132, 133]. One study of mothers born small-for-gestational age found them to be at higher risk for delivering small-for-gestational age infants[134]. Additionally, a pedigree analysis of fifteen families demonstrated a pattern of inheritance across generations for intrauterine growth restriction and further investigated an inherited genetic cause[135]. These correlations suggest that a pregnancy may not be unique in its development and may be influenced by inherited characteristics. For example, folate metabolism genes may be associated with preterm birth or small-for-gestational age birth[136].Another example is a study of a polymorphism in the promoter region of the Interleukin-6 (IL-6) chromosome. This study found that those homozygous for the C/C variant were less likely to have a spontaneous preterm birth[137]. IL-6 is a cytokine involved in the host response to infection and those homozygous with the C/C variant display lower production of IL-6 in general. Women with this variant produce less IL-6 in response to infectious or inflammatory stimuli and are therefore less likely to progress through the inflammatory cascade that characterizes preterm birth[137].

Preterm birth may be related to the formation of the placenta. Abnormal placentation can cause uteroplacental ischemia and has been implicated in preterm delivery[137-139]. Furthermore, vaginal bleeding (as a potential symptom of placental defect) in the first trimester has been associated with preterm birth due to premature rupture of the membranes (PPROM)[140]. Multiple bleeding episodes and larger amounts of blood were associated with earlier preterm birth, PPROM and preterm labor. Specific features of the placenta have bee correlated with increased risk of preterm delivery including chorionic vasculitis, decidual vascular anomalies, and chronic vilits[141]. In addition to the placental abnormalities mentioned previously, chorioangioma, a form of benign placental tumor, has also been associated with intrauterine growth retardation although the sample sizes in these studies are quite small[142]. Placental anomalies have also been implicated in hypertension, which is associated with small-for-gestational age birth[143-145].

Autoimmune disorders may be associated with growth restriction, particularly if the disorder involves the vascular system[146]. Antiphospholipid antibodies (which are autoantibodies) have been associated with growth restriction[147, 148]. The exact mechanism underlying this association is unknown, although one author suggests that autoantibodies lead to coagulation and the formation of thrombi in the placenta[148].

Women who experience one adverse pregnancy outcome may have a greater risk of another adverse outcome. For example, studies have found that women are more likely to deliver preterm if they have a history of small-for-gestational-age birth (RR (CI): 2.7 (2.0, 3.7)[149], late preterm (RR (CI): 4.8 (3.9, 6.0)) or early preterm birth (RR: (CI): 6.0 (4.1, 8.8))[149], miscarriage (effect estimates range from 1.6 to 4)[143, 150], or stillbirth (OR (CI): 2.2 (1.2, 4.3))[151]. Additionally, those with a previous stillbirth had approximately 1.5 times the risk (CI: 0.77, 2.9)[151], and those with a previous miscarriage had six times the risk (no CI given) of a small-for-gestational age infant[150]. Women who are subfertile, as evidenced by time to pregnancy greater than twelve months, may also be at increased risk of preterm delivery (OR: ~1.6, CI: ~1, 3)[152].

Several maternal behaviors and characteristics have been associated with preterm birth, birthweight, and growth restriction. (For an informal comparison of studies, see Appendix C.) A large Swedish study of over a million births found women aged 40-44 to have 1.5 times the risk of preterm birth than women aged 20-29 (CI: 1.5, 1.6); women over 44 were also at higher risk (OR (CI): 1.6 (1.3, 2.0))[153]. For both age groups the associations were stronger for earlier preterm births. Another U.S. study of over 10 million births also found higher risk of moderately preterm birth (32-36 weeks) for women aged 35-39 and 40-49, odds ratios ranged from 1.3 to 1.5 or 1.5 to 1.7, respectively, for primiparae (depending on race/ethnicity)[154]. The associations were slightly stronger for earlier preterm births. Associations for multiparous women tended to be weaker. The same analysis found higher risk of preterm birth for younger (<18 years) mothers (OR: ~1.5), with higher risk for multiparous women (OR: ~1.9). Two other studies also found increased risk of preterm birth for younger mothers with estimates of 1.5 and 1.7[155, 156]. The large Swedish study also found older maternal age to be associated with small-for-gestational age birth (age 40-44: OR (CI): 1.9 (1.8, 2.1) and age ≥ 45 OR (CI): 2.7 (2.0, 3.5))[153]. Younger mothers may also have a slight increase in risk of small-for-gestational age birth (OR (CI): 1.2 (1.1, 1.2))[156].

Lean body mass index (18.5 kg/m2) has been associated with preterm birth (HRs from 1.2 to 1.4 depending on the reason for preterm birth) with the strongest association for spontaneous preterm birth with premature rupture of membranes[157]. A Canadian study showed a similarly small increase for moderate preterm birth (32-36 weeks), OR (CI): 1.1 (1.0, 1.3), but not for early preterm birth (OR (CI): 0.93 (0.70, 1.2))[158]. Women of high body mass index (>35) have approximately twice the risk for preterm birth, although some of this association is likely due to an increase in maternal conditions, such as hypertension, that lead to emergency early delivery[158]. Lower body mass index (<20) has been moderately associated with growth restriction[158].

The prevalence of preterm birth in African-American women is approximately twice that of white women[159-161]. The recurrence risk of preterm birth (gestational age 20-34 weeks) in African-American women may be five times that of white women[160]. Poor socioeconomic status is another suspected risk factor for preterm birth and growth restriction[162, 163]. The association between socioeconomic status and growth restriction may be mediated by cigarette smoking[164] and low gestational weight gain, suspected risk factors for growth restriction[165]. For preterm birth, the socioeconomic gradient may be explained by differences in bacterial vaginosis and cigarette smoking[166], both risk factors for preterm birth[165]. Alcohol consumption is associated with fetal alcohol syndrome which is associated with growth restriction[167]. While smaller amounts of alcohol may also lead to growth restriction[168], a systematic review found no 'convincing evidence of adverse effects' of lower levels of alcohol intake[169]. Multiple gestations are also at increased risk for both growth restriction[170, 171] and preterm delivery[161].

Maternal stress may also be associated with preterm birth, although the evidence is difficult to synthesize as a result of the disparate definitions of 'stress' in the literature. One review of stress during pregnancy and preterm birth lists five categories of stress with nine sub-categories in the 'psychosocial' category alone[172]. Pregnancy-related anxiety, negative life events, and a perception of racial discrimination have been associated with preterm birth[173]. One author suggests that stress during pregnancy may not be the only pertinent time period to consider for pregnancy outcome. Instead, constant lifetime exposure to stressful conditions such as poverty, racism, and insecure neighborhoods may lead to an increased risk for preterm birth due to a general 'wear and tear' on the female body, making preterm birth resemble a chronic condition[174]. A role for stress in preterm birth is supported by evidence that maternal cortisol and placental corticotrophic-releasing hormone (CRH) (hormonal responses to stress) are higher in women who deliver preterm (mean CRH at 31 weeks for mothers of term infants:260 pg/ml preterm: 400 pg/ml; mean cortisol at 15 weeks for mothers of term infants: 7.25 ug/dl, preterm: 9 ug/dl)[175].

Physical Activity and Preterm Birth, Birthweight, and Growth Restriction

The physiological changes associated with physical activity may lead to growth restriction or changes in birthweight of the fetus as oxygen and nutrients may be shunted from the uterus. Moreover, physical activity increases the release of catecholamines which may lead to uterine contractions. These contractions may culminate in preterm labor or preterm birth [176].

1. Recreational physical activity

The epidemiologic literature regarding recreational physical activity and preterm birth or growth restriction is inconclusive. (For an informal comparison of these studies, see Appendix D.) A recent Cochrane review of randomized trials suggested that the risk of preterm birth may be higher in women who perform recreational physical activity during pregnancy (RR (CI): 1.8 (0.35, 9.57)) (although mean gestational age appears unaffected), but also pointed out that the data are insufficient to draw conclusions mostly due to small sample sizes[177]. Observational studies are split between no of recreational physical activity on preterm birth[178-186] (including one meta-analysis[187]), decreased risk of preterm birth[188-195]. Studies finding decreased risk report effect estimates of 0.1 to 0.8, depending on the timing of the measure during pregnancy (six of eight achieved statistical significance). The largest study reported an overall estimate of 0.82 (0.76, 0.88). One study found that an earlier onset of labor for women who performed recreational activity and had female infants, although all the women went into labor at 39 weeks of gestation or later[196].

Similarly, studies examining recreational physical activity and birthweight do not show consistent associations. Some studies suggest an increase of 140-240 g with activity (although differences were not statistically significant)[178, 197, 198] and others report no differences[179, 184, 185, 196] (including one meta-analysis[187]). One study reported babies of active women to be almost 1000 g lighter[181] (although this may be a typographical error as the p-value for the comparison was 0.3). One final study found that women who continued their pre-conception exercise into the third trimester delivered infants who were 600 g lighter than sedentary women and women who discontinued activity in the second trimester[199]. One study did not examine birthweight continuously, but found that women who did not engage in regular leisure activity before and during pregnancy were more likely to have a very low birthweight infant (but not a low birthweight infant) compared to women who were active both before and during[182]. Women who were active before pregnancy, but not during, were more likely to give birth to a low birthweight or very low birthweight infant[182].

The previously described literature has investigated birthweight as a measure of fetal size instead of a measure that is adjusted for the age of the infant at birth. Several studies have investigated birthweight adjusted for gestational age, but still the results are inconclusive. One study reported an increase in birthweight (276 g (CI: 54, 497)) for mothers who expended more than 1000 kcal/week[200] while another study found only a very small (statistically non-significant) increase (<20 g) with swimming during pregnancy[201]. Three studies have looked at the association of recreational activity on small-for-gestational age birth, one finding no association (OR (CI): 0.8 (0.3, 2.3))[188] and one finding an increase for both high and low frequency of exercise (≥ 5 times/week, OR (CI): 4.6 (1.7, 12.3), < 3 times/week, OR (CI): 2.6 (1.3, 5.4)) [202]. In the third, women who continued exercising into the third trimester had a higher frequency of small-for-gestational age birth compared with women who discontinued earlier in pregnancy (N=11 vs. 0). Comparisons of small-for-gestational age studies are complicated by the use of differing standard distributions, one from the U.S.[188], one from Canada[202], and one from the study populace[199].

Even if recreational activity has effects on fetal size, the changes may not be considered detrimental. While birthweight may be lower in the offspring of exercising mothers, it may be a non-uniform shift in the right side of the birthweight distribution towards normal, i.e., there are less heavy infants. One study has suggested that the decrease in fetal weight is, in large proportion, due to reduced fat mass[203].

2. Other modes of physical activity

Few studies have examined other modes of physical activity as separate exposures. One previous study suggested no association of housework or child care activity with preterm birth[189]. In a second study from Guatemala the authors defined their exposure as having at least three children and no household help (presumably a composite of housework and child care activities). They found no association with preterm birth, but reported an increase in small-for-gestational age[204].

The point estimates from studies of occupational physical activity and preterm birth range from 0.7 to 4, with most less than 2[205]. Authors of a review of these studies could not perform a meta-analysis due to the disparate exposure measures: some studies combined physical activity with mental stress or chemical exposures, others focused on standing or lifting, and others calculated an exertion score[205]. Although not all statistically significant, most studies have consistently reported small increases in risk of preterm birth with heavy lifting (RR ~1.3)[113, 117, 195, 206, 207] and standing for long hours (RR: ~1.3)[189, 195, 204, 207-210].

Of the five studies with adjusted estimates of occupational activity and small-for-gestational age, two have point estimates above one, one of which is also the most precise estimate (OR: 1.3 (1.1, 1.6)[204])[204, 211-214]. Four studies found no association of lifting with small-for-gestational age (ORs from 0.5-1.03 and CIs from 0.1-1.8)[117, 206, 211, 214], while one found a small elevation in risk (OR (CI): 1.2 (0.7, 2.0))[207]. One large cohort study suggests an increase in small-for-gestational age with standing (OR (CI): 1.2 (1.0, 1.4))[204]. While other cohort studies find no association (OR (CI): 0.59 (0.2, 1.7) and 1.1 (0.7, 1.7)[206, 207] or an elevated, but imprecise, point estimate (OR (CI): 2.0 (0.7, 5.4))[214]. The largest cross-sectional studies also report elevated risk (ORs ~1.3, and CIs of ~1, 2)[211, 215]. Differences across studies may be due to different exposure measures as each study has assessed activity differently and in different populations.

Four studies have investigated the association between a composite physical activity measure (one that includes several modes including housework, occupational, and recreational, for example) and preterm birth, birthweight or small-for-gestational age[210, 212, 216]. One of these studies suggested a reduced risk of preterm birth for higher levels of energy expenditure (proportion preterm, >2500 kcal/week: 8 vs. 10 for ≤ 2500)[212] and another reported no association with heavy activity and reduced risk with light activity[210]. The exposure measure in the latter study was less rigorous and the study populations were from different countries (U.S. and Australia). A small study with internally calculated MET values, found that fetal growth ratio (birthweight divided by median birthweight for gestational age) decreased as physical activity during pregnancy increased (beta = -0.2 (CI: -0.33, -0.08))[216].

As described previously (see Physical Activity and Spontaneous Abortion), physical activity can be described in four dimensions: type, frequency, intensity, and duration. Some of the studies of preterm birth, birthweight, and growth restriction have not measured all four, leaving them vulnerable to misclassification. In some studies, what specific activities are measured is vague and it is unknown whether all types of activities have been identified for each participant.

3. Summary

Recreational activity does not appear to be associated with length of gestation, although previous measures lack detail. There may be a small association of recreational activity with birthweight or growth restriction, but this association may reflect decreased fat mass in the infant and may not be detrimental. Household activity and child care activity have rarely been investigated as independent exposures. Occupational activity has been investigated, but exposure measures lack consistency and detail. We did not find any studies assessing the dimensions of physical activity (frequency and duration of physical activity) as separate exposures.

Characteristics of Women Who Are Physically Active

Recreational physical activity is considered beneficial for pregnant women and is recommended by both the American College of Obstetrics and Gynecology (ACOG) and more recently in the national “Guidelines for Americans”[217, 218]. Despite these recommendations, many pregnant women are not physically active[219]. Moreover, among active women, the intensity and duration of recreational activity tend to decline during pregnancy[220-229]. Low levels of physical activity may lead to higher weight gain, and excess weight gain during pregnancy may be related to higher body mass index in the long term, even fifteen years later[230]. In order to design and target interventions for maintaining or safely increasing activity during pregnancy, it is useful to understand factors that are correlated with physical activity during pregnancy.

In general, recreational activity intensity and duration decline over pregnancy[224, 231]. Women tend to chose less intense forms of exercise that are more comfortable and have a lower risk of maternal or fetal injury[231]. While some of this decrement may occur early in pregnancy, the decrease is more pronounced in the third trimester[227, 231]. If time and energy are limited, recreational physical activity may be decreased, before other forms of physical activity. For example, in one study recreational activity decreased over pregnancy while domestic activity remained the same[227].

The factors influencing women’s decisions to be active during pregnancy are not well-understood. For the pre-pregnancy period, one study of women in Canada found that women were more likely to retrospectively report participation in structured exercise if they had some college education, they had no children, they were non-smokers, and they engaged in leisure activities (bowling, skiing, racquet sports, and golf)[228]. Interestingly, there were some characteristics that are often assumed to be correlated with exercise performance that were not predictive of pre-pregnancy exercise in this study: marital status, age, social drinking, body mass index, walking at work, lifting at work, working shifts, and hours of employment per week.

In the same study, among women who exercised before pregnancy, factors associated with stopping structured exercise in the third trimester were the presence of other children, pre-pregnancy body mass index of at least 25 and higher weight gain during pregnancy. These results are similar to four other studies which found that exercise during pregnancy was less likely in older women[219, 232, 233], women with less education[219], women who had children[224, 232, 233], Asian[233] or non-white[232] women, and women who were overweight[233], who smoked[232], who had a previous abortion or still birth[233], or who had multiple gestations[233]. Finally, one of the strongest predictors of physical activity during pregnancy is pre-pregnancy activity[224, 232]; physical activity as an adolescent may also be predictive[232].

In the Canadian study, “doctor’s advice to quit exercising” was associated with a decrease in structured exercise in the univariate analysis, but it was not important in the multivariate analysis suggesting that other characteristics may explain the association[228]. Conversely, in a Mississippi study, women who reported being encouraged by their physician to exercise were in fact more likely to exercise than those who were not[234]. Similarly, ‘responding to advice’ was the most frequent reason given for ceasing or reducing exercise during pregnancy in a British study of 57 low-risk primigravidas[235]. However, the source of the advice in this study could have been magazines, antenatal clinic materials, family, friends, and health care professionals. Other general reasons reported for discontinuing exercise in this study included, risks or dangers associated with activity (falls, muscle strain, health of the baby, miscarriage and premature birth), less motivation to exercise, and difficulty finding an exercise facility.

Most of the women in the British study reported general confusion over what physical activities and intensities would be safe during pregnancy, often citing conflicting advice from several sources (including nurses and general practitioners). It seems then, that women may be receiving conflicting health messages that reflect the indecision in the literature regarding exercise and pregnancy outcome.

Statement of Specific Aims

Study Aims

The following specific aims were investigated using data from the Right From the Start cohort and the Pregnancy, Infection, and Nutrition 3 cohort.

1. Using data from the Pregnancy, Infection, and Nutrition 3 study, maternal characteristics, health behaviors and characteristics of pregnancy that were correlated with recreational activity (in minutes/week) and any physical activity at approximately gestational weeks 20 and 28 were identified.
2. Associations were examined between vigorous recreational activity, occupational activity, indoor/outdoor household activity, and adult/child care activity reported at 13-16 weeks of gestation and length of gestation and birthweight for gestational age using data from the Right From the Start cohort.
    a. Effect modification was examined between time spent in each mode of physical activity and change in vigorous physical activity from pre-pregnancy.
3. Associations were examined between vigorous recreational activity, occupational activity, indoor/outdoor household activity, and adult/child care activity reported at 13-16 weeks of gestation with the hazard of pregnancy loss using data from the Right From the Start cohort and a time to event analysis (given staggered-start study design).

a. Effect modification was examined between time spent in each mode of physical activity and change in vigorous physical activity from pre-pregnancy.

Rationale

As the obesity problem continues to escalate in the United States[1], health care providers are becoming more committed to advocating regular recreational physical activity to their patients[2]. Women often find it difficult to control pregnancy-related weight gain and to return to their pre-pregnancy weight in the postpartum period[236]. Excess weight gain during pregnancy may be related to higher body mass index in the long term, even fifteen years later[230]. Pregnancy is therefore a key point in women's lives for weight control. If women can maintain a healthy weight during and after pregnancy it may help them maintain their weight for the rest of their lives, potentially alleviating their risks for obesity related illnesses.

Recreational activity is a key component of weight management, and is therefore important to incorporate as a habit in daily life. Given the difficulties women have with pregnancy-related weight gain, it would be even more important for pregnant women to maintain activity levels throughout their pregnancies. However, the safety of vigorous recreational activity has not been definitively established. Recreational activity has been hypothesized to increase risk for miscarriage, preterm birth, and growth restriction. Miscarriage can be physically and emotionally traumatic for the woman and her family, and preterm birth and growth restriction may have important influences on the infant's survival and future health. Therefore, to better understand the influence of physical activity during pregnancy we explored the associations between vigorous physical activity and length of gestation, birthweight, and spontaneous abortion. Additionally, we investigated the maternal characteristics (demographic and behavioral) and pregnancy characteristics that are correlated with physical activity across pregnancy. This can help researchers and policy-makers understand the factors that influence women's activity levels and possibly present opportunities for intervention.

II. METHODS

Overview of Methods

The Pregnancy, Infection and Nutrition study enrolled women at less than or equal to 20 weeks of gestation with follow-up interviews at 17-22 and 27-30 weeks of gestation. These questionnaires included an assessment of the type, frequency, and duration of moderate or vigorous recreational activity in addition to a host of maternal characteristics and behaviors and pregnancy characteristics (see Appendix E for physical activity questions). This information was used to examine the correlates of recreational activity across pregnancy through a repeated measures framework.

Right From the Start is a study of early pregnancy health, enrolling both pregnant and pre-pregnant women. At approximately 13-16 weeks gestation women complete a detailed phone interview that includes vigorous recreational, indoor and outdoor household, occupational, and adult/child care physical activity (see Appendix F for questionnaire). The total minutes per week were calculated for each mode of activity and then summed to create a measure of total vigorous physical activity. Also, metabolic equivalents were assigned to each recreational activity[237, 238], multiplied by the reported minutes per week, and summed over each activity to obtain the total MET-minutes per week of recreational activity. We also examined the components of recreational activity: frequency of sessions and duration of sessions. The association of all of these exposures (vigorous recreational activity (minutes/week), recreational activity (MET-minutes/week), frequency of recreational activity sessions, duration of recreational activity sessions, vigorous occupational activity (minutes/week), indoor/outdoor household activity (minutes/week), child/adult care activity (minutes/week), and total vigorous activity (minutes/week)) with all of the following outcomes was examined.

Medical record information was solicited for all women. Date of birth was obtained from one of three sources (participant report, medical record or vital statistics). Using survival analysis techniques we estimated the change in length of gestation (calculated from week 22 until the date of birth) for a given change in exposure. Additionally, we dichotomized length of gestation into preterm and term categories and estimated the odds of a preterm delivery for a given change in exposure level. Finally, we investigated the association of birthweight and growth restriction (defined as birthweight at less than the tenth percentile for gestational age in our dataset) with the described physical activity exposures. Analogous to the above analyses, we examined the interaction between physical activity variables and the change in total vigorous physical activity from pre-pregnancy.

Women were followed from the time of enrollment for the occurrence of a spontaneous abortion. Using a time to event analysis, we estimated the hazard of pregnancy loss for a given increase in exposure. Additionally, we investigated whether the hazard associated with the current amount of each mode of physical activity is modified by whether total vigorous activity has increased, decreased, or stayed the same from pre-pregnancy levels.

Design

Right From the Start

1. Source population

The purpose of the Right From the Start study (phase 2 and 3) was to investigate influences on early pregnancy health. The study recruited women who were either less than 10 weeks pregnant or were trying to conceive. Women trying to conceive were pre-enrolled in the study and fully enrolled once they conceived. The study area included a large geographic area in North Carolina, including at least 13 counties in the Research Triangle area.

Participants were recruited through several mechanisms. Health practitioners disseminated information to their patients either directly or through printed study materials. Brochures, flyers and information cards were placed at churches, retail outlets, libraries, and drug stores. Advertisements were placed in local newspapers, magazines, ValPak mailings, public service announcements, movie theater screens, city buses, door flyers at apartments/residences, email mailing lists, and on ‘hold’ messages for businesses. Announcements were made at some prenatal classes. Mass mailings of letters with study information were sent to women in the study area as identified by mortgage closing records, Department of Motor Vehicle records, marriage license records, and other publicly available records. Participants in the study were encouraged to share information about the study with their friends, family, and co-workers. All of these recruiting materials encouraged women to contact study staff through a toll free phone number.

2. Eligibility

When contacted, study staff completed a screening interview to determine eligibility. Eligibility was dependent upon a woman's ability to recall her last menstrual period since women had to be less than 10 weeks from onset of their most recent menses (or currently trying to conceive) in order to participate. Women also had to meet all of the following criteria: at least 18 years of age (and less than 45 years if currently trying to conceive), willing to have a first trimester ultrasound, not using assisted reproductive technology to conceive, intending to remain in the area for the next 18 months, able to access one of the study's ultrasound locations, intending to carry the pregnancy to term, able to access a telephone, fluency in either English or Spanish, and with an identified prenatal or primary care provider at the time of screening. The potential participant did not need to have had her first prenatal visit at the time of screening, but study staff did need to know where the woman would go for care in the event of an abnormal ultrasound. This information was required so that when she completed the first early ultrasound there would be a health care provider who knows her to send the ultrasound results to, particularly if they were notable.

Women were excluded from the study if they did not get pregnant within 12 months of pre-enrolling (these women were able to call back to enroll once they were pregnant).

3. Study protocol

Participants completed a 15-minute telephone baseline interview and scheduled an appointment to meet a staff member, sign a consent form and get the first trimester ultrasound. The ultrasound was performed for all women as early as 6 completed weeks gestation and no later than 12 weeks. The results of this ultrasound were forwarded to the patient's identified medical caregiver. The sonographers were instructed to take additional steps if the ultrasound raised concerns for the health of the mother or the infant. At this first visit, maternal weight and height were measured and the viability of the pregnancy was assessed.

If a woman had a pregnancy loss before her early ultrasound, she was invited to return for an ultrasound within two to four weeks of the loss, but no later than 3 months post-loss. Women with losses completed the modified first trimester interview, preferably within 2 weeks of the pregnancy loss but no later than what would have been their 16th completed week of gestation or 2 months after the loss, whichever date was later.

Women were given a paper diary in which to document any episodes of nausea, vomiting or bleeding, and any medications taken. These diaries were not required but were provided in order to assist the women with the first trimester computer-assisted telephone interview (CATI), in which questions about these experiences would be asked. The CATI occurred preferably, during week 13, and no later than week 16. If a participant had a pregnancy loss prior to the first interview, she completed a modified interview with the same content as the questionnaire for continuing pregnancies, modified to acknowledge her loss and to obtain additional details about medical care received related to the loss.

The participants completed a form documenting their pregnancy outcome within 2 weeks of the pregnancy's end. The form confirms the participant's contact information and the name and location of the care she received (either delivery or loss). The participants gave consent to have their prenatal care, hospital care, and medical records abstracted. A trained abstractor reviewed the records for medical history, reproductive history, lab results, ultrasound results, blood pressure changes and the labor and delivery summary. A vital records match was performed to confirm birth date information and obtain birthweight information.

Pregnancy, Infection, and Nutrition 3 (PIN3) Study

<u>1. Source population</u>

The participants for PIN3 were recruited between January, 2001 and June, 2005 from the University of North Carolina prenatal care centers in Chapel Hill, North Carolina. Participants were identified by study staff through their medical records. They were recruited at up to 20 weeks gestation. If women agreed to participate, demographic and pregnancy-related information was abstracted from their medical record. This information was entered into a computerized file used to track participants and date their pregnancies. The PIN study included two telephone interviews and two self-administered questionnaires. Permission was obtained to abstract medical charts after delivery.

2. Eligibility

Women were excluded if they were less than 16 years of age, did not speak English, did not plan to continue care or deliver at the study site, were carrying multiple fetuses, or did not have access to a telephone from which they could complete phone interviews.

3. Study protocol

At recruitment the women were given a self-administered questionnaire to be completed and mailed back to the PIN study office in a stamped, self-addressed envelope (~15-20 weeks gestation). This questionnaire assessed social support, state-trait anxiety, and depression
Between gestational weeks 17 and 22 the first telephone interview was completed and covered the following topic areas: general health & recognition of pregnancy, perceived stress, demographic info, household composition, income, current student status, employment history, physical activity in the past 7 days (occupational, recreational, indoor/outdoor household activities, and transportation), vaginal bleeding, menstrual history, contraception, and reproductive history.

The women were also given a second self-administered questionnaire between gestational weeks 24 and 29 to assess depression and state anxiety.

The second telephone interview was performed at 27 to 30 weeks gestation, and included assessments of: vaginal bleeding during pregnancy, changes to employment status and job control, physical activity in the past 7 days, perceived stress, health behaviors (use of tobacco, alcohol, and drugs), and vitamin and mineral supplement use.

Delivery logs at the study hospital were examined daily to ascertain delivery information for the study participants. When the medical records were obtained, information was abstracted regarding: pregnancy complications (gestational diabetes, pregnancy-induced hypertension, pre-eclampsia, vaginal bleeding) and adequacy of prenatal care (Kotelchuck[239]).

Methods for Proposed Study

1. Assessment of physical activity

Pregnancy, Infection, and Nutrition 3 (PIN3) study

During the interviews at 17-22 and 27-30 weeks, the women were asked, "In the past week, did you participate in any recreational activity or exercise, such as walking for exercise, swimming, or dancing that caused at least some increase in breathing and heart rate?" If she said yes, she was asked to describe the type of activities, the number of times she performed each one in the past week, for how many minutes or hours she usually did the activity at each time, and how hard the activity felt to her in terms of breathing and heart rate. She was also asked how far she did the activity, i.e. how many miles she walked, or laps she swam (and the size of the pool). (The physical activity questions are presented in Appendix E.) From this information a metabolic equivalent (MET) value from the Compendium of Physical Activities was assigned to each reported activity[237, 238]. The Compendium of Physical Activities (originally published in 1993, updated in 2000) was developed to allow researchers to compare the intensities of different physical activities across studies. The Compendium assigns a MET value to various physical activities. A MET is defined as the ratio of work metabolic rate to a standard resting metabolic rate of 1.0 (4.184 kJ x kg/hour). One MET is approximately the rate at which energy is expended during quiet sitting.

The respondent was similarly asked to describe her moderate and vigorous work activities. She was also asked to describe her indoor and outdoor household activities, her child and adult care activities, and any transportation activities such as walking to work or biking to the store in the same manner.

Right From the Start

Women involved in the Right From the Start study complete a telephone questionnaire at approximately 13-16 weeks of gestation. First, the participants are asked if, in a typical week, “At this time, do you do any recreational physical activity or exercise, like brisk walking, jogging, swimming, biking, tennis, soccer, or dancing?” If she said no, further questions regarding recreational activity are skipped. If she said yes, she was asked, “Do any of these recreational activities feel hard or very hard, meaning that the activity caused large increases in breathing and heart rate?” The description ‘hard’ or ‘very hard’ corresponds to vigorous activity. If the woman reported performing any recreational activity she was asked to describe the type of activity, how many times per week and for how many minutes or hours, on average, she performs the activity each week. (The physical activity questionnaire is presented in Appendix F.) The total minutes per week were calculated for each mode of activity and then summed to create a measure of total vigorous physical activity. Also, metabolic equivalents were multiplied by the reported minutes per week of recreational activity, and summed over each recreational activity to obtain the total MET-minutes per week of recreational activity. We also examined the components of vigorous recreational activity: frequency of sessions and duration of sessions. The associations of all of these exposures (vigorous recreational activity (minutes/week), recreational activity (MET-minutes/week), frequency of recreational activity sessions, duration of recreational activity sessions, vigorous occupational activity (minutes/week), vigorous indoor/outdoor household activity (minutes/week), vigorous child/adult care activity (minutes/week), and total vigorous activity (minutes/week)) was examined with all of the subsequently defined outcomes.

From this information we used the Compendium of Physical Activities to assign a metabolic equivalent (MET) value to each activity reported[237, 238]. This was done first by the first author (AMZJ) and a co-author (KRE) reviewed the assignments. The Compendium of Physical Activities (originally published in 1993, updated in 2000) was developed to allow researchers to compare the intensities of different physical activities across studies. The Compendium assigns a MET value to various physical activities. A MET is defined as the ratio of work metabolic rate to a standard resting metabolic rate of 1.0 (4.184 kJ x kg/hour). One MET is approximately the rate at which energy is expended during quiet sitting.

At the end of the recreational physical activity questions one question was asked about current recreational activity habits relative to pre-pregnancy: "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?" This question was used to determine if the association between physical activity and pregnancy outcome differs depending on whether vigorous physical activity has increased, decreased or stayed the same compared with before pregnancy. Other modes of physical activity (occupational, indoor/outdoor household, child/adult care) were quantified with questions structured in the same way as those described for recreational activity.

2. Definition of outcomes

Spontaneous Abortion

Spontaneous abortion was defined as an involuntary termination of pregnancy at <20 completed weeks of gestation. Gestational age for this outcome was determined by last menstrual period (errors in last menstrual period dates are negligible for the cohort as a whole[240]). Weeks of gestation that occurred prior to enrollment date were not counted because the time before a woman enrolled is methodologically immune (if her loss had occurred before the enrollment date she would not be included in this study). Women called to enroll in the RFTS when they had a positive pregnancy test (either a home test or a physician test). In most cases, women also called the study when they experienced a spontaneous abortion. Spontaneous abortions were also detected when women came in for their early ultrasound, when the women were called after missing their ultrasound appointment, or when pregnancy outcome forms were returned. Evidence of a spontaneous abortion might also come from medical records with presumptive vital records confirmation showing the lack of a live birth in the related time frame.

Length of Gestation

We measured length of gestation as the time (in weeks) from the 22nd completed week of gestation until delivery. (Gestational age was estimated by last menstrual period.) Delivery date was obtained from three sources, participant self-report, hospital delivery medical record and vital statistics.

Growth Restriction

Birthweight of the infant was obtained from vital statistics. We also assigned each birth a percentile based on the distribution of birthweight for each gestational week, starting with gestational week 37. A previous analysis including approximately 370,000 term births found that the distribution of birthweight within each week of gestational age is approximately normal[241]. In addition to analyzing birthweight as a continuous variable, we defined small-for-gestational age as birthweight less than the tenth percentile for gestational week based on our data.

Babies born preterm were not included in this analysis as growth restriction and prematurity are related; growth restriction may be on the causal pathway to preterm birth. Growth restriction would be difficult to operationalize for preterm infants since their gestational age is partially dependent on their attained size.

Data Analysis

<u>1. Analyses to address specific aim 1: Correlates of physical activity</u>

This was an exploratory analysis meant to identify the maternal physical, sociodemographic, and behavioral factors that predict the amount of recreational activity and any physical activity. The characteristics of interest included: maternal age, race, income, pre-pregnancy body mass index, smoking, alcohol use, vitamin use, bleeding during pregnancy, gestational diabetes, gestational hypertension, nausea, stress, depression, and anxiety. Because physical activity was measured at two time points, we used a repeated measures framework for the analyses.

Four outcomes were of interest in this analysis and each one was assessed at 20 weeks and again at 28 weeks. First, women were categorized as performing *any recreational activity* if they performed at least 10 minutes per week of moderate (“somewhat hard”) to vigorous (“hard/very hard”) recreational activity. Second, we examined the *total minutes of moderate or vigorous recreational activity*. The distribution of minutes per week of recreational activity was not normally distributed, with a high frequency of women with zero minutes of recreational activity. To address this, the analysis was limited to those who reported at least 10 minutes per week of recreational activity.

We also explored higher levels of recreational activity. Women were classified as performing recommended recreational activity if: 1) they reported engaging in “somewhat hard” recreational activity for at least 150 minutes/week, 2) they reported engaging in ”hard/very hard” recreational activity for at least 75 minutes/week, or 3) the sum of their “somewhat hard” minutes/week and twice their “hard/very hard” minutes per week was at least 150 minutes/week. The first part of our definition of “recommended recreational activity” (item 1) resembles the recommendation for activity during pregnancy supported by the ACOG. They recommend, “an accumulation of 30 minutes or more of moderate exercise a day should occur on most, if not all, days of the week.”[218] Their recommendation specifies exercise (not all recreational activity) and includes only moderate intensity activity, not vigorous. For population research this definition is limited since participants may perform vigorous activities (and presumably should not be considered as not meeting the recommendation) and the difference between recreational activity and exercise is subjective. To address these issues, we defined our criterion to include all recreational activity at both moderate and vigorous intensities. The US governmental recommendation is similar to the ACOG recommendation, but is not limited to exercise and allows for vigorous activity (although specific amounts are not given).

Finally, we defined a dichotomous outcome that encompassed all modes of physical activity, not just recreational. Women who performed a total of at least

10 minutes of “somewhat hard” or “hard/very hard” physical activity in the past week met the criteria for *any* moderate or vigorous physical activity.

We employed two types of multivariable models. First, when limited to women who performed any recreational activity, the distribution of the natural log of minutes per week of recreational physical activity appeared to be normally distributed. We therefore employed a linear mixed model[242] to examine the associations of our predictors with the log-transformed outcome; we used a random intercept to account for within-woman correlation. Beta estimates from this model represent the change in natural log minutes of activity for a given change in exposure level. For ease of interpretation, these beta estimates (and confidence intervals) were exponentiated to give the ratio of minutes associated with a change in exposure level.

The data are unbalanced in that the measurements of the outcome (physical activity) occurred at slightly different times during gestation. Additionally, some of the women may be missing for this variable at either time point. The linear mixed model can accommodate these features of our data. The linear mixed model included a random intercept for each woman that allows each woman to differ in her initial level of recreational activity; random slopes allow each woman to change her recreational activity differently over gestation. The variance-covariance matrix for the random effects was unstructured, and the variance-covariance matrix for the random errors was assumed to be homogeneous. The formulation of this model can be written,

$$Y_i = X_i'\beta + b_{1i}(time) + b_{2i} + e_i$$

Where Y_i is the vector of responses (recreational activity level at time i), X_i is a matrix of predictor variables (such as age, nausea) whose values are allowed to change over time, β is a vector of the fixed effects for the predictor variables in X_i, b_{1i} is the random slope for each woman, b_{2i} is the random intercept for each woman, and e_i is the vector of errors. The b_i's are assumed to be normally distributed with mean 0 and an unstructured covariance matrix, G. The e_i's are also assumed to be normally distributed with a mean of zero and covariance matrix $\sigma^2 I_{ni}$ (n_i is the number of observations per woman).

We tested the importance of the random slopes through likelihood ratio tests based on the difference in the restricted maximum likelihood log-likelihoods and testing this difference against a test statistic derived from a mixture of chi-square distributions. We used the final model to describe the average changes in recreational activity between time points, the variables that predict this change and the variables that predict baseline recreational activity levels.

Second, for the three dichotomous outcomes we used a logistic regression model estimated with generalized estimating equations[243, 244] using a compound symmetric working correlation[245] to account for the dual measurements for each woman. Exposures measured at each interview were treated as time-dependent. We found no correlation between the outcomes measured at 20 weeks and the exposures measured at 28 weeks.

We used backward selection to obtain a more parsimonious model. Variables with a p-value of less than 0.2 were retained in the model. Interactions with time were evaluated for all predictors and retained if $p<0.1$.

We identified four influential individual observations in our linear mixed model using the MDFITTS statistic. When the paper records were reviewed for three of the observations, we could not determine whether their physical activity data were in error (the fourth observation was extreme, but possible). These three women were excluded from all analyses. We re-ran the final model without the fourth participant, but the parameter estimates were essentially unchanged so she was retained. We examined the distribution of scaled residuals from the final linear mixed model to assess model fit. These residuals appeared to be approximately normally distributed.

2. Analyses to address specific aim 2.1: Length of gestation

Length of gestation was examined in a survival analysis framework, in addition to the dichotomous outcome. Women with induced abortions after 22 weeks were censored at the time of abortion.

The first outcome of interest was the time until birth with the risk period for birth beginning at 22 completed weeks of gestation based on last menstrual period. We evaluated the association between physical activity and length of gestation using discrete time hazards models and the logistic regression framework described by Cole and Ananth[246]. This framework is advantageous because it accommodates discrete, interval censored survival time. In RFTS, gestational age was measured in weeks rather than in days or hours even though birth could have happened at any time point within that week. The model predicts the probability of birth at week j, given that the woman has not experienced birth prior to that week. This model can be written,

$$\log it\left[\frac{\Pr(Y_i = j \mid x_{ik})}{\Pr(Y_i \geq j \mid x_{ik})}\right] = \alpha_j + \sum_{k=1}^{n} \beta_k x_{ik}$$

Where Y_i is the event time for woman *i*, and $j = 1, \ldots, J$ is the list of event times with *J* indicating either the last event time if the final observation is a failure or a last observation time if the final time is censored. The α_j represent the baseline log odds at each time *j*. These baseline odds are allowed to vary over time as the probability of birth may not be constant over gestation. The x_{ik} represent the values of the $k=1,\ldots,n$ predictor variables (exposure, covariates) for woman *i*. The β_k represent the effect estimates of exposure x_k on timing of birth. We determined whether the association of physical activity variables with length of gestation was constant over time by testing interaction terms between physical activity and gestational age.

We also examined effect-modification for each mode of vigorous physical activity and whether total vigorous physical activity had increased, decreased, or stayed the same as before pregnancy. Interaction terms were retained if they were significant at $p<0.1$.

The dichotomous outcome was preterm versus term, with preterm defined as birth at <37 completed weeks of gestation. We estimated the odds of preterm birth associated with a given change in the minutes per week (or MET-minutes per week) of vigorous recreational activity, indoor/outdoor household activity (in minutes per week), occupational activity (in minutes per week), and adult/child care activity (in minutes/week) estimated through logistic regression. Confounders for length of gestation were chosen based on a directed acyclic graph (see Appendix G).

3. Analyses to address specific aim 2.2: Growth restriction

We graphically inspected the correlation of birthweight with each continuous measure of physical activity, among term infants, to determine the crude associations. We finely categorized each mode of vigorous physical activity and crudely modeled the association between activity and birthweight using a linear regression model. As described previously, these graphs were used to examine categorization schemes for each exposure variable. Analyses proceeded similarly to the previous outcomes with regard to univariate analyses, effect modification assessment, and confounding; however, this outcome was based on a linear regression framework instead of a survival analysis or logistic regression structure. Small-for-gestational age was examined through a logistic regression framework with analyses proceeding as previously described.

4. Analyses to address specific aim 3: Spontaneous abortion

Recreational activity (measured in metabolic equivalent-minutes per week and minutes per week) and the other modes of physical activity (minutes/week) are continuous variables; we began by graphically examining plots of the physical activity variables (in fine categories) and odds of spontaneous abortion.

Categorizations were chosen based on these graphs and if no loss of information occurred ($p>0.05$). The model structure was analogous to the length of gestation analyses and was carried-out as described above.

We identified potential confounders through a literature review and a directed acyclic graph (see Appendix G). All covariates were assessed univariately analogously to the main exposure.

In the survival analysis, induced abortions at <20 weeks (N = 7) were censored at the time of abortion. Live births were censored at 20 weeks.

Figure 5. Flow chart depiction of data analyses, by specific aim

Specific Aim 1: Correlates of Physical Activity (PIN3 data)

Examine univariate associations between four physical activity variables and maternal behavioral and pregnancy characteristics at both time points.

↓

Using a mixed model, investigate the association between maternal and pregnancy characteristics natural log minutes of recreational activity. Test for the importance of the random slopes. Using a logistic regression model and generalized estimating equations investigate the associations between dichotomous physical activity variables and maternal and pregnancy characteristics. Test the importance of time interactions.

Specific Aim 2.1: Gestational Length (RFTS data)

Plot continuous physical activity variables by survival time

↓

Examine time until birth within fine categories of physical activity and decide on structure of physical activity variables.

↓

Construct a discrete time hazard model and determine whether interactions with gestational age are appropriate.

↓

Examine effect modification by stratifying on change in vigorous physical activity from pre-pregnancy.

↓

Identify potential confounders using a directed acyclic graph. Investigate univariate associations between potential confounders and gestational length.

↓

Build a survival model including physical activity and the identified confounders. Interpret hazard ratio estimates (and confidence intervals) of birth for a change in physical activity level.

Figure 4. Flow chart depiction of data analyses, by specific aim

Specific Aim 2.2: Growth Restriction (RFTS data)

Assign each birth a percentile based on the birthweight distribution for each week of gestational age. (Among term infants only.) Define small-for-gestational age as <10th percentile of birthweight for age.

↓

Describe the crude associations between physical activity variables and birthweight. Decide on structure of physical activity variables.

↓

Examine effect modification by stratifying on change vigorous physical activity from pre-pregnancy.

↓

Identify potential confounders using a directed acyclic graph. Investigate univariate associations between potential confounders and birthweight or small-for-gestational age.

↓

Using a linear regression, investigate the influence of physical activity variables on birthweight, adjusted for confounders. Using a logistic regression, investigate the influence of physical activity variables on small-for-gestational age, adjusted for confounders.

Specific Aim 3: Spontaneous Abortion (RFTS data)

Plot continuous physical activity variables by survival time

↓

Examine survival time within fine categories of physical activity and decide on structure of physical activity variables.

↓

Construct a discrete time hazard model and determine whether interactions with gestational age are appropriate.

↓

Examine effect modification by stratifying on change in total vigorous activity from pre-pregnancy.

↓

Identify potential confounders using a directed acyclic graph. Investigate univariate associations between potential confounders and spontaneous abortion.

↓

Build a survival model including physical activity and the identified confounders. Interpret hazard ratio estimates (and confidence intervals) of a spontaneous abortion for a unit change in physical activity level.

III. CORRELATES OF PHYSICAL ACTIVITY DURING PREGNANCY

Abstract

Objective: Correlates of prenatal physical activity can inform physical activity intervention strategy, but are not well-understood. We sought to identify correlates of recreational physical activity and total physical activity around gestational week 20 and week 28.

Methods: Participants in the Pregnancy, Infection, and Nutrition 3 Study were recruited before 20 weeks gestation from the University of North Carolina prenatal care centers. Women self-reported physical activity sociodemographic, lifestyle, and pregnancy-related characteristics. We used a linear mixed model to identify predictors of the minutes of recreational activity in the past week performed at both time points (among those who did any recreational activity) and logistic regression to identify predictors of any recreational activity ($\geq$10 minutes), recommended recreational activity, and any physical activity.

Results: Our analysis included 1875 women. At 20 weeks, 36% of women engaged in any recreational activity, 15% in recommended recreational activity, and 58% in any physical activity. These percentages declined slightly at 28 weeks. Correlates of any recreational activity were mostly sociodemographic while most sociodemographics were not correlates of the other outcomes. Several associations differed by gestational age, including indoor and outdoor

household activity, bed rest, history of miscarriage, parity and prenatal care initiation. All four measures of physical activity were positively associated with enjoyment of physical activity.

Conclusions: These associations may help target interventions to increase physical activity during pregnancy.

Introduction

Recreational physical activity is considered beneficial for pregnant women and is recommended by both the American College of Obstetrics and Gynecology (ACOG) and more recently in the national "Guidelines for Americans"[217, 218]. Despite these recommendations, many pregnant women are not physically active[219]. Moreover, among active women, the intensity and duration of recreational activity tend to decline during pregnancy[220-229]. Low levels of physical activity may lead to higher weight gain, and excess weight gain during pregnancy may be related to higher body mass index in the long term, even fifteen years later[230]. In order to design and target interventions for maintaining or safely increasing activity during pregnancy, it is useful to understand factors that are correlated with physical activity during pregnancy.

The factors that are correlated with a woman's decision to be physically active during pregnancy are not well understood and the literature is inconclusive. Studies have been small (N=25 to 74)[221, 226, 227, 229], limited to a crude comparison of all pregnant women to non-pregnant women[219, 233, 247], or measured recreational activity at only one time point[219, 222, 224, 226, 232, 233, 247, 248], which precluded assessment of whether predictors vary over the course of pregnancy. Measurements of recreational activity have not always included dimensions of activity such as frequency (number of sessions in a given unit of time), intensity (the exertion required to complete the activity), time (duration of each session) and type (a description of the activity i.e., walking, playing soccer, swimming), nor have they allowed the women to enumerate all their physical activities. In addition, some potentially important predictors have not been investigated, including psychosocial characteristics and barriers to physical activity.

Physical activity includes recreational activity, which is elective and usually the most amenable to change, as well as more obligatory forms of activity such as occupational or household activities. The predictors of recreational activities may differ from those of other modes of physical activity. If time and energy are limited, recreation may decrease over the course of pregnancy, while non-recreational physical activity may be more likely to remain constant[220, 227].

In order to understand the characteristics that are associated with physical activity we undertook an analysis of physical activity during pregnancy. The Pregnancy, Infection, and Nutrition 3 (PIN3) Study collected detailed information on physical activity during pregnancy and characteristics that may be predictive of activity. Our aim was to identify characteristics that were associated with recreational and total physical activity at two different time points during pregnancy.

Methods

Study participants and protocol

Participants in the PIN3 study were recruited before 20 weeks gestation between January, 2001 and June, 2005 from the University of North Carolina prenatal care centers in Chapel Hill, North Carolina. Women were excluded if they were less than 16 years of age, did not speak English, did not plan to continue care or deliver at the study site, had twins or higher order multiple gestations, or did not have access to a telephone from which they could complete phone interviews. The PIN3 cohort included 2,006 pregnancies, with some women contributing up to three pregnancies. We limited our analysis sample to the first study pregnancy for each woman leaving 1,875 pregnancies in our analysis. This study was reviewed by the Institutional Review Board at the University of North Carolina, and informed consent was provided by all participants.

Participants provided access to their medical records and completed two telephone interviews to assess physical activity patterns and other characteristics; one interview was administered between gestational weeks 17 and 22 (“20 week interview”) and the other between weeks 27 and 30 (“28 week interview”). Women also completed two self-administered questionnaires between gestational weeks 15 and 20 and again between weeks 24 and 29 which provided data on several psychosocial measures.

Outcomes

At both phone interviews women were asked to describe their physical activities in the past week, not including the day of the interview. Each woman was asked, “In the past week, did you participate in any recreational activity or exercise, such as walking for exercise, swimming, or dancing that caused at least some increase in breathing and heart rate?” If she answered “yes,” she was asked “What type of recreational activities did you do during the past week?”, “How many times in the past week did you [activity]?”, “On average, for how many minutes or hours did you usually [activity] at a time?”, and “Thinking about your breathing and heart rate, how hard did this usually feel to you (fairly light, somewhat hard, or hard/very hard)?” The same series of questions was asked for other types of activity, including occupational activity, household activity (indoor and outdoor), child or adult care activity, and transportation activity (i.e., biking or walking to work).

Four outcomes were of interest in this analysis and each one was assessed at 20 weeks and again at 28 weeks. First, women were categorized as performing *any recreational activity* if they performed at least 10 minutes per week of moderate (“somewhat hard”) to vigorous (“hard/very hard”). Second, we examined the *total minutes of moderate or vigorous recreational activity*. The distribution of minutes per week of recreational activity was not normally distributed, with a high frequency of women reporting zero minutes of recreational activity. To address this, the analysis of minutes per week of recreational activity was limited to those who reported at least 10 minutes per week of recreational activity.

We also explored higher levels of recreational activity. Women were classified as performing *recommended recreational activity* if: 1) they reported "somewhat hard" recreational activity for at least 150 minutes/week, 2) they reported "hard/very hard" recreational activity for at least 75 minutes/week, or 3) the sum of their "somewhat hard" minutes/week and twice their "hard/very hard" minutes per week was at least 150 minutes/week. The definition of "recommended recreational activity" resembles the recommendation for activity during pregnancy supported by the ACOG. They recommend, "…an accumulation of 30 minutes or more of moderate exercise a day should occur on most, if not all, days of the week."[218] Their recommendation specifies exercise and includes only moderate intensity activity, not vigorous. To address these issues, we defined our criterion to include all recreational activity at both moderate and vigorous intensities. The current US Health and Human Services recommendation is similar to the ACOG recommendation, but is not limited to exercise[217].

Finally, we defined a dichotomous outcome that encompassed all modes of physical activity, not just recreational. Women who performed a total of at least 10 minutes of "somewhat hard" or "hard/very hard" physical activity in the past week met the criteria for *any* moderate or vigorous physical activity.

Correlates

Variables were assessed for their correlation with participation in physical activity based on two criteria: if they could inform intervention strategies for increasing activity during pregnancy or if they had been correlated with activity in previous studies.

We considered the following self-reported sociodemographic characteristics: age, race, marital status, education, income (expressed as a percentage of the 1996 poverty level), and employment status. Poverty index was assessed independently, in fine categories to determine the shape of its crude associations. Predicted outcomes (either log-minutes of recreational activity or the probability of meeting the criteria) were plotted against the continuous predictor. The structure of the poverty index variable was chosen based on a visual inspection of these graphs.

Behavioral variables included: pre-pregnancy body mass index, prenatal care use (assessed as month of initiation and as observed versus expected number of visits and categorized according to Kotelchuck[239]), multivitamin intake, alcohol use, smoking and other types of physical activity (occupational, child and adult care, indoor household, outdoor household, transportation). We categorized the other modes of activity (rather than assessing them as continuous variables) since their distributions were peaked (around zero).

For participants' reproductive histories, we had data on parity and previous pregnancy outcomes (miscarriage, preterm birth). The health of the current pregnancy was evaluated by presence or absence of pregnancy-induced hypertension, bed rest (any report of bed rest or physician advice to not be active[249]), vaginal bleeding and nausea/vomiting.

Maternal psychosocial health was characterized by state-trait anxiety (based on the State-Trait Anxiety Inventory[250]), perceived stress (Cohen Perceived Stress Scale[251]) and depression (Center for Epidemiologic Studies Depression (CES-D) Scale[252]). The 14-item perceived stress scale was administered at 20 weeks while the 10-item scale was used at 28 weeks, thus the category cutpoints differ for each time point. We also assessed exercise self-efficacy and enjoyment of physical activity on the subset of the women who were interviewed later in the study period, after these questions had been added to the second phone interview (11/2003).

Finally, as potential external influences, we had data on partner support of activity, free time available for recreational activity, health professional advice regarding physical activity, and season of the year.

Analysis

We employed two types of multivariable models. First, when limited to women who performed any recreational activity, the distribution of the natural log of minutes per week of recreational physical activity appeared to be normally distributed. We therefore employed a linear mixed model[242] to examine the associations of our predictors with the log-transformed outcome; we used a random intercept to account for within-woman correlation. Beta estimates from this model represent the change in natural log minutes of activity for a given change in exposure level. For ease of interpretation, these beta estimates (and confidence intervals) were exponentiated to give the ratio of minutes associated with a change in exposure level.

Second, for the three dichotomous outcomes we used a logistic regression model estimated with generalized estimating equations[243, 244] using a compound symmetric working correlation[245] to account for the dual measurements for each woman. Exposures measured at each interview were treated as time-dependent. We did not find any correlation between the outcomes measured at 20 weeks and the exposures measured at 28 weeks.

We used backward selection to obtain a more parsimonious model. Variables with a p-value of less than 0.2 were retained in the model. Interactions with time were evaluated for all predictors and retained if p<0.1.

We identified three influential individual observations in our linear mixed model using the MDFITTS statistic. When the paper records were reviewed, we could not determine whether their physical activity data were in error. These three women were excluded from all analyses. We examined the distribution of scaled residuals from the final linear mixed model to assess model fit. These residuals appeared to be approximately normally distributed.

All analyses were carried out with SAS software, Version 9.2 of the SAS System for Windows.

Results

Most women in our analyses were 26-35 years of age (59%), white (69%), married (71%), at least college educated (55%), with incomes of at least 200% of the poverty level (73%), and employed (69% at 20 weeks, 67% at 28 weeks) (Table 1). A substantial proportion of the women were obese (26%) while few were smokers (12%) and almost half were nulliparous (48%).

Correlates of any recreational activity

Forty percent (N=678) of women reported performing at least 10 minutes of recreational activity per week at 20 weeks and 35% (N=553) reported this level at 28 weeks. Women were less likely to do any recreational activity at 28 weeks compared with 20 weeks (Figure 1, panel A).

Women were more likely to take part in any recreational activity if they were 26-35 years of age (compared to older and younger), white, had some graduate education, were not employed, or had higher family income (Figure 1, panel A). At 20 weeks, lean women were more likely to perform any recreational activity than normal weight women, while at 28 weeks overweight or obese women were less likely. Women who began prenatal care later were less likely to perform any recreational activity. Child/adult care activity and outdoor household activity were positively associated with the performance of any recreational activity.

Parous women were less likely than nulliparous women to perform any recreational activity (Figure 1, panel D). History of miscarriage was negatively associated with any recreational activity at 20 weeks, but positively associated at 28 weeks. Bed rest was negatively associated with the performance of recreational activity at 28 weeks. Women who reported having a supportive partner and women who reported enjoying physical activity were more likely to perform recreational activity.

Correlates of the minutes of recreational physical activity performed

The amounts of recreational physical activity performed at 20 and 28 weeks were correlated (Spearman r=0.41 (95% confidence interval (CI): 0.37, 0.45)). Among women who performed at least 10 minutes of recreational activity, the average was 2.5 hours per week at 20 weeks and 2.4 hours per week at 28 weeks (median 2 hours at both time points).

Women reported 6% fewer minutes of recreational activity at 28 weeks compared with 20 weeks (Figure 2). Women who were single, reported daily multivitamin intake, performed any outdoor physical activity, had a history of preterm birth, whose daily activities were not affected by nausea, or who reported enjoying physical activity engaged in more minutes of recreational activity.

Correlates of recommended recreational activity

At 20 weeks, 279 women performed recommended recreational activity which constituted 41% of the women who performed any recreational activity and 16% of the total population. At 28 weeks, 216 women engaged in recommended recreational activity which was 39% of the women who performed any recreational activity and 14% of the total population.

Women were less likely to perform recommended recreational activity at 28 weeks (Figure 1, panel B). Education was positively associated with recommended recreational activity. Women with a higher prenatal care visit index, daily multivitamin use or alcohol use were more likely to perform recommended activity. Indoor activity was negatively associated with recommended recreational activity at 20 weeks, but positively associated at 28 weeks.

Parity was negatively associated with recommended recreational activity (Figure 1, panel E). Women who reported lower partner support for physical activity, having less time for recreational physical activity or lower levels of enjoyment of physical activity were less likely to perform recommended recreational activity.

Correlates of performing any physical activity

At 20 weeks, there were 1,096 (64%) women who performed any physical activity. Of these, 62% also performed any recreational activity and 25% performed recommended recreational activity. At 28 weeks there were 971 (62%) women reporting any physical activity, 57% of these also performed any recreational activity while 25% also performed recommended recreational activity.

Women were less likely to perform physical activity at 28 weeks compared with 20 weeks (Figure 1, panel C). Women who engaged in physical activity were also more likely to initiate prenatal care earlier and use alcohol.

Women who reported vomiting were less likely to perform physical activity (Figure 1, panel F). Bed rest was negatively associated with physical activity, particularly at 28 weeks. Perceived stress, partner support and enjoyment of physical activity were all positively associated with any physical activity.

Discussion

We have identified several characteristics related to both recreational physical activity and total physical activity across pregnancy. Sociodemographic variables were predictive of performing any recreational activity including several characteristics that have been reported by previous studies: age[219, 232, 233, 247, 253], white race[232, 233, 247, 253], higher education[219, 222, 232, 247], and higher income[247, 253]. Women who were employed were less likely to perform any recreational activity, while in a previous study employment was not associated (no effect estimate was reported)[228]. In contrast, minutes of recreational activity, recommended recreational activity, and any physical activity (not limited to recreational) were not correlated with most sociodemographic variables.

Previous studies have found lower levels of physical activity during pregnancy among women who smoked[232, 247] or were overweight[233, 254]. In our analysis, women who smoked were less likely to perform any recreational activity. Body mass index was only predictive of the low level of recreational activity, and not recommended recreational activity or any physical activity.

Women who began prenatal care earlier were more likely to be active which supported the hypothesis that women who are physically active may exhibit other healthy behaviors. This is further supported by the association of daily vitamin use with recommended recreational activity. On the other hand, report of alcohol use was positively associated with physical activity. Unlike prenatal care initiation, women at the highest level of the prenatal care visit index were less likely to perform recommended recreational activity. This could potentially reflect the tendency for women who have complications developing in their pregnancies to have more prenatal care visits and to avoid higher levels of activity.

Women who performed other modes of physical activity also tended to perform recreational activity. Unlike the previous studies that suggested women give up recreational activity for other types of physical activity[220, 227], our results suggest that women who do other types of physical activity may live active lifestyles.

Similar to previous studies, parous women were less likely to be physically active[224, 232, 233, 253]. Also, in agreement with one study[233], history of miscarriage was associated with any recreational activity. However, the association was negative at 20 weeks, but positive at 28 weeks. It is possible that once the risk period for miscarriage has passed women are more comfortable with participating in recreational activity.

Consistent with one study[254], women with nausea or vomiting were less likely to be physically active, but the associations were not strong. We asked about physical activities “in the past week” at prenatal weeks 20 and 28 when women rarely experience nausea. If early nausea decreased first trimester physical activity, women may have had ample time to increase their physical activity after nausea subsided. A similar argument could be made for vaginal bleeding, which was not an important predictor.

Women who reported being prescribed bed rest were less likely to engage in physical activity, particularly at 28 weeks. This suggests that the complications that result in bed rest prescription may not affect physical activity levels until later in pregnancy. In one previous study, physician advice was not associated with prenatal exercise[228]. "Responding to advice" was the most frequent reason for reducing prenatal exercise in a British study[235]. However, the source of the advice could have been magazines, family, or health care professionals.

Higher stress score was associated with the performance of any physical activity. It is possible that stress causes participation in physical activity; however, it is also possible that physical activity causes stress. Unlike recreation, other physical activities (housework and occupational) may not be done by choice, which may cause stress rather than relieve it. Recreational physical activity may be positively associated with emotional well-being[255] and a reduction in depressive symptoms[255-257]. In our data, lower trait anxiety was associated with more minutes of recreational activity.

In agreement with previous studies[226, 258], lower levels of reported partner support were associated with lower levels of physical activity. Women who reported enjoying physical activity or having time for recreational activity were more likely to be physically active. Lack of time has been previously reported as a barrier to physical activity[259]. We did not find any previous studies assessing enjoyment of activity.

Limitations

In order to improve interpretability and create parsimonious models we have performed model selection based on a p-value cut-off. Model selection may introduce bias since small associations are less likely to reach significance and variables that are significant may be overestimated[260-262]. We have also measured physical activities by self-report. Women may tend to over-report their activities due to the perceived desirability of being active, or they may not accurately recall the activities they performed. However, the low proportion of active women in our data suggests that over-reporting may not be an issue. Additionally, the women in our study comprise a volunteer population which may limit generalizability. We lacked data to assess some of the characteristics previously associated with physical activity in the literature including, multiple gestations[233, 254], pelvic girdle pain[254], and pre-pregnancy activity[224, 232, 248, 254].

Implications for intervention

Our analysis may have implications for the design and targeting of interventions for increasing or maintaining physical activity during pregnancy. Targeted interventions may be more efficacious in promoting physical activity than their general counterparts[263]. Our analysis has identified several characteristics that are associated with lower levels of physical activity which may be useful in defining population subgroups for intervention. For example, women decrease their activity over pregnancy. An intervention could be aimed at safely increasing or maintaining physical activity later in gestation when women are less likely to be active.

Interventions could also be guided by the desired amount of physical activity change. Our analysis suggests that the correlates of performing any recreational activity may be different from the correlates of performing recommended recreational activity. The targeting of physical activity interventions based on sociodemographic factors may only be useful when considering the most sedentary of women as women who do higher levels of activity did not differ by these characteristics in our sample.

Women who are overweight or obese may need more encouragement to be active later in pregnancy. In our data the differences between normal weight and overweight or obese women were more pronounced at 28 weeks of gestation.

Further research is needed to explore how our results might be applicable to intervention design. For example, future studies could examine whether women with a history of miscarriage avoid physical activity based on their own fears or whether health care providers advise against activity. Additionally, partner support was important across physical activity outcomes and future research is needed to clarify the role partner support plays in women's decisions to be active. Enjoyment of physical activity was strongly associated with the performance of physical activity. It is possible that by exposing pregnant women to different types of physical activities, they may be more likely to find something they enjoy and will be more likely to be physically active during pregnancy. Moreover, a focus group conducted in a subset of this population suggested that the largest barriers to physical activity during pregnancy were time constraints and lack of energy or tiredness[249]. Thus, women may have to really enjoy physical activity in order to overcome these other internal barriers.

Intervention "tailoring"[264] has been suggested to improve the effectiveness of interventions generally[265] and with regard to physical activity[266, 267] (in non-pregnant populations). Further research could determine if the correlates identified here are also effective for tailoring physical activity interventions to the individual.

Summary

This study had the advantage of a large population of women and detailed assessments of their physical activities. Several important and novel characteristics were measured including psychosocial variables and potential barriers to recreational activity. We found several previously unreported correlates of recreational physical activity in pregnancy. We also found that several associations changed over time. This analysis identifies new avenues for investigation into encouraging women to be active during pregnancy.

Acknowledgements

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Table 2. Descriptive characteristics of women in the analysis sample, Pregnancy, Infection, and Nutrition 3 cohort (N=1,875), North Carolina, 2001-2005.

	N (%)
Demographic	
Age[a]	
≤ 25	541 (29)
26 – 30	603 (32)
31 – 35	506 (27)
36 – 40	225 (12)
Race[a]	
White	1,286 (69)
Non-white	580 (31)
Marital status[a]	
Single (widowed, divorced, separated)	549 (29)
Married	1317 (71)
Education[a]	
High school graduate or less	468 (25)
Some college	367 (20)
College graduate	491 (26)
≥ Some graduate school	540 (29)
Income (% of 1996 poverty level)[b]	
<200	440 (27)
200 – 400	423 (26)
400 – 700	476 (29)
>700	300 (18)
Employed at 20 weeks[a]	
Yes	1,170 (69)
Employed at 28 weeks [b]	
Yes	1,045 (67)
Behavioral	
Body mass index (kg/m^2) [a,d]	
<19.8	246 (14)
19.8 – 26.0	872 (49)
>26.0 – 29.0	196 (11)
>29.0	463 (26)
Prenatal care initiation index[a]	
Adequate or less	428 (25)
Adequate plus	1,295 (75)
Expected prenatal care visit index[a]	
Inadequate/Intermediate	202 (12)
Adequate	1,008 (59)
Adequate plus	513 (30)

Multivitamin use in the previous week[b]	
Less than daily	511 (33)
Daily	1,053 (67)
Since the month before you got pregnant, did you drink any alcohol?[b]	
No	838 (53)
Smoked in months 1-6 of pregnancy[b]	
Yes	195 (12)
Occupational physical activity at 20 weeks[a]	
Any	193 (11)
Occupational physical activity at 28 weeks[b]	
Any	192 (12)
Child/adult care physical activity at 20 weeks[a] (minutes/week)	
None	1,409 (83)
1 – 250	198 (12)
>250	98 (6)
Child/adult care physical activity at 28 weeks[b] (minutes/week)	
None	1,305 (83)
1 – 250	192 (12)
>250	72 (5)
Outdoor physical activity at 20 weeks (minutes/week)[a]	
Any	94 (6)
Outdoor physical activity at 28 weeks (minutes/week)[b]	
Any	109 (7)
Indoor physical activity at 20 weeks (minutes/week)[a]	
None	1,304 (77)
1 -100	250 (15)
>100	150 (9)
Indoor physical activity at 28 weeks (minutes/week)[b]	
None	1,175 (75)
1 -100	245 (16)
>100	149 (10)
Transportation physical activity at 20 weeks[a]	
Any	147 (9)
Transportation physical activity at 28 weeks[b]	
Any	138 (9)
Reproductive history	
Parity[a]	
0	897 (48)
1	612 (33)
≥ 2	359 (19)
History of miscarriage[a]	
Any	474 (28)

History of preterm birth[a]	
Any	247 (14)
Current pregnancy	
Have you had any times when you had a feeling of nausea during this pregnancy?[a]	
No	294 (17)
Did nausea cause you to not be able to do your normal daily activities?[a]	
No	945 (56)
Have you vomited during this pregnancy because of nausea related to being pregnant?[a]	
No	826 (49)
Have you had any bleeding or spotting with blood during this pregnancy? (20 weeks)[a]	
Any	501 (29)
Have you had any bleeding or spotting with blood during this pregnancy? (28 weeks)[b]	
Any	97 (6)
Pregnancy-induced hypertension (from medical chart)[a]	
Yes	110 (6)
Psychosocial	
Perceived stress score, 20 weeks[a]	
0 – <17	565 (33)
17 – <23	519 (30)
≥ 23	619 (36)
Perceived stress score, 28 weeks[b]	
0 – <11	532 (34)
11 – <17	545 (35)
≥ 17	491 (31)
CES-D score, 20 weeks[b]	
0 – <17	1,171 (74)
17 – <25	206 (13)
≥ 25	200 (13)
CES-D score, 28 weeks[c]	
0 – <17	984 (74)
17 – <25	202 (15)
≥ 25	138 (10)
State anxiety, 20 weeks[b]	
20 – <29	497 (32)
29 – <39	525 (33)
≥ 39	555 (35)
State anxiety, 28 weeks[c]	
20 – <29	549 (42)
29 – <39	421 (32)
≥ 39	349 (26)
Trait anxiety[b]	

20 – <29	499 (31)
29 – <39	562 (35)
≥ 39	523 (33)
Barriers/External influences	
During this pregnancy, would you say your husband or partner is supportive of you being active…?[b]	
All of the time	940 (60)
Some of the time	356 (23)
None of the time	62 (4)
Refused/Don't know/NA	207 (13)
Would you say that you are able to take time to do recreational physical activities if you want to? That means you could walk for exercise, dance, swim, play soccer or any other activity when you feel like doing them. Would you say…?[b]	
All of the time	535 (34)
Some of the time	946 (60)
None of the time	84 (5)
Bed rest/doctor advice not to be active[b]	
Yes	76 (5)
At any time during this pregnancy has a doctor, nurse, or other health professional told you to change your physical activity rather than following your regular activity routine?[b]	
Yes	367 (23)
How confident are you that you could exercise more?[b,e] Would you say…	
Very	275 (43)
Somewhat	238 (37)
Not at all	132 (20)
Interviewed prior to 11/2003	923
How enjoyable is physical activity or exercise to you at this time? Would you say…[b,e]	
Very	112 (17)
Somewhat	234 (36)
A little	157 (24)
Not at all	134 (21)
Interviewed prior to 11/2003	923
Season of first interview[a]	
Winter	427 (25)
Spring	493 (29)
Summer	396 (23)
Fall	389 (23)
Season of second interview[b]	
Winter	403 (26)
Spring	399 (25)

Summer	466 (30)
Fall	301 (19)

[a]Missing <10%
[b]Missing <20%
[c]Missing <30%
[d]Categorized using Institute of Medicine cutpoints
[e]This question was added to the first telephone interview part way through the study, thus only some of the participants have information for this question. Percentages were calculated among those interviewed after this date (N=645).

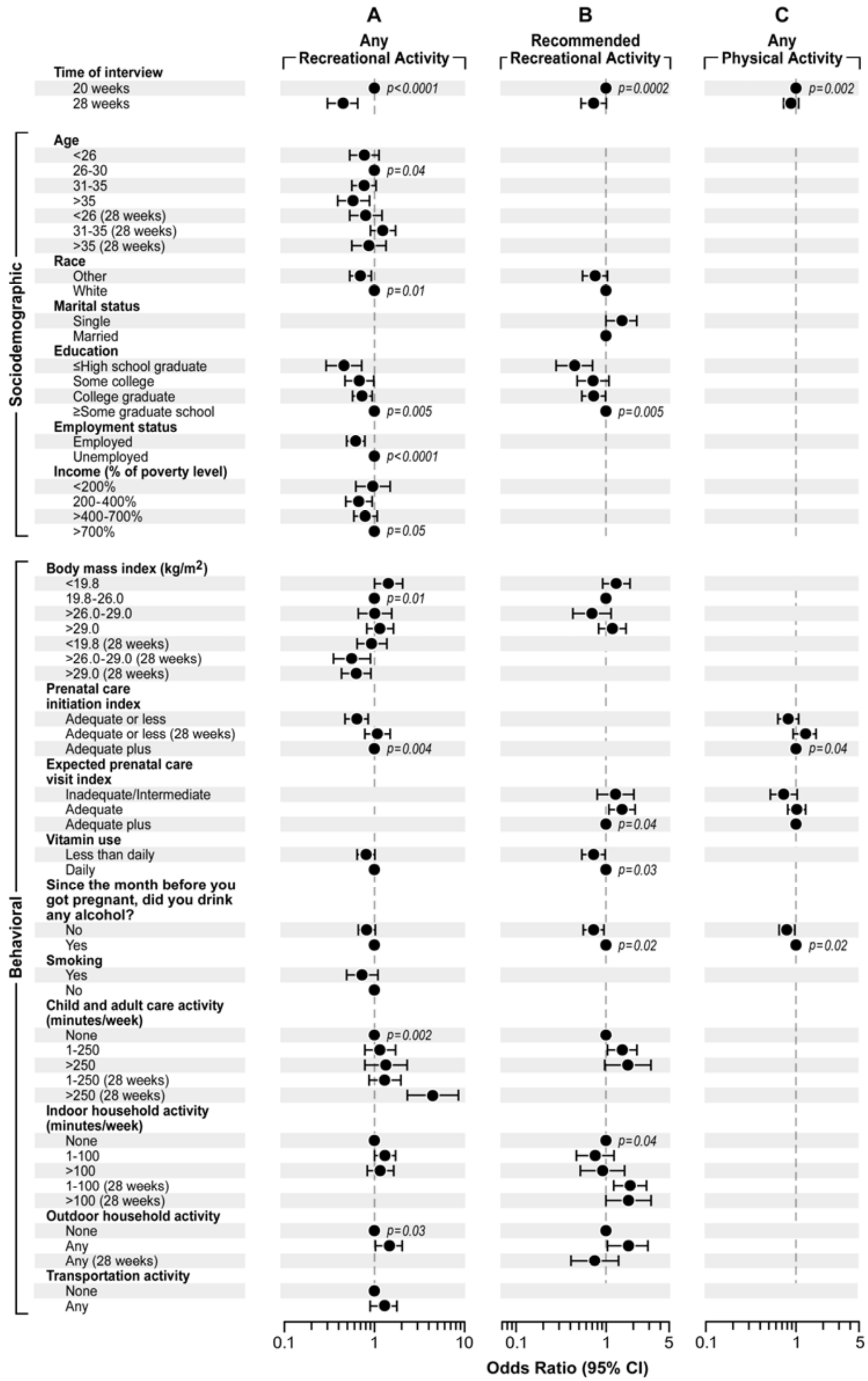

Figure 6. Results of the multivariable analyses identifying correlates of three dichotomous physical activity outcomes, Pregnancy, Infection, and Nutrition 3 Study (2001-2005).

“(28 weeks)” indicates a time-dependent association of the predictor with at least one of the activity outcomes. P-values are from a group test of all coefficients simultaneously and are drawn at the referent level for the variable, p-values greater than 0.05 are not shown. Each variable is adjusted for the other non-missing variables within each outcome.

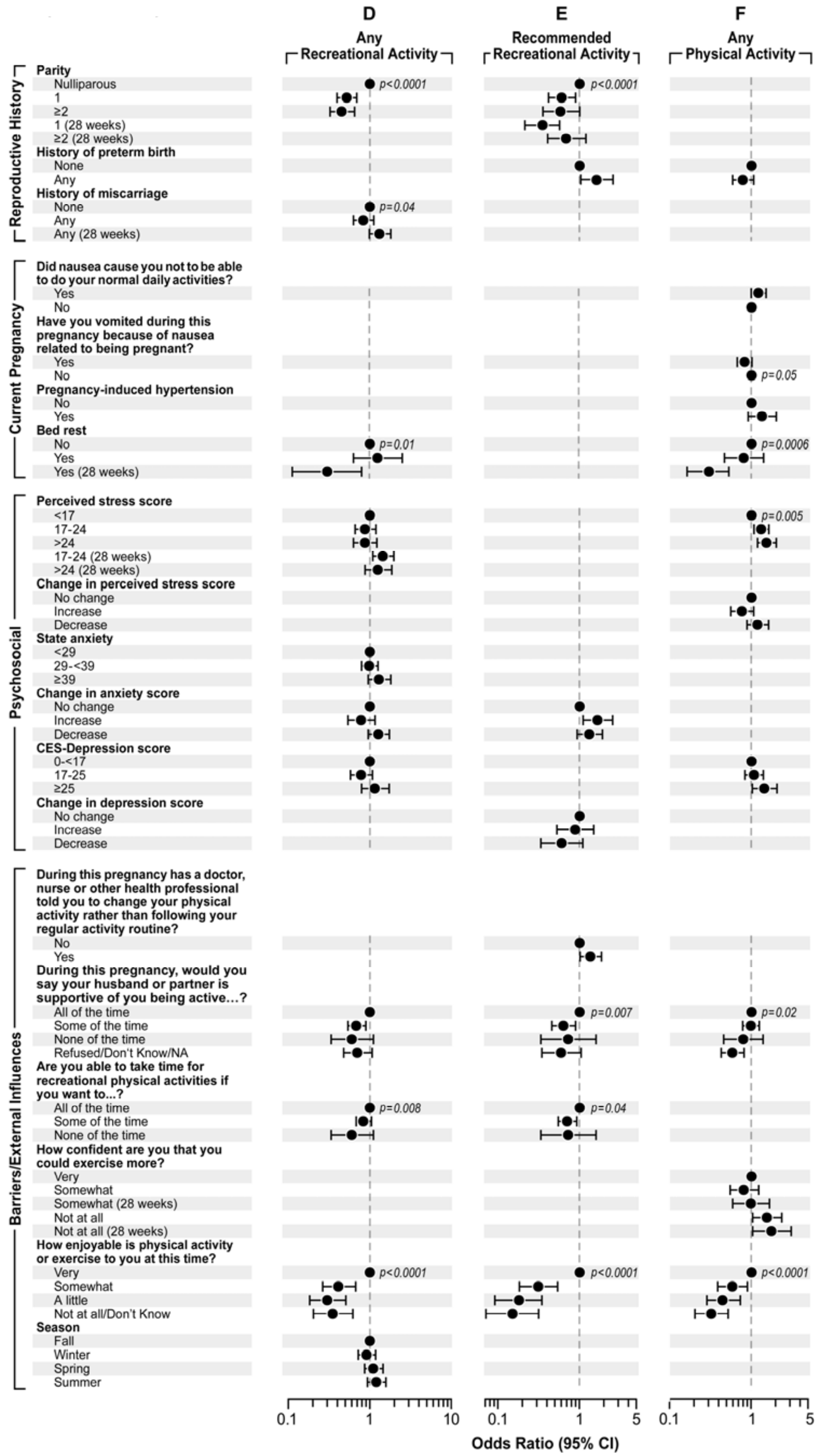
D
Any Recreational Activity
E
Recommended Recreational Activity
F
Any Physical Activity
Reproductive History
Parity
Nulliparous
1
≥2
1 (28 weeks)
≥2 (28 weeks)
History of preterm birth
None
Any
History of miscarriage
None
Any
Any (28 weeks)
Current Pregnancy
Did nausea cause you not to be able to do your normal daily activities?
Yes
No
Have you vomited during this pregnancy because of nausea related to being pregnant?
Yes
No
Pregnancy-induced hypertension
No
Yes
Bed rest
No
Yes
Yes (28 weeks)
Psychosocial
Perceived stress score
<17
17-24
>24
17-24 (28 weeks)
>24 (28 weeks)
Change in perceived stress score
No change
Increase
Decrease
State anxiety
<29
29-<39
≥39
Change in anxiety score
No change
Increase
Decrease
CES-Depression score
0-<17
17-25
≥25
Change in depression score
No change
Increase
Decrease
Barriers/External Influences
During this pregnancy has a doctor, nurse or other health professional told you to change your physical activity rather than following your regular activity routine?
No
Yes
During this pregnancy, would you say your husband or partner is supportive of you being active…?
All of the time
Some of the time
None of the time
Refused/Don't Know/NA
Are you able to take time for recreational physical activities if you want to…?
All of the time
Some of the time
None of the time
How confident are you that you could exercise more?
Very
Somewhat
Somewhat (28 weeks)
Not at all
Not at all (28 weeks)
How enjoyable is physical activity or exercise to you at this time?
Very
Somewhat
A little
Not at all/Don't Know
Season
Fall
Winter
Spring
Summer
p<0.0001
p<0.0001
p=0.04
p=0.05
p=0.01
p=0.0006
p=0.005
p=0.007
p=0.02
p=0.008
p=0.04
p<0.0001
p<0.0001
p<0.0001
0.1
1
10
0.1
1
5
0.1
1
5
Odds Ratio (95% CI)

Figure 6. (continued) Results of the multivariable analyses identifying predictors of three dichotomous physical activity outcomes, Pregnancy, Infection, and Nutrition 3 Study (2001-2005).
"(28 weeks)" indicates a time-dependent association of the predictor with at least one of the activity outcomes. P-values are from a group test of all coefficients simultaneously and are drawn at the referent level for the variable, p-values greater than 0.05 are not shown. Each variable is adjusted for the other non-missing variables, within each outcome.

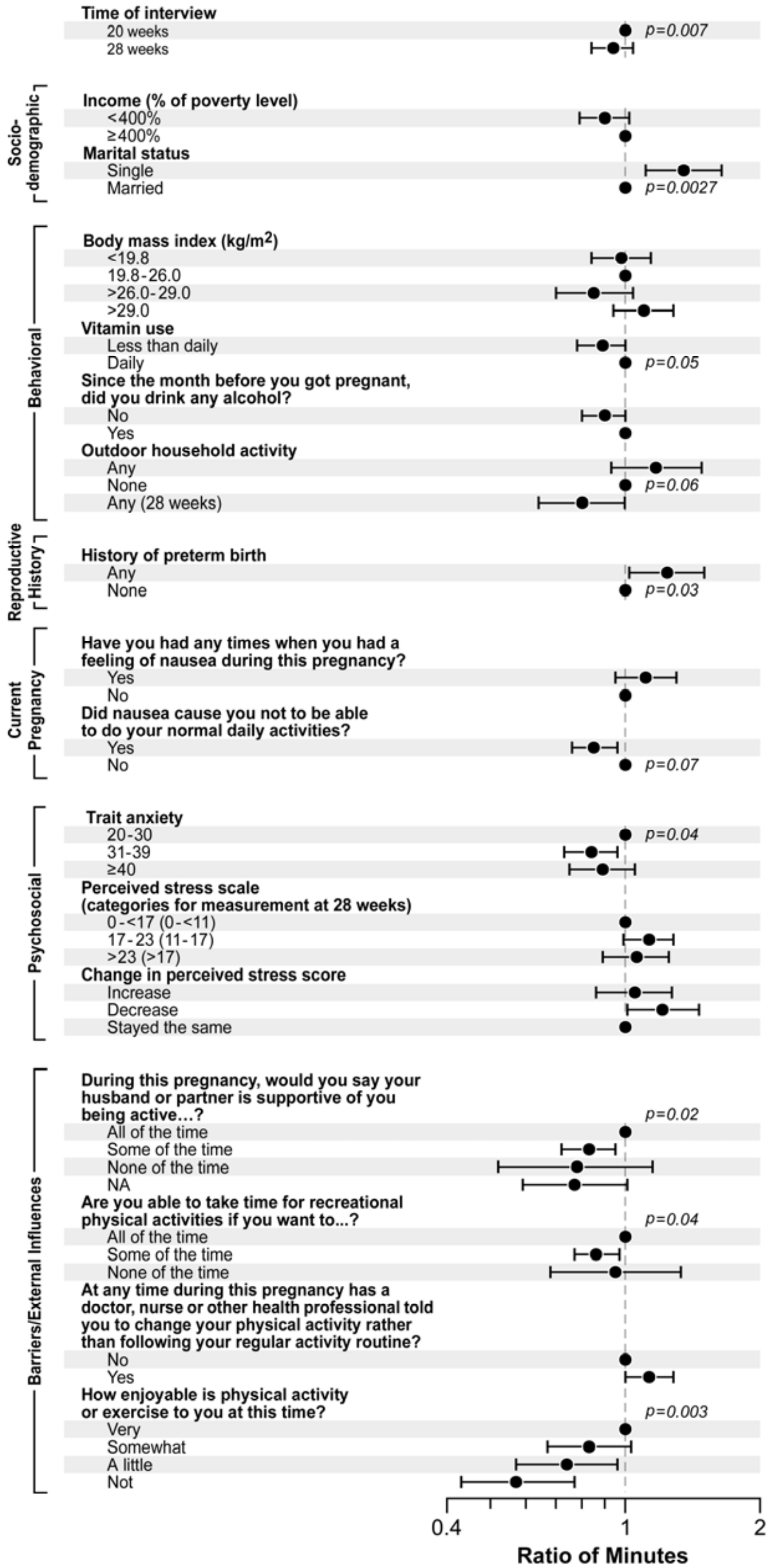
Time of interview
20 weeks
28 weeks
p=0.007
Socio-demographic
Income (% of poverty level)
<400%
≥400%
Marital status
Single
Married
p=0.0027
Behavioral
Body mass index (kg/m2)
<19.8
19.8-26.0
>26.0-29.0
>29.0
Vitamin use
Less than daily
Daily
p=0.05
Since the month before you got pregnant, did you drink any alcohol?
No
Yes
Outdoor household activity
Any
None
Any (28 weeks)
p=0.06
Reproductive History
History of preterm birth
Any
None
p=0.03
Current Pregnancy
Have you had any times when you had a feeling of nausea during this pregnancy?
Yes
No
Did nausea cause you not to be able to do your normal daily activities?
Yes
No
p=0.07
Psychosocial
Trait anxiety
20-30
31-39
≥40
p=0.04
Perceived stress scale (categories for measurement at 28 weeks)
0-<17 (0-<11)
17-23 (11-17)
>23 (>17)
Change in perceived stress score
Increase
Decrease
Stayed the same
Barriers/External Influences
During this pregnancy, would you say your husband or partner is supportive of you being active…?
p=0.02
All of the time
Some of the time
None of the time
NA
Are you able to take time for recreational physical activities if you want to...?
p=0.04
All of the time
Some of the time
None of the time
At any time during this pregnancy has a doctor, nurse or other health professional told you to change your physical activity rather than following your regular activity routine?
No
Yes
How enjoyable is physical activity or exercise to you at this time?
p=0.003
Very
Somewhat
A little
Not
0.4
1
2
Ratio of Minutes

Figure 7. Results of the multivariable analyses identifying correlates of the minutes of recreational activity, Pregnancy, Infection, and Nutrition 3 Study (2001-2005).

"(28 weeks)" indicates a time-dependent association of the predictor with at least one of the activity outcomes. P-values are from a group test of all coefficients simultaneously and are drawn at the referent level for the variable, p-values greater than 0.05 are not shown. Each variable is adjusted for the other variables.

IV. A PROSPECTIVE STUDY OF VIGOROUS PHYSICAL ACTIVITY WITH LENGTH OF GESTATION AND BIRTHWEIGHT

Abstract

Background: Conclusions from previous investigations of the association between physical activity and gestational age and birthweight have been limited by available exposure measurements.

Methods: Women were recruited for a prospective pregnancy study before 10 weeks gestation. Delivery date was obtained from medical or vital records, if unavailable, self-reported delivery date was used. Birthweight (from vital records) was studied only among term births. At 13-16 weeks gestation, participants self-reported vigorous physical activities which included recreational, occupational, household, and child/adult care. We analyzed the association between vigorous activity and gestational age using survival analysis and preterm birth using logistic regression.

Results: Our analyses included 1,647 births. The association of total vigorous activity with preterm birth was U-shaped, such that less than 30 minutes or greater than 435 minutes were associated with higher risk. Total vigorous activity is a summation over all modes of physical activity, one of which is recreational activity. Performing at least 5 sessions of vigorous recreational activity per week

(N=108) was associated with decreased odds of earlier birth compared with 0 or 1 session (odds ratio (OR) (95% confidence interval, (CI)):0.66 (0.36, 1.21)). Women who reported that they started exercising in preparation for pregnancy (N=53) gave birth later than women who did not report starting to exercise OR(CI): 0.65 (0.45, 0.94) and none gave birth preterm. None of the physical activity measures were associated with birthweight.

Conclusions: Very high or low amounts of total vigorous activity may be associated with preterm birth; however, vigorous recreational activity was not associated with adverse changes in gestational age or birthweight. Frequent vigorous recreational activity may result in longer gestation. It is unclear whether the association between starting an exercise regimen and increased gestational length is causal, or reflects a healthy participant bias.

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Introduction

In the United States, the prevalence of preterm delivery has been rising steadily over the last two decades ("preterm" defined as birth <37 weeks gestation) and is now about 12%[119]. This increase is of public health concern because preterm delivery is associated with morbidity and mortality in infants[121-123]. The epidemiologic literature regarding recreational physical activity and preterm birth or growth restriction is large, but inconclusive. A recent Cochrane review of eleven randomized trials with 472 participants suggested that the risk of preterm birth may be higher in women who perform recreational physical activity during pregnancy (although mean gestational age appears unaffected). The authors state, however, that the data are insufficient to draw firm conclusions mostly due to small sample sizes[177].

Several observational studies have reported no association of recreational physical activity with preterm birth[178-186, 188, 198] (including one meta-analysis[187]), while others reported decreased risk of preterm birth[189-195, 212, 268], or decreased risk only for some amounts or intensities[192, 210]. The results from studies examining the associations between recreational physical activity and birthweight are also inconsistent; some suggest an increase[182, 197, 198, 200, 212], some a decrease[202, 216, 269]and others no association[178, 179, 181, 184, 185, 196, 201, 210].

Recreational activity is one mode of physical activity, other modes include household, child care and occupational activity. Few studies have examined housework and child care activities as distinct exposures. A large literature relates occupational physical activities to both preterm birth and birthweight (reviewed by Bonzini et al.[205]), however, the measures of occupational activity in these studies are limited. Some studies only include facets of occupational activity (lifting only, or standing only) and some include composite measures that involve occupational activity and environmental stressors like chemical exposures or noise.

In general, physical activity studies are limited by crude measures of physical activity that do not include multiple modes of physical activity[270]. Many studies did not measure frequency and duration of activity and are therefore unable to assess either dose-response or their independent association with pregnancy outcome. While moderate physical activity is considered safe for pregnant women, it is unknown how much activity is safe. Moreover, current physical activity recommendations do not specify vigorous intensity activity, suggesting that studies of the associations of vigorous activity may be informative to health agencies. Our objective was to examine the association between vigorous physical activity and gestational age and birthweight (among term births) in a large cohort study of pregnancy, *Right From the Start*. Our analyses focus on recreational activity for two reasons. First, recreational activity is an easily modified mode of activity and is the most likely target of intervention. Second, the recommendation for activity during pregnancy refers to recreational activity[218].

Methods

The Right From the Start study invited women to participate in a study of early pregnancy through advertisements and community outreach. Study materials encouraged women planning a pregnancy or in early pregnancy to contact study staff through a toll free phone number. More details of recruitment are published elsewhere[271]. This study was approved by the Institutional Review Board at the University of North Carolina.

When women called to volunteer, study staff completed a screening interview to determine eligibility and collected the woman's age and pre-pregnancy weight. Women were eligible if they were currently trying to conceive or had been pregnant less than 10 weeks based on self-report of last menstrual period. Women also had to be at least 18 years of age, conceived without assisted reproductive technology, willing to have a first trimester ultrasound at one of the study's ultrasound locations, intending to remain in the area for the next 18 months, intending to carry the pregnancy to term, able to access a telephone for the first trimester interview, fluency in either English or Spanish, and had an identified prenatal or primary care provider at the time of screening. There were 1,956 live births delivered at 22 weeks gestation or greater. This analysis further restricted eligibility to North Carolina residents (N=1,861), the first pregnancy among women who participated in the study more than once (N=1,735), singleton gestations (N=1,708) and women who answered the first trimester interview (N=1,647).

Outcomes

Multiple data sources were used to obtain and confirm live birth date. The hierarchy of the sources was hospital discharge summaries and prenatal care records (51%), birth and fetal death records (32%), and participant self-report (17%). The outcome of four pregnancies could not be ascertained from any data source. Birthweight was obtained from vital records for all participants.

Physical activity

In a telephone interview at 14 weeks gestation, on average, (range: 7-20 weeks), women were asked to describe their vigorous physical activities by mode (recreational, occupational, indoor/outdoor household and child/adult care).

Recreational activity was quantified through a series of questions. First, the participants were advised to consider a typical week. They were then asked, “At this time, do you do any recreational physical activity or exercise, like brisk walking, jogging, swimming, biking, tennis, soccer, or dancing?” If she said no, further questions on recreational activity were skipped. If she said yes, she was asked, “Do any of these recreational activities feel hard or very hard, meaning that the activity caused large increases in breathing and heart rate?” The description ‘hard’ or ‘very hard’ was used to capture vigorous activity. If the woman reported performing any vigorous recreational activity she was asked to describe the type of activity, how many times per week (frequency) and for how many minutes or hours, on average, she performed the activity each week. We summed the minutes per week of each reported activity to obtain the total minutes per week of vigorous recreational activity. Other types of physical activity (occupational, indoor/outdoor household, and child/adult care) were assessed with an analogous series of questions. We summed the activities for occupational, household, and child/adult care activity to obtain the total minutes within each mode and we summed over all modes to obtain the total minutes of vigorous physical activity.

We calculated a variable representing the average duration of a recreational activity session by dividing the reported minutes per week by the reported frequency for each activity. If women reported more than one recreational activity, the durations were averaged. The cumulative frequency of recreational activity sessions per week was calculated as the sum of the individual frequencies reported for each activity.

We used the type of recreational activity reported to assign a metabolic equivalent (MET) value based on the Compendium of Physical Activities[238]. The Compendium of Physical Activities (originally published in 1993, updated in 2000[237, 238]) was developed to allow researchers to compare the intensities of different physical activities across participants. The Compendium assigns a MET value to various physical activities. A MET is defined as the ratio of work metabolic rate to a standard resting metabolic rate of 1.0 (4.184 kJ x kg/hour). Thus, one MET is approximately the rate of energy expenditure during quiet sitting. We multiplied the MET value for a given activity by the minutes per week of that activity and summed across activities to obtain total MET-minutes per week. METs were assigned by the first author (AMZJ) and reviewed by the second author (KRE).

Women were also asked two questions to compare current physical activity habits relative to pre-pregnancy: "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?"

Women were also asked an open-ended question regarding changes in lifestyle pre-pregnancy, “Sometimes women make changes in their lifestyles or health habits while planning to become pregnant. Did you do anything in preparation for getting pregnant?” If she answered “yes” she was asked, “What did you do in preparation for getting pregnant?” The interviewer did not read a list of responses, but some women responded that they started exercising (she could give multiple responses).

Covariates

The screening interview and the telephone interview collected information on important covariates including sociodemographics, reproductive history, presence of nausea and vomiting in early pregnancy, and lifestyle factors. Covariates for these analyses were chosen if they were considered to be potential confounders based on directed acyclic graphs constructed for each outcome. We adjusted for maternal age, race/ethnicity, education, income, marital status, alcohol consumption, body mass index, cigarette smoking, illicit drug use, history of miscarriage, history of preterm birth, parity, vaginal bleeding, nausea/vomiting, and history of diabetes.

Statistical analysis

We evaluated the association between physical activity and time to live birth using a discrete time hazards model and the logistic regression framework described by Cole and Ananth[246]. The model predicts the conditional odds of birth at a particular gestational age, given the woman has not experienced birth prior to that age. We included time-varying coefficients (i.e., those interacting with gestational age) if they were significant (group $p \leq 0.05$) in an unadjusted model.

We used a standard multivariable logistic regression to examine the association between physical activity and preterm birth as a dichotomous variable (<37 completed weeks of gestation). Among term births, we used a linear regression model to examine physical activity and birthweight, adjusted for gestational week. Birthweight in preterm infants can reflect either their prematurity or growth restriction or both. Since the outcome is heterogeneous in preterm infants, we limited our analysis of birthweight to term infants. We defined small-for-gestational age by comparing each birthweight to the distribution of birthweights in our study population. Infants were considered small-for-gestational age if their birthweight was less than the tenth percentile of the birthweight distribution for each week of gestational age in our data.

An interaction between each category of physical activity (recreational, occupational, household and child/adult care) and the change in activity from before pregnancy was tested in all three models to determine if the association of each modality differed depending on whether it was more, less, or the same as the amount of activity performed before pregnancy.

Continuous variables, including our exposures of interest, were finely categorized and examined with each outcome variable in an unadjusted analysis. The shape of the crude association of each variable with each outcome was visually inspected to determine the appropriate structure (linear, quadratic, categorical) and, if categorical, the number and location of cutpoints. More parsimonious models with fewer parameters were compared to the full model containing the highly categorized variable. Fewer parameters were used if information was not lost when compared to the highly parameterized model (likelihood ratio test p-value >0.05).

For vigorous recreational physical activity, we conducted separate multivariable analyses were conducted separately for perceived and absolute intensity (MET-minutes per week).

Mean duration of vigorous recreational activity session and frequency of sessions were modeled separately and both were adjusted for the total minutes of recreational activity, the previously described covariates, and the other modes of physical activity.

Analyses were performed with SAS software, version 9.1.

Results

There were 1,647 live births to women who met the inclusion criteria; of these, 110 (7%) were born preterm. The majority of the women in this cohort were 25-34 years of age (71%), white non-Hispanic (78%), college graduates (76%), married (94%), non-smokers (76%), and non-drug users (97%) (Table 3).

In the questionnaire women were asked to report vigorous physical activities, which correspond to a MET value of at least six. The median MET value assigned was 5.5 (interquartile range (IQR): 3.3, 7) suggesting that the perceived intensity of the activities is higher than the corresponding MET value.

Only 44% of the women in this cohort performed vigorous physical activity. The average total vigorous activity was 76 minutes/week (standard deviation (SD): 270), but the median was zero (IQR: 60). The mean of the reported minutes of vigorous recreational activity was 28 (SD: 100) with a median of zero (90^{th} percentile (90%): 90). Vigorous recreational activity was the most commonly reported mode of activity, followed by vigorous adult and child care activity (mean: 24 minutes/week, SD: 186, 90%: 5), vigorous household activity (mean: 14 minutes/week, SD: 101, median: 0, 90%: 20) and vigorous occupational activity (mean: 10, SD: 107). Although occupational activity was less common, the women who performed occupational activities performed a large amount (the 99^{th} percentile was 300 minutes/ week).

Length of gestation

Women who performed vigorous recreational activity had lower odds of earlier birth (Table 4), but we did not find a dose-response association between time spent in vigorous recreational activity (in minutes/week) and length of gestation. Results were similar when the exposure was quantified using absolute intensity (MET-minutes per week, data not shown). The average duration of vigorous recreational activity sessions was not associated with the timing of birth when adjusted for the total time spent in vigorous recreational activity and other covariates. However, the frequency of recreational activity sessions per week was associated with lower odds of earlier birth with women who reported at least five sessions of vigorous recreational activity per week having 0.53 times the odds of birth of women who reported 0 or 1 session per week (CI: (0.31, 0.91).

Vigorous household activity was associated with higher odds of earlier birth for women who reported 31 – 90 or >90 minutes/week of household activity compared with women who did not report any vigorous household activity (Table 4). Higher levels of child/adult care activity were weakly associated with lower odds of earlier birth. Vigorous occupational activity and total vigorous activity did not show any association with timing of birth.

Women who reported that they started exercising in preparation for pregnancy had lower odds of earlier birth (Table 4). We were unable to assess an interaction between this variable and gestational age because none of the 53 women who reported starting to exercise in preparation for pregnancy gave birth prior to term. Women who reported starting to exercise in preparation for pregnancy tended to be 25-34 years of age (81%), white non-Hispanic (87%), at least college educated (89%), at a body mass index of <27 kg/m^2 (70%) and nulliparous (62%). Thirty-two percent were smokers, compared with 23% among women who did not report starting to exercise. A higher proportion of those that reported starting to exercise (compared to those who did not report starting to exercise) also reported doing other things in preparation for pregnancy including: seeing a health care provider (7% vs. 0.9%), abstaining from alcohol (25% vs. 10%), abstaining from caffeine (20% vs. 6%), and stopping smoking (5% vs. 1%).

Preterm birth

Compared with women who performed <30 minutes/week of total vigorous physical activity per week, women who performed 30 – 435 minutes had lower odds of preterm birth while women who performed >435 minutes had higher odds of preterm birth (Table 4). A quadratic trend test with ordinal scores of one to five assigned to the five categories was significant (p=0.01) (Figure 8).

Time spent in vigorous recreational activity (minutes/week) was not associated with preterm birth. The estimates were similar when considering absolute intensity (MET-minutes per week) (low = 0.7 (0.3, 1.8), medium = 0.5 (0.2, 1.5), high = 0.5 (0.2, 1.8), group p-value = 0.37). The odds of preterm birth were lower with increasing frequency of vigorous recreational activity sessions, but confidence intervals were wide. None of the other modalities of physical activity were associated with preterm birth.

Birthweight

Time spent in vigorous recreational activity (minutes/week) was not associated with birthweight (Table 5). When using absolute intensity as the recreational activity measure, the associations did not meaningfully change (lowest tertile (vs. none): beta = -87g (-188, 13), middle: beta=22 g (-78, 121), highest: beta = 3 g (-98, 104)). None of the other measures of physical activity were associated with birthweight.

Small-for-gestational age

Women in the highest tertile of vigorous recreational activity had lower odds of small-for-gestational age birth, but the confidence interval was wide (Table 5). These estimates changed slightly when recreational activity was measured with absolute intensity (MET-minutes/week) (Low: OR(CI): 1.92 (0.88, 4.21), Middle: 0.94 (0.40, 2.25), High: 0.85 (0.32, 2.24)). This was mostly due to three women with small-for-gestational age births who were classified as “high” using MET-minutes/week and “middle” using minutes/week.

Sensitivity analyses

Controlling for previous pregnancy outcome in these analyses may be inappropriate. A woman’s physical activity in the first pregnancy may have influenced her first pregnancy outcome. If the woman tended to perform the same physical activity across pregnancies, controlling for previous pregnancy outcome will, in effect, be controlling for the exposure. To address this, we examined our multivariable results for all four outcomes without pregnancy history variables (history of miscarriage or preterm birth and parity); it did not affect our results or interpretations so all three were retained. Similarly, women could have reported their activities in the wrong category (i.e., gardening as a recreational activity). If this is the case, controlling for other modes of physical activity (i.e., controlling household activity for recreational activity) may be an over-adjustment. We examined each mode of activity without controlling for the others and, for the most part, results did not meaningfully change. The association between adult/child care activity and small-for-gestational age changed slightly, with adjustment OR(CI): 0.76 (0.30, 1.92), without adjustment OR(CI): 0.57 (0.24, 1.32).

Discussion

We found no evidence that vigorous recreational physical activity was associated with adverse changes in length of gestation or birthweight. The performance of recreational activity on most days of the week was associated with lower odds of earlier birth, as was starting exercise in preparation for pregnancy. The associations did not depend on whether the participant reported an increase, decrease or no change in vigorous activity from pre-pregnancy. While we focused on an activity measure based on the women's perceived exertion, the results were similar for the activity measure based on absolute intensity.

Previous studies suggest that recreational physical activity is either not associated[178-188, 198] or associated with lower risk of preterm birth[189, 191, 192, 195, 212, 268]. When limited to studies that have measured frequency, intensity, duration and type of activity the results suggest an overall reduced risk of preterm birth with the performance of recreational activity[190-195]. The most precise estimate from these studies was 0.82 (0.76, 0.88) and the authors found no dose-response association between recreational activity and preterm birth[194]. Our results, while less precise, support these findings.

Our data did not show strong associations of vigorous recreational activity with birthweight. The majority of the literature shows no association of recreational activity with birthweight[178, 179, 181, 184, 185, 196]. Only two studies found an increase in birthweight with recreational activity[197, 198]. We restricted our analysis of birthweight to term infants and also adjusted for gestational week. Of the earlier studies that adjusted for gestational age, three reported higher birthweight for babies of mothers who perform recreational activity[182, 200, 212]. Three others reported a decrease[202, 216, 269] and two reported no association[201, 210]. Two additional studies have examined the association of exercise on small-for-gestational age: one found no association[188] and one found an increase in SGA[202]. These studies include mostly recreational activities, although some have combined recreational with occupational, child care or housework activities[185, 188, 210, 212, 216]. We did not find any studies that have examined the association of components of recreational activity (duration and frequency) with length of gestation and birthweight while controlling for volume of recreational activity.

We did not find convincing associations of other modes of physical activity (household, child/adult care, occupational) with any of the birth outcomes. The point estimates for indoor/outdoor household activity suggest higher odds of earlier birth or preterm birth with higher levels of activity, but these were not statistically significant and the estimates were non-monotonic. Similarly, point estimates for preterm birth and the upper tertiles of occupational activity were above one, but confidence intervals were wide. Few studies have examined household or child/adult care activities as separate exposures. One previous study suggested no association of housework or child care activity with preterm birth[189]. In a second study from Guatemala the authors defined their exposure as having at least three children and no household help (presumably a composite of housework and child care activities). They found no association with preterm birth, but reported an increase in small-for-gestational age[204].

The point estimates from studies of occupational physical activity and preterm birth range from 0.7 to 4, with most less than 2[205]. While we found similar point estimates for women in the two highest categories of occupational activity, these estimates were imprecise and confidence intervals do not exclude larger or null associations. Of the five studies with adjusted estimates of occupational activity and small-for-gestational age, two have point estimates above one, one of which is also the most precise estimate[204, 211-214]. These studies vary widely in terms of their occupational activity measures and do not include detailed assessments of intensity, frequency and duration of activity.

Women who performed more than 435 minutes (7.25 hours) per week of vigorous physical activity had higher odds of preterm birth than women who reported more modest amounts of vigorous activity. However, women who performed less than 30 minutes of vigorous activity per week also had higher odds. This association appears to be driven by household activity and occupational activity as the associations with recreational activity were in the direction of lower odds of preterm birth. Only one previous study measured total physical activity in all of the domains that we have measured (household, occupational, recreational, and household) and examined the relation with preterm birth[212]. The authors reported a slightly higher proportion of preterm birth with lower levels of activity, but differences were small (10% vs. 8%).

We found that women who reported that they started exercising in preparation for pregnancy had lower odds of earlier birth. We did not find any associations with the variable that measured changes in the level of vigorous physical activity from before to during pregnancy. This might suggest that a simple increase in activity does not affect pregnancy outcome, whereas a change from none to some (i.e., a report that the woman "started exercising") does have relevance. Seventy-six percent of women who reported starting to exercise also reported zero minutes of vigorous recreational activity, which is slightly lower than the proportion for the cohort as a whole, 81%. This suggests that either women did not continue activity once they became pregnant or, they limited their activity to light or moderate intensities, which we did not measure.

One interpretation of this association is that recreational activity can affect length of gestation by affecting the uterus or hormonal milieu of the woman prior to, or around the time of, conception. However, it is also possible that women who reported starting to exercise in preparation for pregnancy are a select subgroup of women who made several healthy lifestyle changes prior to conceiving. In other words, this observation could be the result of residual confounding by a "healthy participant" effect. A higher proportion of those who reported starting to exercise also reported doing other things in preparation for pregnancy including seeing a health care provider, abstaining from alcohol and caffeine, and stopping smoking. Controlling for covariates did not largely change the effect estimates, which suggests that residual confounding is less likely. A larger proportion of smokers reported starting to exercise in preparation for pregnancy, which might suggest that smokers attempt to alleviate detrimental effects of smoking with exercise.

Limitations and Strengths

This large study recruited women early in pregnancy and prospectively ascertained their pregnancy outcomes. Our exposure of interest was based on self-report early in pregnancy, and women were asked several detailed questions to describe their physical activities which should have reduced exposure misclassification. Because the physical activity questions were asked early in pregnancy (around 14 weeks gestation) they may not reflect the appropriate exposure window in pregnancy for effects on timing of birth or birthweight. However, the responses at this point in pregnancy would not have been affected by the manifestation of some conditions that commonly lead to medically indicated preterm birth (pre-eclampsia, hypertension). Thus our exposure measurement is less susceptible to reverse causality or differential reporting by case status. The detailed exposure measurements also allowed us to examine the modes of vigorous physical activity as well as frequency and duration of vigorous recreational activities as separate exposures, which as not been reported previously in the literature. The numbers of women performing vigorous occupational activity were small, leading to imprecise estimates for this exposure. An additional limitation is that moderate intensity activities, which are recommended during pregnancy, were not measured[217, 218]. However, the recommendations from the American College of Obstetricians and Gynecologists and the Department of Health and Human Services may exclude vigorous activity because its safety is not well-described, making our analyses informative to these agencies. Transportation physical activity was not assessed separately, although women may have reported them as other modes (for example, she may report biking to work as a recreational activity).

Conclusion

In summary, the amount of recreational physical activity reported in our study does not appear to be detrimental to the timing of birth or birthweight. Low levels and very high levels of total vigorous physical activity may be associated with preterm birth and this association may be driven by household and occupational activity, rather than child care and recreational activity. Further examination of changes in recreational activity peri-conceptually may clarify whether starting to exercise in preparation for pregnancy is truly beneficial or a "healthy participant" effect.

Table 3. Descriptive statistics for the three birth outcomes: gestational age, preterm birth, and birthweight and the covariates of interest, for the Right From the Start cohort, North Carolina.

	N (%)
Total N	1,647
Gestational days at delivery, mean (SD)*	277 (13)
Birthweight, mean (SD)†	3,506 (464)
Preterm birth	
Yes	110 (7)
No	1,537 (93)
Small-for-gestational age†	
Yes	1,074 (91)
No	111 (9)
Total vigorous activity (minutes/week)	
0 – 30	1,166 (72)
31 – 60	90 (6)
61 – 180	208 (13)
181 – 435	109 (7)
>435	53 (3)
Vigorous recreational activity (minutes/week)	
None	1,327 (81)
1 – 75	107 (7)
76 – 140	99 (6)
>140	103 (6)
Frequency of vigorous recreational activity sessions (number/week)	
0 or 1	1,357 (83)
2 – 4	166 (10)
≥5	114 (7)
Duration of vigorous recreational activity session (minutes)	
0 – 10	1,354 (83)
11 – 50	219 (13)
>50	64 (4)
Vigorous outdoor/indoor household activity (minutes/week)	
None	1,443 (88)
1 – 30	68 (4)
31 – 90	69 (4)
>90	59 (4)
Vigorous occupational activity (minutes/week)	
None	1576 (96)
1 – 30	27 (2)

31 – 180	18 (1)
>180	20 (1)
Vigorous child/adult care activity (minutes/week)	
None	1,465 (89)
1 – 30	58 (4)
31 – 120	64 (4)
>120	52 (3)
Reported that she started exercising in preparation for getting pregnant	
Yes	56 (3)
No	1,587 (97)
Change in vigorous activity compared to before pregnancy	
Increase	53 (3)
Decrease	1,042 (63)
Stayed the same	547 (33)
Age	
≤ 24	202 (12)
25 – 29	592 (36)
30 – 34	584 (35)
35 – 39	248 (15)
≥40	21 (1)
Race	
White/Non-Hispanic	1,275 (78)
Black/Non-Hispanic	193 (12)
Hispanic	86 (5)
Native American/Asian/Other	89 (5)
Education	
≤ 12 years	157 (10)
Some college	244 (15)
≥ 4 years of college	1,246 (76)
Annual family income	
≤ $40,000	370 (23)
40,001 -80,000	620 (39)
>80,000	610 (38)
Marital status	
Married/Living as married	1,552 (94)
Other	95 (6)
Alcohol	
Never	245 (15)
Current	80 (5)
Recent quit (≤ 4 months since interview)	815 (50)
Distant quit (>4 months)	503 (31)
Body mass index	
<23	685 (42)

23 – <27	498 (31)
27 – <33	279 (17)
33 – <38	91 (6)
≥ 38	66 (4)
Smoking (First trimester)	
None	1,249 (76)
1 – 10 cigs/day	224 (14)
≥ 10 cigs/day	167 (10)
Drug use‡	
Yes	55 (3)
No	1,588 (97)
History of miscarriage	
Yes	356 (22)
No	1,288 (78)
History of preterm birth	
Yes	135 (8)
No	1,509 (92)
Parity	
0	781 (48)
1	585 (36)
≥ 2	278 (17)
Vaginal bleeding in the first trimester	
Yes	503 (31)
No	1,139 (69)
Nausea in the first trimester	
No	167 (10)
Yes, without vomiting	734 (45)
Yes, with vomiting	741 (45)
Diabetes	
Yes	44 (3)
No	1,598 (97)

*All variables are missing <5% except birthweight which is missing 21%

†Calculated only among term births, N = 1537

‡Items queried: cocaine, crack, heroin, ecstasy, angel dust, PCP, downers, LSD and marijuana.

Table 4. Association of physical activity measures with time to birth, adjusted for covariates*, Right From the Start, North Carolina.

	Total N† (% Preterm)	Time to live birth OR (CI)	Preterm birth OR (CI)
Total vigorous activity			
0 – 30 minutes/week	1,114 (7)	1	1‡
31 – 60	84 (2)	1.06 (0.79, 1.43)	0.25 (0.06, 1.05)
61 – 180	200 (5)	0.85 (0.69, 1.04)	0.65 (0.32, 1.32)
181 – 435	103 (5)	1.07 (0.81, 1.41)	0.81 (0.31, 2.15)
>435	51 (16)	0.86 (0.57, 1.28)	1.64 (0.68, 3.98)
Vigorous recreational activity			
None	1,256 (7)	1	1
1 – 75 minutes/week	100 (4)	0.85 (0.64, 1.12)	0.47 (0.16, 1.40)
76 – 140	97 (5)	0.91 (0.68, 1.20)	0.71 (0.27, 1.90)
>140	99 (4)	0.88 (0.67, 1.16)	0.65 (0.22, 1.89)
Frequency of vigorous recreational activity sessions			
0 or 1 /week	1,284 (7)	1**	1
2 - 4	160 (6)	0.93 (0.63, 1.37)	0.82 (0.14, 4.67)
≥5	108 (2)	0.53 (0.31, 0.91)	0.18 (0.02, 1.74)
Duration of vigorous recreational activity sessions			
0 – 10	1,281 (7)	1	1
>10 – 50	211 (4)	1.12 (0.59, 2.12)	0.68 (0.08, 5.86)
>50	60 (5)	1.00 (0.48, 2.10)	0.67 (0.06, 7.96)
Vigorous outdoor/indoor household activity			
None	1,376 (7)	1	1
1 – 30 minutes/week	59 (7)	1.15 (0.80, 1.65)	0.76 (0.25, 2.32)
31 – 90	64 (6)	1.45 (1.02, 2.07)	0.62 (0.20, 1.92)
>90	53 (11)	1.23 (0.83, 1.82)	1.79 (0.67, 4.74)
Vigorous occupational activity			
None	1,491 (7)	1	1
1 – 30 minutes/week	24 (4)	0.64 (0.37, 1.11)	0.29 (0.03, 2.62)
31 – 180	17 (12)	1.05 (0.53, 2.06)	1.36 (0.26, 7.00)
>180	20 (10)	0.66 (0.35, 1.23)	1.46 (0.29, 7.22)
Vigorous child/adult care activity			
None	1,388 (7)	1	1
1 – 30 minutes/week	53 (9)	1.16 (0.79, 1.70)	1.34 (0.47, 3.86)
31 – 120	63 (6)	0.92 (0.64, 1.32)	1.09 (0.36, 3.35)

>120	48 (6)	0.81 (0.53, 1.22)	0.90 (0.24, 3.36)
Started exercising in preparation for getting pregnant			
Reported	53 (0)	0.65 (0.45, 0.94)	‡‡
Not reported	1,499 (7)	1††	
Change in vigorous activity compared to before pregnancy			
Decrease	989 (6)	1.09 (0.94, 1.26)	0.78 (0.49, 1.22)
Increase	52 (10)	0.98 (0.66, 1.45)	1.14 (0.40, 3.23)
Stayed the same	511 (8)	1	1

*Table items are adjusted for maternal age, race/ethnicity, education, income, marital status, alcohol, body mass index, cigarette smoking, illicit drug use, history of miscarriage, history of preterm birth, parity, vaginal bleeding, nausea/vomiting, diabetes and the last two table items. In addition, each mode of activity is adjusted for the others. Frequency of recreational activity and duration of activity are adjusted for vigorous recreational activity and the other modes of activity.

†Total number of subjects not missing for any variables in the model

‡Group p-value = 0.08

**Group p-value = 0.03

††Group p-value = 0.02

‡‡Inestimable, no events among those who started to exercise

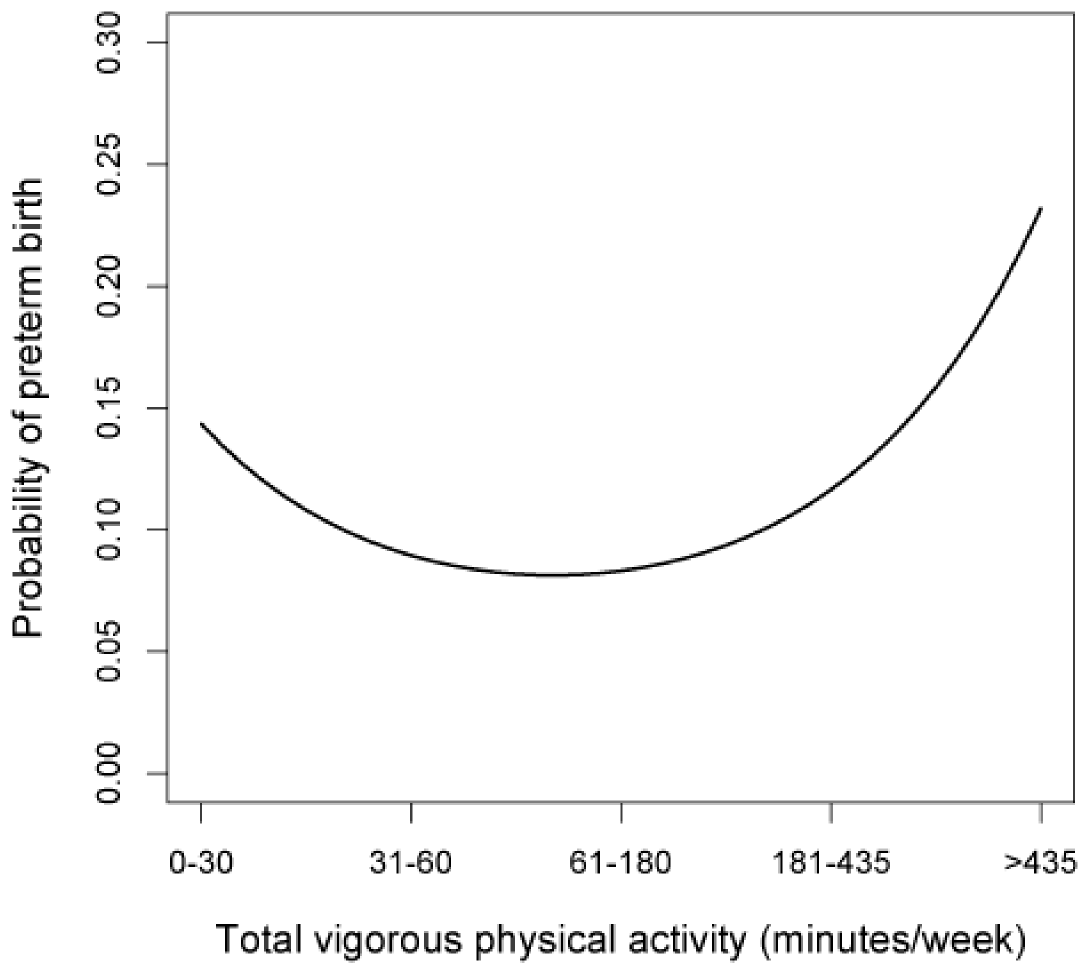

Figure 8. Estimated probability of preterm birth by category of total vigorous physical activity, Right From the Start.

Probabilities were calculated at the referent level of all covariates (vigorous activity compared to before pregnancy stayed the same, 24-29 years of age, white non-Hispanic race, some college education, annual income >$80,000, single marital status, stopped using alcohol within four months of interview, lean body mass index, non-smoker, no illicit drug use, no history of miscarriage, no history of preterm birth, nulliparous, no bleeding in the first trimester, nausea in early pregnancy, no diabetes)

Table 5. Adjusted* associations between physical activity measures and birthweight for gestational age and small-for-gestational age, Right From the Start, North Carolina.

	N (%)†	Beta‡ (CI)	SGA OR (CI)**
Total vigorous activity			
0 – 30 minutes/week	791 (71)	0	1
31 – 60	65 (6)	-45 (-152, 62)	1.77 (0.80, 3.93)
61 – 180	149 (13)	-4 (-78, 70)	1.12 (0.60, 2.10)
181 – 435	78 (7)	69 (-29, 168)	1.05 (0.42, 2.61)
>435	32 (3)	-25 (-174, 124)	0.91 (0.25, 3.37)
Vigorous recreational activity			
None	893 (80)	0	1‡‡
1 – 75 minutes/week	78 (7)	-80 (-178, 18)	1.62 (0.75, 3.53)
76 – 140	71 (6)	-38 (-141, 66)	1.78 (0.82, 3.87)
>140	73 (7)	56 (-44, 156)	0.31 (0.07, 1.32)
Frequency of vigorous recreational activity sessions			
0 or 1 /week	921 (9)	0	1
2 – 4	120 (10)	122 (-79, 323)	0.77 (0.16, 3.62)
≥5	83 (10)	66 (-151, 282)	1.30 (0.24, 6.95)
Duration of vigorous recreational activity sessions			
0 – 10	918 (9)	0	1
11 – 50	162 (12)	29 (-194, 252)	1.81 (0.28, 11.63)
>50	44 (5)	-16 (-274, 243)	1.01 (0.09, 10.72)
Vigorous outdoor/indoor household activity			
None	981 (88)	0	1‡‡
1 – 30 minutes/week	45 (4)	96 (-33, 224)	0.33 (0.07, 1.52)
31 – 90	52 (5)	21 (-100, 142)	1.58 (0.62, 4.00)
>90	37 (3)	111 (-30, 251)	0.20 (0.02, 1.62)
Vigorous occupational activity			
None	1,076 (96)	0	1
1 – 30 minutes/week	17 (2)	-47 (-250, 156)	0.90 (0.19, 4.33)
31 – 180	9 (1)	-126 (-408, 156)	1.24 (0.13, 12.22)
>180	13 (1)	-119 (-345, 107)	1.96 (0.44, 8.75)
Vigorous child/adult care activity			
None	999 (90)	0	1
1 – 30 minutes/week	35 (3)	104 (-42, 250)	0.76 (0.30, 1.92)
31 – 120	43 (4)	-11 (-145, 122)	††

>120	38 (3)	7 (-136, 150)	
Started exercising in preparation for getting pregnant			
Reported	39 (4)	7 (-127, 142)	1.38 (0.45, 4.22)
Not reported	1,076 (96)	0	1
Change in vigorous activity compared to before pregnancy			
Decrease	731 (66)	30 (-24, 84)	1.08 (0.67, 1.75)
Increase	28 (3)	-72 (-231, 86)	2.11 (0.69, 6.46)
Stayed the same	356 (32)	0	1

*Also adjusted for maternal age, race/ethnicity, education, income, marital status, alcohol use, body mass index, cigarette smoking, illicit drug use, history of miscarriage, history of preterm birth, parity, vaginal bleeding, nausea/vomiting, and diabetes

†Total number of subjects not missing for any variables in the model

‡In grams

**Odds ratio for small-for-gestational age birth (<10th percentile of birthweight for gestational week)

††Estimate is for any compared with none, numbers were too small to estimate other categories

‡‡p-value = 0.06

V. VIGOROUS PHYSICAL ACTIVITY AND SPONTANEOUS ABORTION

Abstract

Objective: To investigate the association between vigorous physical activity and spontaneous abortion.

Methods: Women were recruited prior to 10 weeks gestation to participate in a prospective study of pregnancy. Spontaneous abortions were identified through participant initiated contact, a telephone interview, or medical record information. Time spent in vigorous physical activity (including recreational, occupational, household, and child care) was assessed by telephone questionnaire at approximately 13-16 weeks of gestation. A discrete-time hazard model was used to estimate the conditional odds of spontaneous abortion, accounting for gestational age at enrollment.

Results: The time spent in each mode of physical activity was not associated with spontaneous abortion. Women who reported starting to exercise in preparation for pregnancy had lower odds of spontaneous abortion, OR(95% CI): 0.34 (0.10, 1.13). Women who reported decreasing their total vigorous physical activity from before pregnancy to during pregnancy had a lower odds of spontaneous abortion, OR(95% CI): 0.44 (0.32, 0.61). This may indicate residual confounding by pregnancy symptoms.

Conclusions: Vigorous physical activity is not associated with spontaneous abortion. Current physical activity recommendations do not specify vigorous physical activity; it may be safe to recommend vigorous activity during pregnancy.

Introduction

Approximately 50-60% of first trimester spontaneous abortion are associated with a chromosomal defect of the embryo; the remainder are largely unexplained[33]. Our understanding of the early pregnancy events or exposures that may contribute to spontaneous abortion is limited. It has been hypothesized that physical activity may lead to pregnancy loss through its effects on reproductive hormone levels[105], thermoregulation[24], blood flow to the uterus[30], and its related increases in muscular oxygen consumption[30]. Physical activity has also been reported to be detrimental to implantation[109, 110].

Several studies have examined the associations between physical activity and spontaneous abortion[34, 106-116, 118]. The existing literature includes several definitions of physical activity, with some studies addressing occupational activities such as lifting, bending or standing[112-116, 118], one that combines physically stressful activities[109] and others that focused on various recreational activities[34, 106-108, 110, 111]. In some studies, the specific activities that the women are reporting are unclear[34, 107, 108], and all types of activities may not have been identified for each participant. Additionally, in all of the recreational activity studies at least one dimension of activity (intensity of each session, frequency, duration, and the type performed) was not assessed. Many of these studies examine dichotomous measures of activity and do not assess dose-response[34, 106-109, 113].

While moderate intensity physical activity is generally considered safe for pregnant women, the upper limit is not known. Moreover, current physical activity recommendations do not address vigorous intensity activity. Inconsistencies in the physical activity/spontaneous abortion literature and the paucity of data regarding dose-response of vigorous activity suggest that further research incorporating these details about physical activity would be informative. Our objective was to examine the association between vigorous physical activity (including recreational, household, occupational, and child/adult care) and spontaneous abortion in a study of early pregnancy.

Methods

Study population

The Right From the Start Study (phases 2 and 3) (RFTS2/3) invited women to participate in a study of early pregnancy through advertisements and community outreach. Study materials invited women planning a pregnancy or early in pregnancy to contact study staff through a toll free phone number. More details of recruitment are published elsewhere. This study was approved by the Institutional Review Board at the University of North Carolina.

When women called to volunteer, study staff completed a screening interview to determine eligibility and collected each woman's age and pre-pregnancy weight. Women were eligible if they were currently trying to conceive or had been pregnant less than 10 weeks based on self-report of last menstrual period. Women also had to be at least 18 years of age, conceived without assisted reproductive technology, willing to have a first trimester ultrasound at one of the study's ultrasound locations, intended to carry the pregnancy to term, able to access a telephone for the interview, fluent in English or Spanish, had a prenatal or primary care provider prior to enrollment, and intended to remain in the area for the next 18 months. This analysis further restricted eligibility to North Carolina residents and known singleton gestations. This study was approved by the Institutional Review Board at the University of North Carolina.

Outcomes

After providing consent, women were given a pregnancy outcome form and asked to complete it within two weeks of their pregnancy's end. The form solicited information regarding pregnancy outcome including the date of birth or date of pregnancy loss. Women that did not return a form within four weeks of their due date were called to complete the form over the phone.

All of the spontaneous abortions were reported on the pregnancy outcome form. Multiple data sources were used to obtain and confirm other pregnancy outcomes. Data sources were prioritized as hospital discharge summaries and prenatal care records (50%), birth and fetal death records (32%), and participant self-report (18%).

Physical activity

In a telephone interview between 13 and 16 weeks gestation, women were asked to describe their physical activities (recreational, occupational, indoor/outdoor household and child/adult care) and any medical conditions they have. If a participant had a pregnancy loss prior to the interview, she completed a modified interview that referred to the time she was pregnant and contained the same physical activity content as the questionnaire for pregnancies that continued. Participants completed the modified first trimester interview within 2 weeks of the loss when possible, but no later than what would have been her 16th completed week of gestation or 2 months after her loss, whichever date was later.

Recreational activity was quantified through a series of questions that asked participants to refer to a typical week. She was then asked, “At this time, do you do any recreational physical activity or exercise, like brisk walking, jogging, swimming, biking, tennis, soccer, or dancing?” If she said no, no additional questions about recreational physical activity were asked. If she said yes, she was asked, “Do any of these recreational activities feel hard or very hard, meaning that the activity caused large increases in breathing and heart rate?” The description ‘hard’ or ‘very hard’ was used to capture vigorous activity. If the woman reported performing any vigorous recreational activity she was asked to describe the type of activity, how many times per week she performed the activity and for how many minutes or hours she performed the activity each week. The other types of physical activity (indoor/outdoor household, occupational, and child/adult care) were assessed with the analogous series of questions. We summed the minutes per week of each reported activity to obtain the total minutes per week within each mode and we summed over all modes to obtain the total minutes of vigorous physical activity.

We used the type of recreational activity reported to assign a metabolic equivalent (MET) value based on the Compendium of Physical Activities[237, 238]. The Compendium of Physical Activities (originally published in 1993, updated in 2000) was developed to allow researchers to compare the intensities of different physical activities across studies. The Compendium assigns a MET value to physical activities. A MET is defined as the ratio of work metabolic rate to a standard resting metabolic rate of 1.0 (4.184 kJ x kg/hour). One MET is approximately the rate of energy expenditure during quiet sitting. Walking at 5 miles per hour has a MET value of 8.0, meaning that the rate of energy expenditure is 8 times that of quiet sitting. We multiplied the MET value for a given activity by the minutes per week of that activity and summed across activities to obtain the total MET-minutes per week. MET assignments were made by the first author (AMZJ) and reviewed by the second author (KRE).

Women were also asked two questions to compare current physical activity habits relative to before pregnancy: "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?" Women were also asked an open-ended question regarding changes in lifestyle pre-pregnancy. They were asked, “Sometimes women make changes in their lifestyles or health habits while planning to become pregnant. Did you do anything in preparation for getting pregnant?” If she answered yes she was asked, “What did you do in preparation for getting pregnant?” The interviewer did not read a list of responses, but some women responded that they started exercising. Women were able to give more than one response.

Duration of vigorous recreational activity sessions was obtained by dividing the reported minutes of an activity by the frequency of that activity. If she reported more than one vigorous recreational activity, the average duration was calculated. We summed over each activity to obtain the total frequency of vigorous recreational activity sessions. We focused this analysis on vigorous recreational physical activity because it is more amenable to change (compared with occupational or household activity, for example) and it more directly corresponds to existing recommendations for physical activity during pregnancy[218].

Covariates

The screening interview and the telephone interview collected information on important covariates including sociodemographics, reproductive history, nausea and vomiting in early pregnancy, and lifestyle factors. Covariates for these analyses were chosen if they were potential confounders based on a directed acyclic graph. These covariates were, age, race/ethnicity, education, employment, income, marital status, alcohol use, body mass index, cigarette smoking, illicit drug use, history of miscarriage, parity, first trimester fever, vaginal bleeding, nausea/vomiting, and caffeine use.

Statistical analysis

Continuous variables, including our exposures of interest, were finely categorized and examined with each outcome variable in an unadjusted analysis. The shape of the crude association of each variable with each outcome was visually inspected to determine the appropriate structure (linear, quadratic, categorical) and, if categorical, the number and location of cutpoints. More parsimonious models with fewer parameters were compared to the full model containing the highly categorized variable. Fewer parameters were used if information was not lost when compared to the highly parameterized model (likelihood ratio test p-value >0.05).

We evaluated the association between physical activity (based on perceived intensity) and time to miscarriage using a discrete time hazards model and the logistic regression framework described by Cole and Ananth[246]. The model predicts the conditional odds of spontaneous abortion in a chosen gestational week, given the woman has not experienced a loss prior to that week. We included time-varying coefficients (i.e. those interacting with gestational age) if they were significant ($p \leq 0.05$) in an unadjusted model.

Interaction terms between each mode of activity and total activity with the change in vigorous physical activity from pre-pregnancy were tested to determine if the association between physical activity and spontaneous abortion differs depending on whether total vigorous activity has increased, decreased or stayed the same.

The multivariable analysis was repeated using recreational activity measured with absolute intensity (MET-minutes per week).

Results

Of the 1893 singleton pregnancies 201 (11%) ended in spontaneous abortion (Table 6). Most of the population was 25-34 years of age (70%), white non-Hispanic (76%), at least college graduates (75%), employed (69%), earning >$40,000 per year (76%), married (94%), of normal weight (60%), and non-smokers (76%). Sixty-six percent of participants did not report any vigorous physical activities. The average total vigorous activity reported was 72 minutes/week (standard deviation (SD): 256) and the median was zero (interquartile range: 60). The average time spent in vigorous recreational activity was 27 minutes/week (90^{th} percentile (90%): 90). Vigorous recreational activity was the most common mode of activity followed by vigorous child/adult care activity (mean: 21 minutes/week, 90%: 1), vigorous household activity (mean: 14 minutes/week, 90%: 15), and vigorous occupational activity (mean: 10 minutes/week, 99%: 240).

Time spent in each physical activity modality (in minutes/week) was not associated with spontaneous abortion in unadjusted analyses (Table 7). Estimates of the association between child/adult care activity and spontaneous abortion suggested lower risk for higher levels of activity, although confidence intervals were wide. To determine the sensitivity of our physical activity results to the tertile cutpoints we chose we shifted the cutpoints up by 10 minutes for each mode of activity and re-ran the multivariable results. The analysis did not change our interpretations (data not shown).

The three interaction terms between change in vigorous activity from pre-pregnancy and time spent in vigorous recreational activity, vigorous indoor/outdoor household activity and total vigorous activity, were not statistically significant (p = 0.35, 0.73, 0.87, respectively). Interactions with the other modes of physical activity (child/adult care and occupational) could not be evaluated due to small numbers. The main effect of change in vigorous activity from pre-pregnancy was important. Women who reported that their total vigorous activity had decreased compared to pre-pregnancy had 0.4 times the odds of spontaneous abortion of women who reported that their total vigorous activity stayed the same (confidence interval (CI): 0.32, 0.61) (Table 7).

When the intensity of recreational activity was measured using MET values, the adjusted associations were similar to those using perceived intensity (data not shown). The duration and frequency of recreational activity were not associated with spontaneous abortion (Table 8). The point estimates suggested a decrease in risk for longer duration or higher frequency of recreational activity; however the confidence intervals were wide.

Controlling for previous pregnancy outcome in these analyses may be inappropriate. A woman's physical activity in the first pregnancy may have influenced her first pregnancy outcome. If the woman tended to perform the same physical activity across pregnancies, controlling for previous pregnancy outcome will, in effect, be controlling for the exposure. To address this, we examined our multivariable results without pregnancy history variables (history of miscarriage and parity); it did not affect our results or interpretations so both were retained. Women could have reported their physical activities in the wrong category (i.e. gardening as a recreational activity). If this is the case, controlling for other modes of physical activity (i.e. controlling household activity for recreational activity) may be an over-adjustment. We examined each mode of activity without controlling for the others but results did not meaningfully change.

Discussion

We found no evidence that vigorous recreational activity was associated with higher risk of spontaneous abortion. In fact, women who reported that they started exercising in preparation for pregnancy had lower odds of spontaneous abortion. However, women who reported decreasing their total vigorous activity from pre-pregnancy also had lower odds of spontaneous abortion. This appeared to be driven by other forms of physical activity, rather than recreational activity. These measures were adjusted for several factors including nausea/vomiting and vaginal bleeding. We focused on perceived exertion, because absolute intensity (based on MET values) are not adjusted for body size or pregnancy stage, thus it is unclear if MET values are an ideal measure of intensity in a pregnant population; however the results were similar for both methods of measurement.

There were two different change variables in this analysis. The first was a woman's report of starting to exercise in preparation for pregnancy. This variable refers to "exercise" specifically and does not specify intensity. The second variable asks women to gauge their total vigorous activity at interview relative to pre-pregnancy. This measure involves all modes of physical activity and specifies vigorous activity. Starting to exercise in preparation for pregnancy was associated with lower odds of spontaneous abortion. It is possible that exercise is beneficial for pregnancy among women who were previously sedentary. It is also possible that women who start to exercise have other behaviors that lower their risk for spontaneous abortion. The association of decreasing total vigorous activity from before pregnancy might be the result of residual confounding.

Women who did not feel well might have decreased their vigorous activity, and not feeling well may be associated with a pregnancy that is progressing normally. We adjusted our estimates for nausea and vaginal bleeding, but it is possible other symptoms of pregnancy that we have not measured caused a decrease in vigorous activity (for example, difficulty sleeping or dehydration). This is further supported by our analysis of amount of total vigorous physical activity which suggested no association with spontaneous abortion.

Three previous studies suggest a lower risk of miscarriage for women who perform recreational physical activity in pregnancy[106-108], and four suggest a higher risk[34, 109-111]. The estimates from the former three studies were around 0.6 with confidence intervals from approximately 0.3 to 1.0. The first study suggesting lower risk found a reduced proportion of pregnancy loss in women who continued to perform recreational physical activity during pregnancy (compared to those who discontinued early in pregnancy), although the sample size was small and the differences were not statistically significant[106]. This study focused on very physically active women who are not generalizable to the population at large. The second study found a lower proportion of chromosomally normal pregnancy losses among women who performed recreational physical activity compared to women who did not perform recreational physical activity[107]. This comparison between chromosomally normal and abnormal losses is predicated on the idea that recreational activity cannot cause chromosomal abnormalities; this assumption is untested. Moreover, this study is a case-control design, which does not account for potential differences in the gestational age of spontaneous abortions. The third study is an analysis of several Swedish birth cohorts followed for the occurrence of clinical miscarriage[108]. The authors do not describe their "exercise" measurement, but report a decrease in risk that is not statistically significant.

Risk estimates from the four studies that reported increased risk of spontaneous abortion with recreational activity ranged from 1.3 to 3.7. The width of this range may be attributed to differing exposure measures and study populations. Two of the studies suggest that recreational activity may be detrimental to implantation. In a study from an in vitro fertilization population[110], the authors found that women who exercised 4 or more hours per week for 1 to 9 years had twice the odds of pregnancy loss, and twice the odds of implantation failure compared to those who did not exercise. One further study measured daily intensity of "physical strain" which incorporated any physical activity including tennis, running, and heavy lifting. Their results suggested that high levels of physical strain around the time of implantation were associated with approximately twice the risk pregnancy loss[109]. They did not find any association with monthly average leisure activity. We were unable to assess physical activity at the time of implantation since pre-pregnancy activity was not ascertained in our study.

Of the remaining two studies implicating recreational activity, one reported an increased prevalence of spontaneous abortion among anaesthesiologists who exercised during pregnancy (OR: 1.6 (CI: 1.2, 2.1))[34]. However, this study did not describe the exercise exposure, mentioning only that it was performed more than one time per week. Finally, a large study from the Danish National Birth Cohort reported increasing risk of spontaneous abortion with increasing exercise (in hours per week) (HR: 3-4, depending on gestational age of the loss) and with high-impact exercise (HR: 2-4)[111]. However, their assessment of exercise occurred after the pregnancy loss in some cases and data from prospective exposure ascertainment suggested a much weaker and inconsistent association. Further, this analysis was not adjusted for pregnancy symptoms such as nausea/vomiting and vaginal bleeding.

In total, recreational activity has not been consistently associated with spontaneous abortion. The limitations of the previous studies that find detrimental associations include: a unique study population[110], an exposure that combines recreational with other modes of physical activity[109], lack of detail in the description of their exercise measurement[34], or potential recall bias[111].

Several previous studies have examined occupational physical exertion and spontaneous abortion. Increased risk for spontaneous abortion has been reported for women who stand for long hours (OR: 1.3 (CI: 1.1, 3.5)[112], 1.6 (1.1, 2.3)[113]), lift heavy loads (RR: 2.0 (CI:1.5, 2.5)[113], OR: 2.0 (1.7, 2.5)[114]), or spend longer amounts of time in postures that increase intra-abdominal pressure (i.e. bending versus standing) (with estimates from 1.3 to 3.2 depending on the exposure measure used[114, 115]). In contrast, two studies suggest no association of standing with spontaneous abortion (OR: 0.9 (0.6, 1.6)[107], 1.0 (0.7, 1.5)[116]), one reported no association with bending (OR: 1.1 (0.63, 2.0)[116]), and three find no association of lifting during pregnancy (odds ratios of approximately 1)[112, 115,

[117]. One study reported a tendency toward decreased risk with more frequent lifting (OR: 0.40 (0.16, 1.0))[116]. Two studies have suggested associations between occupational fatigue and intensity scores and spontaneous abortion, with odds ratio estimates of 1.2 to 3.3[114, 115]. Physical effort has been associated with spontaneous abortion (RR 1.9 (90% CI: 1.4, 2.3)[113]) while activity level at work[118] and intensity of occupational activity[116] have not.

Only a handful of studies have reported associations for other modes of physical activity and spontaneous abortion. Caring for young children more than 50 hours per week and cleaning house for more than 7 hours per week have been associated with decreased risk of spontaneous abortion (OR: 0.8 (CI: 0.6, 1.0) and OR: 0.6 (CI: 0.5, 0.9), respectively)[112].In a previously described study[107], the odds of chromosomally normal (versus aberrant) pregnancy loss was not related to housework (more than 10 hours/week, OR: 1.2 (CI: 0.5, 2.9)), or childcare ("all day", OR: 1.2 (CI: 0.7, 2.0)). Two studies have suggested an association between spontaneous abortion and increasing hours of housework[114, 116]. One study found this association only among women with a history of spontaneous abortion (OR: 2.3 (1.5, 3.5))[116]. The other (hospital-based) study found higher hours of housework among women who experienced spontaneous abortion in an unadjusted analysis (no effect estimates presented)[114]. While our results are imprecise, our data suggest that child/adult care activity may be associated with reduced risk of spontaneous abortion while household activity may be associated with increased risk. The inconsistencies in these results may suggest that further investigation of household and child/adult care activities should be more specific, obtaining information regarding how the activities are performed or any chemicals used.

Limitations and strengths

Our analysis is limited by the retrospective measurement of physical activity for women who experienced spontaneous abortions. Women who were interviewed after the spontaneous abortion may have been more likely to report what they perceived as detrimental exposures. Of the 189 spontaneous abortions with covariate information, only 12 (6%) occurred after the first trimester questionnaire was administered (i.e. most (94%) reported their activity after the occurrence of the spontaneous abortion), limiting our ability to assess the association among those with prospective reporting. However, the physical activity measurement occurred very close in time to when the activity was being performed. We had detailed measurements of physical activity that included frequency, duration and type of physical activity and we allowed women to enumerate all of their activities.

A strength of this study is the recruitment of women very early in pregnancy enabling us to include early miscarriages in our analysis. This is important as the etiology of earlier spontaneous abortions may differ from later losses and it increased sample size since losses are more likely early in gestation. Our analysis was adjusted for several important confounders.

An additional limitation is that moderate intensity activities were not measured, which are recommended during pregnancy[217, 218]. However, these recommendations do not provide guidelines for vigorous activity, making our analyses informative to both clinicians and patients. We did not assess transportation physical activity separately, although women may have reported them in other domains.

Conclusion

Vigorous recreational activity was not associated with spontaneous abortion. Household activity may be associated with spontaneous abortion and warrants further study. Current physical activity recommendations do not specify vigorous recreational activity but it may be safe to recommend vigorous activity during pregnancy.

Table 6. Descriptive statistics for participants in Right From the Start, North Carolina.

	N (%)
	1,893
Pregnancy outcome	
Spontaneous abortion	201 (11)
Live birth	1,618 (85)
Induced abortion	7 (0.4)
Stillbirth	7 (0.4)
Ectopic/molar	2 (0.1)
Unknown	58 (3)
Gestational days, mean (se)	249 (1.6)
Total vigorous physical activity (minutes/week)	
0	1,240 (66)
1 – 60	207 (11)
61 – 180	241 (13)
181	179 (10)
Missing	26
Vigorous recreational activity (minutes/week)	
None	1,523 (81)
1 – 70	117 (6)
71 – 135	118 (6)
>135	119 (6)
Missing	16
Vigorous outdoor/Indoor household activities	
None	1,667 (89)
1 – 34	68 (4)
35 – 90	76 (4)
>90	71 (4)
Missing	11
Vigorous work activities	
None	1,811 (96)
1 – 20	24 (1)
21 – 180	27 (1)
>180	22 (1)
Missing	9
Vigorous child/adult care activities	
None	1,693 (90)
1 – 30	64 (3)
31 – 120	73 (4)
>120	52 (3)
Missing	11
Started exercising in preparation for getting pregnant	

Reported	60 (3)
Not reported	1,826 (97)
Missing	9
Change in vigorous activity compared to before pregnancy	
Increase	69 (4)
Decrease	1,143 (61)
Stayed the same	673 (36)
Missing	8
Age	
≤24	237 (13)
25 – 29	658 (35)
30 – 34	668 (35)
35 – 39	292 (15)
≥40	38 (2)
Race	
White/Non-Hispanic	1,442 (76)
Black/Non-Hispanic	227 (12)
Hispanic	115 (6)
Native American/Asian/Other	105 (6)
Missing	4
Education	
≤12 years	188 (10)
Some college	287 (15)
≥ 4 years of college	1,417 (75)
Missing	1
Employed	
Yes	1,301 (69)
No	588 (31)
Missing	4
Annual family income	
≤$40,000	436 (24)
40,001 – 80,000	702 (38)
>80,000	694 (38)
Missing	61
Marital status	
Married/Living as married	1,780 (94)
Other	113 (6)
Body mass index (IOM categories)	
Underweight	153 (8)
Normal weight	1,142 (60)
Overweight	242 (13)
Obese	352 (19)
Missing	4
Alcohol	
Never	299 (16)

Current	135 (7)
Recent quit (≤ 4 months since interview)	858 (45)
Distant quit (> 4 months)	594 (32)
Missing	7
Smoking (First trimester)	
None	1,438 (76)
1-10 cigs/day	252 (13)
≥ 10 cigs/day	193 (10)
Missing	10
Caffeine intake, mean (se)	284 (9.0)
Missing (N)	5
Drug use	
Yes	61 (3)
No	1,825 (97)
Missing	7
History of miscarriage	
Yes	418 (22)
No	1,472 (78)
Missing	3
Parity	
0	902 (48)
1	676 (36)
≥2	312 (17)
Missing	3
Fever during the first trimester	
Yes	69 (4)
No	1,810 (96)
Missing	14
Vaginal bleeding in the first trimester	
Yes	656 (35)
No	1,229 (65)
Missing	8
Nausea in the first trimester	
No	243 (13)
Yes, without vomiting	851 (45)
Yes, with vomiting	791 (42)
Missing	8

Table 7. Unadjusted and adjusted associations of physical activity variables with spontaneous abortion (SAB), Right From the Start, North Carolina.

	Total N (% SAB)	Unadjusted odds ratio (CI)	Adjusted odds ratio (CI)*	p-value†
Total vigorous physical activity (minutes/week)‡				
None	1,192 (10)	1	1	0.91
1 – 60	200 (10)	0.81 (0.50, 1.33)	0.98 (0.58, 1.65)	
61 – 180	233 (12)	1.18 (0.79, 1.77)	0.98 (0.64, 1.51)	
>180	173 (9)	0.89 (0.53, 1.47)	0.81 (0.47, 1.42)	
Vigorous recreational activity (minutes/week) ‡				
None	1,455 (10)	1	1	0.43
1 – 70	112 (14)	1.30 (0.76, 2.21)	1.42 (0.79, 2.56)	
71 – 135	116 (10)	0.90 (0.49, 1.67)	0.70 (0.37, 1.35)	
>135	115 (12)	1.35 (0.80, 2.27)	1.01 (0.55, 1.84)	
Vigorous outdoor/Indoor household activities (minutes/week) ‡				
None	1,599 (10)	1	1	0.23
1 – 34	63 (6)	0.55 (0.20, 1.47)	1.03 (0.37, 2.88)	
35 – 90	72 (11)	1.03 (0.50, 2.10)	1.91 (0.87, 4.17)	
>90	64 (16)	1.35 (0.71, 2.57)	1.89 (0.89, 4.00)	
Vigorous work activities (minutes/week) ‡				
None	1,728 (10)	1	1	0.82
1 – 20	23 (22)	2.05 (0.83, 5.03)	1.54 (0.55, 4.31)	
21 – 180	26 (8)	0.71 (0.19, 2.89)	0.75 (0.17, 3.25)	
>180	21 (5)	0.42 (0.06, 2.98)	0.69 (0.09, 5.28)	
Vigorous child/adult care activities (minutes/week) ‡				
None	1,617 (11)	1	1	0.11
1 – 30	60 (7)	0.57 (0.21, 1.53)	0.55 (0.19, 1.58)	
31 – 120	72 (11)	1.00 (0.49, 2.04)	0.59 (0.27, 1.30)	
>120	49 (2)	0.17 (0.02, 1.19)	0.23 (0.03, 1.72)	
Started exercising				

in preparation for getting pregnant				
Reported	57 (5)	0.37 (0.11, 1.23)	0.34 (0.10, 1.13)	0.04
Not reported	1,741 (11)	1	1	
Change in vigorous activity compared to before pregnancy				
Increase	64 (16)	0.93 (0.50, 1.73)	0.71 (0.34, 1.45)	<0.0001
Decrease	1,095 (6)	0.34 (0.25, 0.45)	0.44 (0.32, 0.61)	
Stayed the same	639 (17)	1	1	

*Adjusted for other table items and age, race/ethnicity, education, employment, income, marital status, alcohol use, body mass index, cigarette smoking, illicit drug use, history of miscarriage, parity, first trimester fever, vaginal bleeding, nausea/vomiting and caffeine use. Total vigorous activity is adjusted for all of the previous except the individual modes of activity (recreational, household, occupational, adult/child care).

†p-values are from a type 3 group test of all the coefficients simultaneously from the adjusted model

‡The categories shown are tertiles plus a separate category for zero

Table 8. Adjusted* associations of frequency and duration of vigorous recreational physical activity sessions with spontaneous abortion (SAB), Right From the Start, North Carolina.

	Total N (% SAB)	Odds ratio* (95%CI)	p-value†
Average duration of recreational activity sessions (minutes/week)			
≤10	1,508 (10)	1	0.31
11 – 50	247 (10)	0.71 (0.23, 2.23)	
>50	69 (8)	0.38 (0.10, 1.52)	
Maximum duration of recreational activity sessions (minutes/week)			
≤10	1,508 (10)	1	0.35
11 – 50	221 (12)	0.70 (0.22, 2.18)	
>50	95 (11)	0.42 (0.11, 1.57)	
Cumulative frequency of recreational activity (sessions/week)			
0 or 1	1,510 (10)	1	0.54
2 – 6	262 (13)	1.14 (0.39, 3.35)	
≥7	52 (8)	0.61 (0.13, 2.84)	

*Adjusted for total recreational activity, indoor/outdoor household activity, occupational activity, child/adult care activity, age, race/ethnicity, education, employment, income, marital status, alcohol use, body mass index, cigarette smoking, illicit drug use, history of miscarriage, parity, first trimester fever, vaginal bleeding, nausea/vomiting and caffeine use.
†p-values are from a type 3 group test of all coefficients simultaneously

VI. CONCLUSIONS

Review of study results

This dissertation was undertaken to contribute to the understanding of physical activity during pregnancy. Recreational physical activity is considered beneficial for pregnant women and is recommended by both the American College of Obstetrics and Gynecology (ACOG) and more recently in the national “Guidelines for Americans”[217, 218]. Despite these recommendations, many pregnant women are not physically active[219]. In order to inform interventions aimed at promoting physical activity we examined the correlates of physical activity. Additionally, the current recommendations for physical activity during pregnancy are limited to moderate intensity activity as the safety of vigorous intensity activity is not well-established. Thus, we also analyzed the associations between vigorous physical activity and spontaneous abortion, length of gestation and birthweight.

Correlates of physical activity

Many characteristics were correlated with the performance of recreational physical activity. Consistent with previous studies, several sociodemographic[219, 222, 232, 233, 247, 253] variables and body mass index[233, 254] were associated with recreational activity. However, most sociodemographic variables and body mass were correlated with low levels of activity, and not the higher recommended amount. For body mass index, this may be because as physical activity increases, muscle mass develops and body mass index is a measure that is unable to differentiate people who are heavy because they are muscular and people who are heavy due to fat mass.

Healthy behaviors were also associated with recreational activity including early prenatal care initiation, daily vitamin use, and household and child/adult care activity. Reproductive history was also correlated with recreational physical activity. Similar to previous studies[224, 232, 233, 253], parous women were less likely to be active, however, child care activity was positively correlated with activity. This may suggest that women who stay home with their children have more opportunity for recreational activity (playing outside, walks to school, etc.).

Higher stress score was associated with the performance of any total physical activity while higher trait anxiety was associated with less minutes of recreational activity. General physical activity includes several modes of activity that are compulsory in nature; for example occupational activity may be an unavoidable requirement of one's job. If this is the case, then these forms of activity may cause stress. On the other hand, recreational physical activity may be positively associated with emotional well-being[255] and a reduction in depressive symptoms[255-257], which is consistent with our observation of lower anxiety with more minutes of recreational activity.

Partner support, enjoyment of physical activity and time for recreational activity were correlated with several of the physical activity outcomes. In addition, these were some of the strongest point estimates with a tendency towards monotonic associations.

Vigorous physical activity and pregnancy outcome

We found no evidence that vigorous recreational activity was associated with the occurrence of spontaneous abortion or with adverse changes in length of gestation or birthweight. The performance of recreational activity on most days of the week was associated with later birth. Child/adult care activity may be associated with reduced risk of spontaneous abortion while household activity may be associated with increased risk. Point estimates for indoor/outdoor household activity suggest higher odds of earlier birth or preterm birth with higher levels of activity, but these were not statistically significant and the estimates were non-monotonic. Similarly, point estimates for preterm birth and the upper tertiles of occupational activity were above one, but confidence intervals were wide.

The association between total vigorous physical activity and preterm birth was U-shaped. This association appeared to be driven by household activity and occupational activity as the associations with recreational activity were in the direction of lower odds of preterm birth.

Two change variables were included in these analyses. The first assessed the change in total vigorous activity from pre-pregnancy to interview. The second asked women if they did anything in preparation for pregnancy and it was noted if she mentioned that she started exercising. The odds of spontaneous abortion were lower among women who reported decreasing their vigorous activity from pre-pregnancy. Women who reported that they started exercising in preparation for pregnancy had lower odds of spontaneous abortion and gave birth later.

Limitations and strengths

Correlates of physical activity

One of the goals of the analysis was to determine if pregnancy symptoms were predictive of participation in recreational activity. While nausea and bleeding variables were included in this analysis, they were not important predictors. This seems counterintuitive, as these are important symptoms that are likely to affect behavior. The questionnaire queried women about their physical activities “in the past week” at prenatal weeks 20 and 28 when women rarely experience nausea. If early nausea decreased first trimester physical activity, women may have had ample time to increase their physical activity after nausea subsided. A similar argument could be made for vaginal bleeding, which was not an important predictor. In order to truly assess the affects of these characteristics an earlier measurement of physical activity would be needed.

We intended to examine the importance of pregnancy-induced hypertension but few women had this condition in our dataset. Our analysis of race is similarly limited as most women were of white race and other races were collapsed into one “other” category. We also lacked data to assess some of the characteristics previously associated with physical activity in the literature including, multiple gestations[233, 254], pelvic girdle pain[254], and pre-pregnancy activity[224, 232, 248, 254].

In order to improve interpretability and create parsimonious models model selection was performed based on a p-value cut-off. Model selection may introduce bias.[260-262] Physical activities were measured by self-report and women may tend to over-report their activities due to the perceived desirability of being active, or they may not accurately recall the activities they performed. However, the low proportion of active women in the data suggests that over-reporting may not be an issue. Additionally, the women in this study comprise a volunteer population which may limit generalizability.

This study had the advantage of a large population of women and detailed assessments of their physical activities including type, frequency, duration and intensity. Several important and novel characteristics were measured including psychosocial variables and potential barriers to recreational activity. Physical activity was measured at two points in gestation which allowed us to detect changes in correlates over time.

Vigorous physical activity and pregnancy outcome

Right From the Start is a large study that recruited women early enough in pregnancy to observe early losses and then followed them prospectively for pregnancy outcomes. Pregnancy outcomes were identified in several ways including medical records. Our exposure of interest was based on self-report, and women were asked several detailed questions to describe those activities which should have reduced exposure misclassification. In addition, several modes of physical activity have been quantified including household and occupational which will control confounding that may have been present in previous studies. The detailed questions of physical activity also allowed the examination of dose-response. The numbers of women performing vigorous occupational activity were small, leading to imprecise estimates for this exposure. An additional limitation is that moderate intensity activities were not measured which are recommended during pregnancy[217, 218]. However, these recommendations exclude vigorous activity because its safety is not well-described, making our analyses informative to policy-makers. We did not assess transportation physical activities separately, although women may have reported them in other domains. Because the physical activity questions were asked early in pregnancy (around 13-16 weeks gestation) they may not reflect the appropriate exposure window in pregnancy for effects on timing of birth or birthweight. However, the responses at this point in pregnancy would not have been affected by the manifestation of some conditions that commonly lead to medically indicated preterm birth (pre-eclampsia, hypertension). Thus our exposure measurement is less susceptible to reverse causality or differential reporting by case status with respect to birth outcomes.

Our spontaneous abortion analysis is limited by the retrospective measurement of physical activity for women who experienced spontaneous abortions. For these women, the measurement of physical activity may be influenced by her pregnancy experience. Women who were interviewed after the spontaneous abortion may have been more likely to report what they perceived as detrimental exposures. Additionally, the earlier the loss occurred in gestation the further back in time the participant would need to remember in order to describe her recreational activity ‘during pregnancy’. Of the 189 spontaneous abortions with covariate information only 12 occurred after the first trimester questionnaire was administered (i.e. they reported their activity prior to the occurrence of the spontaneous abortion), thus we were unable to stratify our analyses by prospective versus retrospective exposure reporting.

Both spontaneous abortion and preterm birth are uncommon events and the prevalence of vigorous physical activity was relatively low in this analysis causing some of the estimates to be imprecise or unstable.

We do not have any quantification of physical activity prior to pregnancy and were confined to examining physical activity during pregnancy. Women in this study were volunteers who may be healthier or have better pregnancy outcomes than the population at large. This study may not be generalizable to populations with larger proportions of high-risk women.

Public health implications and future directions

Correlates of physical activity

The work describing correlates of recreational activity may facilitate the targeting of interventions towards women in most need of change. Several characteristics were associated with lower levels of physical activity. For example, interventions could be aimed at safely increasing or maintaining physical activity later in gestation when women are less likely to be active. This study also suggests that interventions focus on the desired amount of change in physical activity, since the correlates of any recreational activity differed from the correlates of recommended recreational activity. For example, sociodemographic variables were correlated with the performance of any recreational activity, but less so with recommended recreational activity. If the goal of an intervention is to increase women's recreational activity during pregnancy from none to any, they should target that intervention based on the sociodemographics which were associated with any recreational activity. However, if the goal is to increase the amount of activity from none to recommended, sociodemographics may be less useful.

Interventions should also be targeted to a particular stage of gestation as the predictors of recreational activity differ early in gestation versus later in gestation. For example, the differences between normal weight and obese women were more pronounced at 28 weeks which suggests that interventions targeted to obese women could focus on later gestation. Similarly, associations with prenatal care initiation index, child/adult care activity, indoor household activity, parity, history of miscarriage, bed rest and perceived stress score changed over gestation.

Further study of the mechanisms underlying the observed associations would also inform interventions. For example, future studies could examine whether women with a history of miscarriage avoid physical activity based on their own fears or whether health care providers advise against activity. Also, more research is needed to determine why partner support was an important correlate of recreational activity. For example, partner support may mean that women are encouraged by their partners to be active when they lack motivation or energy. Partner support might also mean the partner provides child care or performs household chores so that women have the opportunity to be active. It may even be as simple as the partner not outwardly contradicting a pregnant woman’s desire to be physically active.

Enjoyment of physical activity was strongly associated with being physically active. Enjoyment of physical activity may motivate women to be active in spite of internal barriers to activity. A focus group conducted in a subset of this population suggested that the largest barriers to physical activity during pregnancy were time constraints and lack of energy or tiredness[249]. The more a woman enjoys physical activity the more likely she is to overcome these barriers. The association between enjoyment of physical activity and being physically active seems intuitive; however, this is a novel approach for interventions that usually randomize women to some form of activity or not, with no consultation with the women to decide those activities. The most successful interventions may be those that expose pregnant women to different types of physical activities with the goal of finding something they really enjoy. Alternatively, interventions could assess what women dislike about physical activity and attempt to match women with activities that don't involve those characteristics. Ultimately, interventions that help women find or participate in activities they enjoy might be the most successful.

Vigorous physical activity and pregnancy outcome

The amount of vigorous recreational physical activity reported in our study was not associated with spontaneous abortion and did not appear to be detrimental to the timing of birth or birthweight. This suggests that vigorous recreational physical activity may be safe for healthy pregnant women. This analysis has only considered a handful of pregnancy outcomes and further studies should expand on our results by investigating additional outcomes such as placental abruption or stillbirth. Additionally, women who are physically active during pregnancy may be at risk for injury as the changes they experience in body shape and weight may affect balance and coordination. Additionally ligaments relax during pregnancy, which makes joints more unstable. Thus safety of physical activity during pregnancy should also be investigated in future studies.

In this analysis frequent recreational activity sessions were associated with later birth and less risk of preterm birth even after controlling for total volume of recreational activity. Moreover, starting to exercise in preparation for pregnancy may be associated with reduced risk of spontaneous abortion or preterm birth. Further examination of changes in recreational activity peri-conceptually may clarify whether this is truly beneficial or a “healthy participant” effect. However, it is also possible that vigorous recreational activity is beneficial for pregnancy. Participation in physical activity causes physiological changes in the non-pregnant individual and many of these changes are identical to pregnancy adaptations[30]. For example, blood volume, heart size, stroke volume, and cardiac output are improved with regular exercise as are the ability to sweat and divert blood flow to the skin. Recreational activity during pregnancy may improve the body’s ability to adapt to pregnancy. A prior section of this work describes the mechanisms by which physical activity may harm a developing pregnancy (See “How physical activity may affect pregnancy outcome”). A theme of that section could be that competition between mother and fetus, if it exists, is most likely transient. Whereas long-term consequences of the activity may be beneficial, stimulating the woman’s body to increase blood volume, increase heart size, and so on. Our findings lean towards decreased risk of preterm birth with recreational activity during pregnancy, which suggests that the long-term benefits of activity may outweigh the potential short-term risks.

Another mechanism by which recreational activity may benefit pregnancy is placental development. The placentae of women who continued running throughout pregnancy had greater villous vascular volume and a higher proliferation index than placentae from women who were physically active but did not perform any regular sustained exercise[272]. Increased villous vascular volume may improve the delivery of oxygen and nutrients to the fetus[272]. Any potential connection between these findings and a reduced risk of preterm birth is purely speculative. It is possible that improved placental function supports fetal growth in the face of any stressful stimuli that in other cases may trigger preterm labor or rupture of membranes.

While the previous paper focused on women who were runners prior to pregnancy and continued throughout pregnancy, similar results were found for women who began exercising during pregnancy[273]. Women who did not exercise regularly were randomized to an exercise program or no exercise at 8 weeks of gestation[273]. Women randomized to the exercise group had a higher midtrimester placental growth rate and higher indices of placental function[273]. These results are particularly interesting given our observed association of starting to exercise pre-pregnancy with reduced risk of preterm birth. While it is possible that the observed association in our study is a healthy participant effect, the Clapp et al. results provide a biological basis for a true causal effect.

The details of the biology underlying the association of recreational activity with placental development are unknown. One hypothesis is that placental development is affected by the rate at which it receives oxygen and nutrients[274]. A relative increase in the rate of delivery to the placenta stimulates placental growth while a decrease suppresses growth[274]. These changes in substrate delivery must be intermittent with increases followed by decreases and vice-versa, in order to affect placental growth[274]. Persistent low or high levels of substrate do not have the same affects on placental growth[274]. Thus, recreational activity, as an intermittent activity may stimulate placental growth. Moreover, we observed an association of frequent recreational activity with reduced risk of preterm birth. This is particularly intriguing given that the more frequent recreational activity sessions are, the more increases and decreases there will be in substrate delivery to the placenta. Frequency of recreational activity sessions may represent the intermittent stimulation of the placenta and therefore improved placental development. This in turn may confer reduced risk of preterm birth, although the biological details are unknown.

The reduced risk of preterm birth seen with recreational activity was not observed for other modes of physical activity. Low levels and very high levels of total vigorous physical activity may be associated with preterm birth and this association may be driven by household and occupational activity, rather than child care and recreational activity. Recreational activity is performed according to the participant's wishes, while other modes of activity are often not as volitional. The participant can avoid body positions that are uncomfortable, take breaks, lower the intensity of activity, drink water or eat snacks when needed, avoid over-heating, or participate with a partner. Further studies of the separate modes of physical activity would help to determine if they truly have different associations with pregnancy outcome. Measurement of other modes of activity should be more specific, obtaining information regarding how the activities are performed (bending, standing) or any chemicals used. Detailed measurement of pregnancy symptoms and pre-pregnancy activity may clarify whether a reduction in total vigorous activity is associated with decreased risk of spontaneous abortion or the result of residual confounding.

Subsequent investigations should collect detailed information regarding pre-conception recreational activity patterns and possibly even lifetime patterns so that the recreational activity performed during pregnancy can be placed in the appropriate context for that woman (i.e., a conditioned state versus sedentary). These studies should also include assessments of dose-response so that the optimal amount and intensity of physical activity can be described for pregnant women.

APPENDICES

Appendix A: Informal Assessment of Spontaneous Abortion Literature

Table 9. Summary of research findings from investigations of risk factors for spontaneous abortion.

Exposure	Measure of exposure	Measure of Effect	Comments
Maternal Age			
Warburton and Fraser, 1964	(age at conception)	Proportion SAB:	5304 pregnancies in the study
	<20	11.7	Proportions are among women with no history of abortion
	20-24	11.9	Study Population: Women with one child who attends the Department of Medical Genetics for a defect or malformation, and a control series of random hospital admissions
	25-29	12.0	
	30-34	13.6	
	35-39	17.9	
	40-44	18.0	SAB: self-reported previous pregnancies/outcomes
Wilson, 1986	(At date of confinement)	%SAB	<30: 5 SABs, 30-34:6 SABs, >35: 6 SABs
	<30	1.4	SAB: Pregnancy termination <20 weeks
	30-34	2.6	Retrospecitve Canadian study, selected by ultrasound scans done at wks 7-12, med records reviewed for outcome data
	>35	4.3	
Coste, 1991	<25	0.74 (0.44, 1.24)	Cases=279, Controls=279
	25-29	1.	SAB: expulsion of fetus <500g, 7 maternity hospitals in Paris
	30-34	1.18 (0.75, 1.86)	Controls: women giving birth at same hospitals whose delivery was closest chronologically to case
	35-39	2.37 (1.33, 4.17)	Recall bias?
	>=40	1.66 (0.64, 4.30)	Adjusted for history of SAB, Ethnic origin
Dominguez-Rojas, 1994	<25	15.8%	Cases=169, Controls=522
	26-30	19.6	Study pop.: All female, gravid hospital

	31-35 >35	30.2 50.9 Didn't give adjusted ORs	workers at a hospital in Madrid, only considered first pregnancy SAB: fetal loss ≤20th week, obtained hospital care for SAB Non-cases: women with pregnancies >20 weeks Exposure collected prior to event
Goldstein, 1994	 <30 30-35 >35	Rate: 9.3% 10.7 18.4	Women with a positive hCG test from a private university-based practice (low-risk population), age determined with early ultrasound. No losses between 8.5 and 14 weeks. Differences in rates were non-significant, small numbers.
Gauger, 2003	>35 vs <=35	Not given	Members of Society for Pediatric Anesthesia and American Society of Anesthesiologists Age was not exposure of interest, only p-value given
Cleary-Goldman, 2005	<35 35-39 >=40	Ref 2.0 (1.5, 2.6) 2.4 (1.6, 3.6)	<35: 28,398, %SAB=0.8, 35-39: 6294, %SAB:1.5, >=40: 1364, %SAB: 2.2 SAB: fetal loss after enrollment but <240/7wks, enrolled from 10-14wks gestation
Maconochie, 2007	Age at concept : <25 25-29 30-34 35-39 ≥40	1.09 (0.81, 1.45) 1. 1.06 (0.85, 1.31) 1.75 (1.37, 2.22) 5.16 (3.54, 7.52)	Cases: N=447, Controls: N=4878 Adjusted for nausea SAB: <13 weeks gestation, "most recent pregnancy" or "had a miscarriage since 1995." Multiple records/woman, robust standard errors
History of Miscarriage			
Buss, 2006	Previous SAB Not previously pregnant	OR 0.7 (0.6, 1.0)	~1900 women, Danish population-based cohort study, SAB information from the

	0	1	Hospital Discharge Register, interviewed at enrollment and at 2yr follow-up,
	1	1.2 (0.8, 1.8)	
	>2	2.3 (1.1, 4.5)	
Paternal Age			
Warburton and Fraser, 1964	(age at conception)	Did not present summary estimates	5304 pregnancies in the study Proportions are among women with no history of abortion Study Population: Women with one child who attends the Department of Medical Genetics for a defect or malformation, and a control series of random hospital admissions SAB: self-reported previous pregnancies/outcomes
Kleinhaus, 2006	<25	0.59 (0.45, 0.76)	Cases:1506, Controls: 12,359
	25-29	1	Combined two samples of women: one from antenatal clinics and one from postpartum hospital stays
	30-34	1.4 (1.2, 1.6)	
	35-39	1.9 (1.6, 2.3)	
	>=40	1.6 (1.2, 2.0)	SAB: previous pregnancy ended in an SAB before 20 weeks of gestation, controls: previous pregnancy ended in live birth
Maconochie, 2007	Age at concept :	OR:	Cases: N=447, Controls: N=4878
	<25	1.18 (0.80, 1.73)	Adjusted for nausea
	25	1.	SAB: <13 weeks gestation, "most recent pregnancy" or "had a miscarriage since 1995."
	30	1.05 (0.83, 1.33)	
	35	1.22 (0.94, 1.59)	
	40	1.04 (0.71, 1.53)	Multiple records/woman, robust standard errors
	≥45	1.63 (1.08, 2.47)	
Body Mass Index			
Lashen, 2004	Normal (19-24.9 BMI)	1	Prospectively collected UK database, all women had a live birth, asked about previous pregnancy outcomes Age matching
	Obese (>30 BMI)	1.2 (1.01, 1.46)	

Nohr, 2005	BMI <18 18.5-25 25-30 >=30	SAB at 14-19wks 1.3 (0.7, 2.4) 1 1.0 (0.7, 1.5) 1.6 (1.0, 2.5)	SAB:~200, <28 wks, from National Discharge Register Danish National Birth Cohort Associations got stronger as # of completed weeks went up, BMI causes later fetal death
Maconochie, 2007	<18.5 18.5-24.9 25.0-29.9 >=30.0	1.72 (1.17, 2.53) 1 0.95 (0.76, 1.19) 0.92 (0.65, 1.31)	
Smoking			
Kline et al., 1977	Questionnaire: Any/None	OR : 1.8 (1.3, 2.5)	Cases: N=574, Controls: N=320 Hospital-admission based case-recruitment Recall bias Gestational age of miscarriages unknown? Controls interviewed later in gestation? (More time to quit?)
Himmelberger, 1978	Questionnaire: Smoking “during pregnancy” None 1-19 cigs/day (moderate) ≥20 cigs/day (heavy)	Reported effect mod: smk x age, smk x operating room exp, smk x gravidity If unexposed to OR, no previous SAB, and age= 20: RR=1.69 40: RR=1.22	12,914 pregnancies Medical professionals SAB: any reported loss of product of conception ≤20 weeks Retrospective exposure info They reported several interactions, but they don’t all appear important, maybe age only?
Harlap, 1980	Questionnaire (per day) (N, losses) ½ pack (10 cigs) (113) 1 (20 cigs) (53) 1 ½ (30 cigs) (23) >2 (>40 cigs) (5)	RR (1st trimester loss): 1.13 (.59, 2.91) 0.76 (0.39, 1.48) 1.28 (0.63, 2.58) 1.31 (0.66, 2.60)	Women were members of Kaiser Foundation Health Plan. Smoking/Drinking reported for 1st 3 months of pregnancy at enrollment (first antenatal visit), self-administered quest. SAB identified from hospital admissions, additional info from medical records

			Also looked at 2nd trimester loss, similar pattern
Hemminki, 1983	Questionnaire: None >0-10 cigs/day >10 cigs/day	Proportions 9.8 11.6 16.2	Finnish study of sterilization gases and pregnancy, postal survey of nurses Unclear how SAB assessed in Q. Gestational age? Prospective? Timing of smoking? Adjusted for age, parity, alcohol, coffee
Coste, 1991	Questionnaire : No/Yes (at the time of conception)	OR: 0.83 (0.57, 1.21)	Cases=279, Controls=279 SAB: expulsion of fetus <500g, 7 maternity hospitals Controls: women giving birth at same hospitals whose delivery was closest chronologically to case Recall bias
Parazzini, 1991	Questionnaire: Never 1-9 cigs/day >=10 Exsmokers	RR 1.3 (0.6, 2.5) 1.6 (0.7, 3.2) 1.1 (0.4, 2.5)	Cases=94 women with 2+ unexplained SABs, referred to a fertility clinic Controls=176 normal delivery at same clinic Adjusted for age Positive trend test
Armstrong, 1992	Questionnaire: # of cigs in 1st trimester: 1-9 10-19 20+	OR: 1.07 (0.97, 1.18) 1.22 (1.13, 1.32) 1.68 (1.57, 1.79)	SABs=10,191, Pregnancies:47,146 Delivery or SAB in 11 Montreal hospitals Used previous pregnancies as hospitalized SABs are not representative, "previous pregnancies" overrepresent SABs since they are more likely to be followed by a pregnancy Definition of SAB? Assessed by self-report Gestational ages of SABs?? Retrospective exposure assessment Allowance for dependence of outcomes through inclusion of parity and previous miscarriage (?).

Windham, 1992	Questionnaire: cases:	OR:	SAB: <20 weeks gestation, pathology
	entire preg, Ctrl:<20 wks		specimen submitted at 11 hospitals in
	Adjusted for strong		California
	predictors of SAB :		Controls: randomly selected from county
	None		residents with a live birth, matched by LMP
	1-10 cigs/day	0.90 (0.65, 1.2)	Calculated a 1st trimester average amount
	>10	1.0 (0.73, 1.4)	smoked incorporating changes in smoking
	Excluding non-smokers		over gestation
	exposed to passive smk:		Adjusting for passive smoke is over-
	1-10	1.0 (0.73, 1.4)	adjustment?
	>10	1.3 (0.85, 1.9)	Adjusted for alcohol, caffeine, nausea (and
	Adjusted for passive smk		more)
	1-10	0.84 (0.59, 1.2)	
	>10	0.76 (0.49, 1.2)	
Dominguez-Rojas, 1994	None	OR:	Cases=169, Controls=522
	1-10 cigs/day	0.95 (0.59, 1.54)	Study pop.: All female, gravid hospital
	>10 cigs/day	3.35 (1.62, 6.92)	workers at a hospital in Madrid, only
			considered first pregnancy
			SAB: fetal loss ≤20th week, obtained
			hospital care for SAB
			Non-cases: women with pregnancies >20
			weeks
			Exposure collected prior to event
Kline, 1995	Smoking at LMP:	Public ORs:	Public Cases:1550, Controls 3090; Private
	Ex-smokers	1.1 (0.9, 1.4)	cases: 826, controls: 1133
	1-13 cigs/day	1.2 (1.0, 1.5)	SAB: Chromosomally normal termination of
	≥14 cigs/day	1.5 (1.2, 2.0)	intrauterine pregnancy <28 completed wks
	(vs Never)	Private:	from 3 New York City hospitals
		0.8 (0.6, 1.1)	Controls: women who registered for PNC
		1.1 (0.8, 1.7)	<22 weeks in the medical centers and
		0.9 (0.6, 1.4)	delivered at >28 weeks
			Also made case-case comparisons using
			trisomy and other

Dlugosz, 1996	0 (cigs/day)	1	Enrolled pregnant women seeking prenatal
	1-10	1.49 (0.83, 2.67)	care at <16 weeks at 11 private practices
	>10	1.16 (0.56, 2.42)	and 2 HMOs in Connecticut, caffeine
			estimated from subject reported coffee, tea
			and soda intake, frequency and size
			SAB: nondeliberate interruption of an
			intrauterine pregnancy at <28 weeks; fetus
			was dead at birth
			Adjusted for maternal age, GA at interview,
			alcohol, cigs
Chatenoud, 1998	Questionnaire:		Cases: 782, Controls:1543
	Never		SAB: Women admitted for SAB ≤12 weeks
	Former (quit 1 yr prior)	0.9 (0.7, 1.2)	in the largest obstetric hospital in Milan
	Before pregnancy	0.7 (0.5, 1.0)	Controls: Delivered at term (>37 weeks)
	Before and during 1st tri	1.3 (1.0, 1.6)	Retrospective smoking information
			Adjusted for nausea, coffee, alcohol (and
	Also:		more)
	Cigs/day before concept		Duration and age at starting smoking were
	0		not related to SAB
	1-4	0.9 (0.5, 1.4)	
	5-9	0.9 (0.6, 1.4)	
	≥10	1.1 (0.8, 1.3)	
	Cigs/day 1st trimester		
	0		
	1-4	1.3 (0.9, 1.9)	
	5-9	1.4 (0.9, 2.2)	
	≥10	1.4 (1.0, 2.1)	
Mendola, 1998	Questionnaire:		Cases: 2+ SABs lifetime, Controls: 2+
	Smoking during repro yrs		livebirths
	No		From a study of breast cancer in New York
	Yes	1.34 (0.63, 2.86)	Did not see any interaction with NAT2 or
			GSTM1

Ness, 1999	Smoking at enrollment: Never In the past Current Cotinine in urine	ORs (all SABs) 0.9 (0.6, 1.3) 1.4 (1.0, 1.9) 1.9 (1.4, 2.6)	Cases=400, Controls=570 Women presenting to the U of Penn ED, pregnancy was identified at this visit, tested women for pregnancy if LMP was 28 days to 22 weeks earlier, followed women for SAB (<22 weeks), included adolescents (ages 14-40) Also separated SABs into at baseline or during follow-up Mean GA at enrollment ~10 weeks, 75% ≤12 weeks
Windham, 1999	Smoking in the week before interview: 0 cigs/day 1-4 ≥5 Smoking the of LMP:	ORs 0.91 (0.56, 1.5) 1.3 (0.91, 1.9)	Non-smokers: 4607 SAB=9.4%, 1-4cigs/day=209, SAB: 9.6%, >=5:327 SAB: 13.5% California health plan participants, ≤12 weeks SAB: hospital admission records, medical records, pregnancies ended by 20 completed weeks Median GA at loss=11 wks
Rasch, 2003	Questionnaire: 0 cigs/day 1-9 10-19 20+	OR: 0.81 (0.52, 1.23) 1.01 (0.64, 1.59) 0.95 (0.40, 2.20)	Cases: 330, Controls: 1168 SAB: Gestational week 6-16, Controls: women in PNC Hospital-based, Denmark Adjusted for alcohol and caffeine (and more)
George, 2006	Serum Cotinine <0.1 0.1-≤15 (passive) >15 (active smoking)	 Ref 1.67 (1.17, 2.38) 2.11 (1.36, 3.27)	Cases=463, Controls=864 Blood drawn at hospitalization (cases), interview (controls) Excluded women who used snuff, patches, gum No effect modification by nausea
Maconochie, 2007	Questionnaire: Frist 12 weeks:	OR:	Cases: N=447, Controls: N=4878 Adjusted for nausea

	Any	0.96 (0.78, 1.19)	SAB: <13 weeks gestation, "most recent
	stopped when pregnant	0.83 (0.54, 1.26)	pregnancy" or "had a miscarriage since
	<5 cigs/day	0.87 (0.61, 1.24)	1995."
	5-10	0.81 (0.52, 1.24)	Multiple records/woman, robust standard
	11-20	1.41 (0.97, 2.06)	errors
	21-30	1.25 (0.55, 2.86)	
Paternal Smoking			
Wyndham, 1992	Questionnaire of mother:		(see above)
	None		
	1-10	0.9 (0.6, 1.3)	
	11-20	1.1 (0.7, 1.5)	
	>20	1.0 (0.6, 1.5)	
Chatenoud, 1998	Questionnaire, partner smoking:		
	Never		
	Former	0.8 (0.6, 1.1)	
	Current	0.8 (0.7, 1.0)	
	Cigs/day before concept		
	≤10	0.8 (0.6, 1.0)	
	>10	0.9 (0.7, 1.1)	
	Cigs/day 1st trimester		
	≤10	0.8 (0.6, 1.0)	
	>10	0.9 (0.7, 1.1)	
Windham, 1999	Questionnaire:		Non-smokers: 3550 %SAB:9.6, 1-20:591
	0 cigs/day		%SAB~9.3, >20: 55 %SAB:10.9
	1-20	0.98 (0.73, 1.3)	
	>20	0.97 (0.41, 2.3)	
Venners, 2004	Questionnaire: husbands and wives (vs none)		Nonsmokers: 245 conceptions, <20: 288, >=20: 100
	All conceptions:		Workers from textile mills in China
	<20 cigs/day	1.12 (0.77, 1.65)	Prospective, used hCG to test for
	≥20cigs/day	1.64 (0.92, 2.93)	pregnancy: early loss and clinical loss
	Early losses:		

	<20 cigs/day	1.04 (0.67, 1.63)	
	≥20cigs/day	1.81 (1.00, 3.29)	
Maconochie, 2007	Questionnaire: 3 mo before conception	OR:	Cases: N=447, Controls: N=4878 Adjusted for nausea
	Any	1.04 (0.87, 1.25)	SAB: <13 weeks gestation, “most recent pregnancy” or “had a miscarriage since 1995.”
	<5/day	0.68 (0.43, 1.07)	
	5-10/day	1.03 (0.71, 1.50)	
	11-20/day	1.13 (0.88, 1.44)	Multiple records/woman, robust standard errors
	>20/day	1.19 (0.86, 1.66)	
Environmental Smoke			
Wyndham, 1992	Questionnaire: 1 hour or more/day in a room where someone else was smoking during pregnancy”	OR 1.5 (1.2, 1.9)	Estimate doesn’t change if limited to women who did not actively smoke
Windham, 1999	Questionnaire: “# hrs/day near other people smoking”		Analyzed ETS exposure among non-smokers only Found some effect modification, ETS x >300mg/day caffeine and ETS x >3drinks/wk associated with increased SAB
	Any ETS at home	1.15 (0.86, 1.55)	
	Any ETS at work	0.88 (0.66, 1.17)	
	Any ETS, either place	1.01 (0.80, 1.27)	
	Any ETS,>300mg caff	3.4 (1.7, 7.0)	
	Any ETS, >3 drinks/wk	2.9 (0.72, 11.6)	
Maconochie, 2007	In 1st 12 weeks: Did not smoke in presence of mother		Cases: N=447, Controls: N=4878 Adjusted for nausea
	Did	1.14 (0.95, 1.37)	SAB: <13 weeks gestation, “most recent pregnancy” or “had a miscarriage since 1995.” Multiple records/woman, robust standard errors
Caffeine			
Fenster, 1991	Caffeine mg/day		Same population as Windham, 1992

	Yes, nausea		SAB: <20 weeks gestation, pathology
	0	1	specimen submitted at 11 hospitals in
	1-150	1.07 (0.78, 1.47)	California
	151-300	1.01 (0.64, 1.59)	Controls: randomly selected from county
	>300	2.10 (1.20, 3.70)	residents with a live birth, matched by LMP
			Adjusted for alcohol, smoking, nausea (and
	No, nausea		more)
	0	1	Exposure info collected through phone
	1-150	0.97 (0.66, 1.42)	interview for "during the month before
	151-300	1.38 (0.82, 2.33)	pregnancy" and during pregnancy
	>300	0.53 (0.27, 1.04)	
Parazzini, 1991	Coffee consumption		Cases=94 women with 2+ unexplained
	No	1	SABs, referred to a fertility clinic
	Yes	1.4 (0.7, 2.6)	Controls=176 normal delivery at same clinic
			Coffee consumption assessed during
			pregnancy for SABs, during 1st trimester for
			controls, only adjusted for age
Armstrong, 1992	Coffee (cups/day)		SABs=10,191, Pregnancies:47,146
	0	1	Delivery or SAB in 11 Montreal hospitals
	1-2	0.98 (0.93, 1.04)	Used previous pregnancies as hospitalized
	3-4	1.02 (0.94, 1.12)	SABs are not representative, "previous
	5-9	1.17 (1.03, 1.32)	pregnancies" overrepresent SABs since
	10+	1.19 (0.97, 1.45)	they are more likely to be followed by a
			pregnancy
			Definition of SAB? Assessed by self-report
			Gestational ages of SABs??
			Retrospective exposure assessment
			Allowance for dependence of outcomes
			through inclusion of parity and previous
			miscarriage (?).
Infante-Rivard, 1993	Before pregnancy		SAB: 331, controls: 993
	<48 mg/day	1	Cases were hospitalized w/diagnosis of
	48-162	1.29 (0.85, 1.95)	SAB or fetal death, Montreal, >90% of
	163-321	1.37 (0.92, 2.04)	women w/SAB are hospitalized Controls:

	>321	1.85 (1.18, 2.89)	same GA of case based on LMP, presented
	During pregnancy		for routine blood analysis at the hospital
	<48 mg/day	1	Excluded women w/history of SAB
	48-162	1.15 (0.82, 1.63)	Caffeine assessed through questionnaire,
	163-321	1.95 (1.29, 2.93)	coffee, tea, cola, month prior to conception
	>321	2.62 (1.38, 5.01)	and an average over pregnancy
			Adjusted for smoking and alcohol, not nausea
Mills, 1993	Caffeine		Cohort of 431 women enrolled <=21 days of
	None	1	conception, selected from pregnancy
	Any	1.15 (0.89, 1.49)	planners, prospective
	>300mg/day	Not significant	Caffeine assessed several times throughout pregnancy, asked about coffee (caff and decaf), tea, cocoa, iced tea, cola drinks (caff and decaf), medications, calculated 1^{st} trimester average
			62% consumed <100mg/d, these are low users
			No adjustment for nausea
Dominguez-Rojas, 1994	Mg/day		Cases=169, Controls=522
	140	1	Study pop.: All female, gravid hospital
	141-280	2.20 (1.22, 3.96)	workers at a hospital in Madrid, only
	281-420	4.81 (2.28, 10.14)	considered first pregnancy
	>420	15.43 (7.34, 32.43)	SAB: fetal loss $\leq 20^{th}$ week, obtained hospital care for SAB
			Non-cases: women with pregnancies >20 weeks
			Exposure collected prior to event
			Caffeine estimated from coffee sources only, only 6 non-drinkers who were excluded
Dlugosz, 1996	0	1	Enrolled pregnant women seeking prenatal
	1-150	0.81 (0.54, 1.20)	care at <16 weeks at 11 private practices
	151-300	0.89 (0.48, 1.64)	and 2 HMOs in Connecticut, caffeine

	>=301	1.75 (0.88, 3.47)	estimated from reported coffee, tea and
			soda intake, frequency and size, "since
			becoming pregnant"
			SAB: nondeliberate interruption of an
			intrauterine pregnancy at <28 weeks; fetus
			was dead at birth
			Adjusted for maternal age, GA at interview,
			alcohol, cigs
Fenster, 1997	Before pregnancy		~5000 women, 9.7% SAB
	0 mg/day caffeine	1	Women recruited from Kaiser Program
	1-150	1.05 (0.82, 1.35)	facilities in California, <13 weeks gestation
	151-300	1.04 (0.77, 1.39)	SAB: pregnancy ended <20 weeks,
	>300	1.25 (0.90, 1.73)	identified from hospital records, medical
			records, follow-up phone interviews, vital
	1st trimester		records
	0 mg/day caffeine	1	Women were asked about coffee, tea, soda
	1-150	1.01 (0.82, 1.25)	intake in the week before interview (1st
	151-300	1.18 (0.84, 1.66)	trimester), and at week of LMP
	>300	1.29 (0.80, 2.06)	Adjusted for nausea, cigarettes, alcohol
Chatenoud, 1998	Coffee intake		Cases: 782, Controls:1543
	No	1	SAB: Women admitted for SAB ≤12 weeks
	Yes	1.8 (1.5, 2.2)	in the largest obstetric hospital in Milan
			Controls: Delivered at term (>37 weeks)
			Adjusted for nausea, smoking, alcohol (and
			more)
			Retrospective report of coffee intake in the
			1st trimester
Cnattingius, 2000	Non-smokers		Cases:562, controls: 953
	0-99 mg/day	1	SAB: Identifed from the only hospital in
	100-299	1.3 (0.9, 1.8)	Sweden that provides care for SAB, 6-12
	300-499	1.4 (0.9, 2.0)	weeks GA
	>=500	2.2 (1.3, 3.8)	Controls: attending PNC, frequency
			matched by GA
			Reported caffeine on weekly basis starting

			4 weeks before LMP and ending the most recently completed week, included coffee, tea, cocoa, chocolate, soft drinks, medications, calculated a mean caff consumption
			Adjusted for nausea, significant interaction between smoking and caffeine, no assoc in smokers, some suggestion of higher risk in normal karyotype fetuses
Signorello, 2001	CYP1A2 below median		See Cnattingius, 2000, this is same study
	0-99 mg/day	1	population
	100-299	0.32 (0.08, 1.23)	Cases: 101, Controls 953 (used only
	>=300	0.46 (0.12, 1.73)	normal karyotype losses)
	CYP1A2 above median		Phenotyped Cyp1A2 and genotyped NAT2
	0-99 mg/day	1	Low Cyp activity: protective, high cyp
	100-299	2.42 (1.01, 5.80)	activity: detrimental
	>=300	3.17 (1.22, 8.22)	Slow acetylators: caffeine detrimental, Fast:
	Slow acetylators		no/weakly detrimental
	0-99 mg/day	1	
	100-299	2.38 (1.04, 5.49)	
	>=300	1.65 (0.67, 4.06)	
Wen, 2001	First trimester intake,		Live births: 575, SAB:75
	after nausea occurred		Women planning pregnancy selected from
	<20	1	HMO in Minnesota, SAB: medical records,
	20-99	1.8 (0.8, 3.9)	interviewed every 3 months until
	100-299	2.4 (0.9, 6.2)	conception, monthly during pregnancy,
	>=300	5.4 (2.0, 14.6)	calculated mean daily caffeine intake before and during pregnancy
			No association of caffeine intake before pregnancy, before nausea occurred, or in women who never had nausea, and SAB
Gianelli, 2003	<=150 mg/day	1	Cases:159, Controls:310
	151-300	1.19 (0.67, 2.12)	SAB: women w/clinically diagnosed SAB
	301-500	1.94 (1.04, 3.63)	Cntrls: women attending PNC, no SAB in

	>500	2.18 (1.08, 4.40)	1st 2 trimesters Included only nulliparous women from the UK Interviewed ~3 weeks post-SAB, controls interviewed at PNC, caffeine includes coffee, tea, cola asked before and during pregnancy No significant assctn of caffeine before preg w/SAB Adjusted for nausea
Rasch, 2003	Caffeine (mg/day)		Cases: 330, Controls: 1168
	0-199	1	SAB: Gestational week 6-16, Controls:
	200-374	1.31 (0.92, 1.86)	women in PNC
	375+	2.21 (1.53, 3.18)	Hospital-based, Denmark Adjusted for alcohol and smoking (and more) Exposures are "during pregnancy", caffeine estimated from coffee, soda, tea and chocolate
Tolstrup, 2003	<75 mg/day	1	1381 pregnancies, 303 SAB (18%)
	75-300	1.26 (0.77, 2.06)	Study population randomly selected from
	301-500	1.45 (0.87, 2.41)	general population of Copenhagen, women
	501-900	1.44 (0.87, 2.37)	interviewed at enrollment reported
	>900	1.72 (1.00, 2.96)	coffee/tea intake, 2 yrs later interviewed again, asked about pregnancies also linked to Danish Hospital Discharge Register SAB: nondeliberate fetal loss <28th week of gestation No significant interaction between caffeine and smoking and caffeine and alcohol Women may have changed caffeine intake? No adjustment for nausea.
Bech, 2005	Coffee consumption		Danish National Birth Cohort
	0 (cups/day)	1	Women are approached at 1st antenatal

	½ - 3	1.11 (0.93, 1.34)	visit, most women are eligible, few exclusions
	4 – 7	1.22 (0.93, 1.60)	Information obtained from telephone interviews
	>=8	1.48 (1.01, 2.17)	SAB: identified from National Hospital Discharge Register, stratified by GA at death, these estimates are for <140 days
Karypidis, 2006	Val/Val (non-smokers)		Cases 507, controls:908
	<100 mg/day	0.91 (0.40, 2.07)	Same population as Cnattingius, 2000
	100-299	3.32 (1.67, 6.58)	Significant interaction between Cyp1b1 and caffeine, interaction not significant when restricted to non-smokers, but point estimates indicate caffeine is detrimental for all genotypes, highest (and significant) for Val/Val genotype
	300-499	2.20 (0.93, 5.21)	
	>500	3.66 (1.12, 11.93)	
	Leu/Leu, <100	1 (ref)	Adjusted for alcohol and nausea
Maconochie, 2007	Caffeine mg/day		Cases: N=447, Controls: N=4878
	0	1	Adjusted for nausea (there was assoctn before adjusting)
	<151	1.03 (0.71, 1.49)	SAB: <13 weeks gestation, "most recent pregnancy" or "had a miscarriage since 1995."
	151-300	0.93 (0.64, 1.33)	Multiple records/woman, robust standard errors
	301-500	1.04 (0.72, 1.50)	Recalled exposures for 1st 12 weeks of pregnancy
	>500	1.14 (0.79, 1.66)	
Alcohol			
Harlap, 1980	Drinks/day	RR	Women were members of Kaiser Foundation Health Plan. Smoking/Drinking reported for 1st 3 months of pregnancy at enrollment (first antenatal visit), self-administered quest.
	Occasional (<1)	1.03 (0.57, 1.86)	SAB identified from hospital admissions, additional info from medical records
	1-2	1.98 (1.04, 3.77)	
	>=3	3.53 (1.77, 7.01)	

			Also looked at 1st trimester loss, very small
			RRs (<1.2) non-significant
Kline, 1980	Frequency of drinking		Cases:616, public facilities of 3 Manhattan
	Never	1	hospitals
	<=2x / month	0.78 (0.56, 1.08)	controls:632, delivered >28 weeks,
	<2x / week	1.02 (0.62, 1.68)	attended PNC <22 wks, matched to cases
	2-6 days/week	2.33 (1.33, 4.08)	on age and hospital
	Daily	2.58 (0.93, 7.14)	Analysis is unmatched? "Matched analysis
			gave similar results" even for CIs?
			Not adjusted for nausea
Parazzini, 1991	Any		Cases=94 women with 2+ unexplained
	No	1	SABs, referred to a fertility clinic
	Yes	0.9 (0.6, 1.5)	Controls=176 normal delivery at same clinic
			Alcohol intake assessed during pregnancy
			for SABs, during 1st trimester for controls,
			only adjusted for age
Armstrong, 1992	None (drinks/week)	1	SABs=10,191, Pregnancies:47,146
	1-2	1.11 (1.05, 1.18)	Delivery or SAB in 11 Montreal hospitals
	3-6	1.23 (1.13, 1.34)	Used previous pregnancies as hospitalized
	7-20	1.47 (1.31, 1.65)	SABs are not representative, "previous
	21+	1.82 (1.21, 2.34)	pregnancies" overrepresent SABs since
			they are more likely to be followed by a
			pregnancy
			Definition of SAB? Assessed by self-report
			Gestational ages of SABs??
			Retrospective exposure assessment
			Allowance for dependence of outcomes
			through inclusion of parity and previous
			miscarriage (?).
Parazzini, 1994	During 1st trimester		SAB: 462, 4-12 wks GA, confirmed by
	0 or occasional	1	uterine curettage/pathology Controls: 814,
	1-7 drinks/week	1.1 (0.8, 1.4)	gave birth >37 weeks
	>7	0.8 (0.5, 1.2)	Assessed alcohol for year before and
			during 1st trimester, self-report (bias?)

			No adjustment for nausea
Chatenoud, 1998	Alcohol intake		Cases: 782, Controls:1543
	No	1	SAB: Women admitted for SAB <u><</u>12 weeks in the largest obstetric hospital in Milan
	Yes	1.2 (1.0, 1.4)	Controls: Delivered at term (>37 weeks) Adjusted for nausea, smoking, alcohol (and more) Retrospective report of alcohol intake in the 1st trimester
Rasch, 2003	0 units/week	1	Cases: 330, Controls: 1168
	1-4	1.00 (0.74, 1.34)	SAB: Gestational week 6-16, Controls: women in PNC
	5+	4.84 (2.87, 8.16)	Hospital-based, Denmark Adjusted for caffeine and smoking (and more) Exposures are “during pregnancy”, “units”?
Tolstrup, 2003	<1 drink/week	1	1381 pregnancies, 303 SAB (18%)
	1-3	0.92 (0.64, 1.32)	Study population randomly selected from general population of Copenhagen, women interviewed at enrollment reported alcohol intake, 2 yrs later interviewed again, asked about pregnancies also linked to Danish Hospital Discharge Register
	4-6	0.98 (0.67, 1.45)	
	7-13	0.79 (0.51, 1.20)	
	>13	1.28 (0.71, 2.32)	SAB: nondeliberate fetal loss <28th week of gestation No significant interaction between caffeine and alcohol Women may have changed alcohol intake? No adjustment for nausea, adjusted for smoking and caffeine
Maconochie, 2007	Standard UK units	Adj for nausea	Cases: N=447, Controls: N=4878
	None	1	Adjusted for nausea, point estimates are about the same
	<1	0.94 (0.73, 1.21)	
	1-7	1.23 (0.98, 1.53)	SAB: <13 weeks gestation, “most recent

	>7-14	1.20 (0.83, 1.74)	pregnancy” or “had a miscarriage since 1995.”
	>14	1.44 (0.92, 2.26)	Multiple records/woman, robust standard errors Recalled exposures for 1st 12 weeks of pregnancy
NSAIDs			
Nielsen, 2001	Time from taking up prescription		Cases: 4268, 1st recorded miscarriages Controls: 29,750, live births
	1-12 weeks	1	Exposure: women who had “taken up” a
	1 week	6.99 (2.75, 17.74)	prescription for NSAIDS <=12 weeks before
	2-3	3.00 (1.21, 7.44)	miscarriage or during 1st trimester, looked
	4-6	4.38 (2.66, 7.20)	at timing of prescription
	7-9	2.69 (1.81, 4.00)	Information obtained from prescription
	10-12	1.26 (0.85, 1.87)	registry, Danish birth registry, hospital discharge registry
Nielsen, 2004	1-12	1	Reanalyzed above data to include
	1	3.35 (0.88, 12.79)	gestational age
	2-3	1.50 (0.58, 3.86)	
	4-6	1.50 (0.91, 2.47)	
	7-9	1.59 (0.93, 2.70)	
	10-12	0.58 (0.18, 1.85)	
Li, 2003	NSAID use	1.8 (1.0, 3.2)	Members of the Kaiser Permanente
	Non-use	1	Medical Care Program, interviewed at
	Use at conception	5.6 (2.3, 13.7)	enrollment which was soon after +
	Use after conception	1.2 (0.5, 2.6)	pregnancy test, outcome obtained from
	Duration of use $\leq$1 week	1.3 (0.7, 2.6)	medical records, databases and patient
	>1 week	8.1 (2.8, 23.4)	contact
	Asprin use	1.6 (0.6, 4.1)	SAB: natural abortion <20 weeks
	Non-users	1	Cox model for PH regression
	At conception	4.3 (1.3, 14.2)	Did not see any association between
	After conception	1.1 (0.3, 4.5)	paracetamol and SAB, suggesting that the
	$\leq$1 week	1.4 (0.4, 4.5)	effect is of the drugs, not the indication for
	>1 week	3.0 (0.7, 12.9)	prescription

Keim, 2006	Aspirin anytime during pregnancy None	 0.79 (0.62, 1.01) 1	CPP data, women enrolled at 1st PNC visit SAB: 542, <140 days after LMP Controls: 2587, live-born infant >=28 weeks GA 4:1 matching on gestational age at assessment visit Medication use assessed at 1st visit for month before LMP and current, also searched med records,
Stress			
Fenster, 1995	Young, non-smoking, multigravid women, <2 previous SABs Stressful work and: age>32 Smokers Primigravid	Ref 2.45 (1.03, 5.81) 2.96 (1.16, 7.52) 2.27 (0.97, 5.27)	Members of Kaiser Medical Program, recruited at 1st PNC appointment, <=13 weeks gestation, who worked during pregnancy SAB: identified from Kaiser hospital records, medical records, follow-up phone calls Interviews occurred after recruitment but <=13 weeks, assessed job stress, life events 6 months before interview Observed 2-way interactions of stressful work with age, smoking, and gravidity
Neugebauer, 1996	>=1 Negative life event None	2.6 (1.3, 5.2)	Women from public/private facilities of a New York hospital SAB: involuntary termination of intrauterine pregnancy <28 weeks, conceptus dead at expulsion, compared chromosomally normal (n=111) to abnormal (81) Life events assessed for ~6 months prior to SAB, but at 2 or 6 weeks post-SAB
Maconochie, 2007	General feelings Happy, relaxed,… Stressed, anxious… Periods of both	 1 3.04 (2.46, 3.76) 1.22 (0.88, 1.70)	Adjusted for nausea

Other	1.70 (1.26, 2.29)
# stressful events	
None	1
1	1.47 (1.19, 1.80)
2	1.72 (1.15, 2.58)
>=3	3.27 (1.39, 7.68)

Appendix B: Informal Assessment of Physical Activity and Spontaneous Abortion Literature

Table 10. Summary of research investigating exercise or recreational physical activity and spontaneous abortion

First author, year	Exposure measurement	Effect Estimates	Covariates
Exercise/Recreational Activity			
Clapp, 1989		% aborted	None, matched design
	Runners	17	
	Aerobic Dancers	18	
	Controls	25	
Latka, 1999	"…jogged, swam, played tennis, or exercised regularly while pregnant"	OR 0.6 (0.3, 0.9)	Chromosomally normal vs abnormal, no adjustment
	None	1	
Hjollund, 2000	Absolute physical strain score (around implantation)	RR	Center, age, BMI, smoking, caffeine, alcohol, female reproductive disease, partner's sperm count
	<=1	1	
	>1	1.9 (1.0, 3.7)	
	Cycle-specific score		
	<= mean score	1	
	> mean score	2.5 (1.3, 4.6)	
Gauger, 2003	"Exercise" >1/week	None presented, p=0.006	Age
Morris, 2006	No exercise	OR	Age, BMI, year of in vitro fertilization
	1-3hrs/wk for 1-9 yrs	1.3 (0.8, 2.2)	
	>=4 for 1-9 yrs	2.0 (1.2, 3.4)	
	1-3 for 10-30 yrs	1.3 (0.8, 2.0)	
	>=4 for 10-30 yrs	0.9 (0.6, 1.4)	
	All categories	1.3 (1.0, 1.8)	
Other Physical Activity			
Occupational activity			
Florack, 1993	Intensity Score	RR	None
	Low	1	
	High	1.2 (0.5, 2.6)	
El Metwalli, 2001	Intensity Score		None
	Low	1	
	High	3.35 (2.7, 4.1)	
Florack, 1993	Fatigue Score	RR	None
	Low	1	
	Moderate	0.7 (0.3, 1.8)	
	High	1.4 (0.6, 3.5)	

El Metwalli, 2001	Fatigue Score Low Moderate High	 1 1.6 2.9 (2.3, 3.8)	None
Standing			
McDonald, 1988	Standing ≥8 hrs/day	 1.12 (SAB:<10wks) 1.20 (10-16) 1.23 (16-28)	None (all p-values <0.05, no confidence intervals presented)
Eskenazi, 1994	Standing <3 hours/day 3-7 ≥8	 1 1.1 (0.8, 1.4) 1.6 (1.1, 2.3)	Race, age, history of SAB, smoking, alcohol, caffeine, tap water, marital status, insurance status, parity, education, nausea
Fenster, 1997	Standing at work <3 hrs/day 3-7 >7	 1 0.9 (0.71, 1.1) 1.0 (0.73, 1.5)	Age, gestational age at interview, pregnancy history, smoking alcohol, caffeine, marital status
Latka, 1999	Any standing at work None	0.9 (0.6, 1.6) 1	Chromosomally normal vs abnormal, no adjustment
Housework			
Eskenazi, 1994	Housework (hrs/wk) 0 1-2 3-7 >7	 1 0.9 (0.6, 1.2) 0.9 (0.7, 1.3) 0.6 (0.5, 0.9)	Race, age, history of SAB, smoking, alcohol, caffeine, tap water, marital status, insurance status, parity, education, nausea
Fenster, 1997	Housework/yard work <3 hrs/week 3-7 >7	 1 0.94 (0.69, 1.3) 1.1 (0.81, 1.5)	Age, gestational age at interview, pregnancy history, smoking alcohol, caffeine, marital status
Latka, 1999	>10 hrs/wk housework none	1.2 (0.5, 2.9) 1	Chromosomally normal vs abnormal, no adjustment
El Metwalli, 2001	Housework hrs/day 2-3 4-5 ≥6	Figure presented, no estimates	"Significantly higher"
Lifting /Bending			

Florack, 1993	Bending <1 hr/working day ≥1	 1 3.2 (1.3, 9.8)	Exposure to vibration, correction fluid, education, alcohol, noise
Fenster, 1997	Bending at work <3 hrs/day 3-7 >7	 1 0.80 (0.58, 1.1) 1.1 (0.63, 2.1)	Age, gestational age at interview, pregnancy history, smoking alcohol, caffeine, marital status
McDonald, 1988	Lifting heavy weights ≥15x daily	O/E ratio 1.33 (SAB:<10wks) 1.51 (10-16wk) 1.61 (16-28wk)	None (all p-values <0.05, no CIs presented)
Florack, 1993	Lifting <1hr/working day ≥1	 1 1.1 (0.34, 3.4)	Exposure to vibration, correction fluid, education, alcohol, noise
Eskenazi, 1994	Lifting >15 lbs 0 times/day 1-9 10-15 >15	 1 1.3 (0.9, 1.7) 0.6 (0.3, 1.3) 1.1 (0.6, 2.0)	Race, age, history of SAB, smoking, alcohol, caffeine, tap water, marital status, insurance status, parity, education, nausea
Fenster, 1997	Lifting >15 lbs at work 0 times/day 1-9 10-15 >15 or constantly	 1 1.14 (0.77, 1.7) 0.99 (0.47, 2.1) 0.40 (0.16, 1.0)	Age, gestational age at interview, pregnancy history, smoking alcohol, caffeine, marital status and solvent exposure
Florack, 1993	Peak Pressure Score <4 ≥4	 1 3.1 (1.1, 8.9)	Exposure to vibration, correction fluid, education, alcohol, noise
Et Metwalli, 2001	Peak Pressure Score High Low	 2.9 (2.3, 3.6) 1	None
Et Metwalli, 2001	Chronic Pressure Score Low High	 1 2.7 (2.2, 3.3)	None
Child care			

Latka, 1999	Childcare “all day” during an average wk	1.2 (0.7, 2.0)	Chromosomally normal vs abnormal, no adjustment
	None	1	
Eskenazi, 1994	Hours/week		Race, age, history of SAB, smoking, alcohol, caffeine, tapwater, marital status, insurance status, parity, education, nausea
	0	1	
	1-2	0.9 (0.6, 1.2)	
	3-7	0.9 (0.7, 1.3)	
	>7	0.6 (0.5, 0.9)	

Appendix C: Informal Assessment of Preterm Birth and Growth Restriction Literature

Table 11. Summary of maternal and pregnancy characteristics associated with preterm birth (PTB) or small-for-gestational age (SGA).

First author, year	Exposure classification	Effect Estimates	Comments
Bacterial vaginosis			
Gravett, 1986		OR (PPROM)	534 gravid women,
	None	1	BV diagnosed by
	Vaginosis	2.0 (1.1, 3.7)	gas-liquid
		Preterm labor	chromatography,
	None	1	women w/and
	Vaginosis	2.0 (1.1, 3.5)	w/out BV had similar demographics
Martius, 1988	None	1	Cases: 97 women
	Vaginosis	2.3 (1.1, 5.0)	w/preterm labor Controls: 115, no PTL GA from LMP & ultrasound
Vaginal bleeding			
Yang, 2004	No bleeding	1	Heaviness, number
	First trimester bleeding	1.6 (1.1, 2.4)	of bleeding episodes, and
	Second trimester	1.5 (0.8, 2.9)	duration of bleeding
	Both	1.5 (0.6, 3.9)	were associated w/PTB at <34 wks, PTB at 35-36 wks showed weaker/non-significant associations
Previous pregnancy outcome			
Kristensen, 1995	First birth outcome:	RR	Denmark, National
	SGA	2.7 (2.0, 3.7)	Birth Registry,
	LGA	1.2 (0.64, 2.3)	National Registry of
	AGA	1	Hospital Discharges, 13,967 women
	Gestational age		
	<32 wks	6.0 (4.1, 8.8)	SGA:2 SD below
	32-36	4.8 (3.9, 6.0)	mean
	>36	Ref	

Henriksen, 1997	Time to pregnancy ≤6 months 7-12 >12	 1 1.3 (0.8, 2.1) 1.7 (1.1, 2.6)	Women attending PNC in Denmark, ~4000 women Presented data from another cohort w/nearly identical estimates.
Heinonen, 2000	 History of stillbirth Controls	OR 2.2 (1.2, 4.3) 1	History of stillbirth n=92 Controls:11,818 Birth registry in Finland
Jivraj, 2001	 Recurrent miscarriage Control	%PTB 13 3.9 (P<0.01)	Patients at a recurrent (≥3) miscarriage clinic, case notes from delivery retrieved Controls: all hospital deliveries
Zeitlen, 2001	Obstetric history Primigravid No previous problem 1st trimester SAB 2nd trimester SAB	OR (non-SGA) 1.52 1 1.56 3.52	Point estimates for SGA/PTB were not statistically different, but slightly higher
Age			
Fraser, 1995	 ≤17 yrs 18-19 20-24	RR (<37 wks) 1.5 (1.4, 1.6) 1.3 (1.2, 1.3) 1	Babies born in Utah 1970-90
daSilva, 2003	 <18 18-19 25-29	OR (primiparas) 1.77 (1.02, 3.08) 0.67 (0.36, 1.23) 1	Second order births had similar odds ratios, age x parity interaction significant Hospital study from Brazil, ~2300 births, GA measured by LMP
Jacobsson, 2004	 20-29 yrs 40-44 >45	OR (<37 wks) 1 1.54 (1.47, 1.60) 1.63 (1.32, 2.00)	Swedish Medical Birth Register, N=~1,000,000 Point estimates increase slightly if PTB is defined as <34 or <32 weeks

Schempf, 2007	White, primiparous	OR (32-36 wks)	Higher ORs for
	<18	1.43 (1.40, 1.46)	multiparae <25,
	18-19	1.16 (1.14, 1.18)	Higher ORs for
	20-24	1.02 (1.00, 1.03)	multiparae >25
	25-29	1	among black
	30-34	1.08 (1.06, 1.09)	women only
	35-39	1.28 (1.26, 1.30)	National Center for
	40-49	1.50 (1.45, 1.55)	Health Statistics'
	Black, primiparous		Natality Data Sets
	<18	1.49 (1.45, 1.53)	GA based on LMP
	18-19	1.16 (1.13, 1.19)	
	20-24	1.00 (0.98, 1.03)	
	25-29	1	
	30-34	1.16 (1.12, 1.20)	
	35-39	1.45 (1.39, 1.51)	
	40-49	1.72 (1.60, 1.86)	
Body mass index			
Nohr, 2007	Pre-pregnancy BMI	Spontaneous PTB w/PPROM	Danish National Birth Cohort, GA
	<18.5	1.4 (1.1, 1.9)	based on early
	18.5-24.9	1	ultrasound
	25.0-29.9	1.1 (0.9, 1.3)	
	≥30	1.5 (1.2, 1.9)	
Abenhaim, 2007	Pre-pregnancy BMI	OR (32-36 wks)	McGill Obstetrical
	≤19.9	1.14 (1.00, 1.30)	and Neonatal
	20-24.9	1	Database
	25-29.9	1.20 (1.04, 1.38)	Estimates for PTB
	30-39.9	1.60 (1.32, 1.94)	at <32 wks were
	≥40	2.43 (1.46, 4.05)	smaller and non-significant
Race			
Ananth, 2005		%PTB in 2000	U.S. natality files
	White	9.4	GA based on LMP
	Black	16.2	
Kistka, 2007		PTB (20-<35 wks)	368,633 births
	White	1	Missouri linked
	Black	2.99 (2.89, 3.08)	birth/death certificate database Used only multiparous women
Martin, 2006		<32 wks	U.S. National Vital
	White	1.63	Statistics report for
	Black	4.05	2004
	Hispanic	1.77	
		<37 wks	
	White	11.5	
	Black	17.9	
	Hispanic	12.0	
SES			

Parker, 1994	Education <12yrs 12 13-15 ≥16	Black mothers 2.08 1.68 1.22 1	p<0.05 No association of education with PTB for white women
Zeitlin, 2001	Age at end of schooling <16 16-17 18-20 ≥21	Non-SGA PTB 1.48 1.24 1.19 1	Estimates for SGA PTB were similar, not statistically different, thus it is a risk factor for PTB (vs term) in general
Smoking			
Meyer, 1976	Packs /day None <1 ≥1	Adjusted rate 77.1/1000 92.2 115.9	50,000 births Ontario Perinatal Mortality Study
Multiple Gestations			
Martin, 2006	Plurality Singleton Twins Triplets Quads Quintuplets+	% PTB 10.8 59.7 93.0 95.9 100	National Vital Statistics report for 2004
Stress			
Dole, 2004	Black women: Perceived Racial discrimination None Some High Distancing as a coping mechanism Low Medium High White women: Negative life events Low stress Medium/low Medium/high High stress Living with a partner Yes No	 1 1.1 (0.5, 2.1) 1.8 (1.1, 2.9) 1 1.2 (0.6, 2.1) 1.4 (0.8, 2.5) 1 1.3 (0.8, 2.0) 1.3 (0.8, 2.1) 1.8 (1.2, 2.8) 1 1.8 (1.2, 2.7)	No association found for depression or social support, PTB: delivery <37 wks GA determined by LMP if discrepancy w/ultrasound ≤14 days otherwise ultrasound used.

Rich-Edwards, 2005	Review		Cumulative stressors over the lifetime impact pregnancy outcomes
Sandman, 2006	Cortisol at 15 wks Cortisol at 19 wks	p=0.03 p=0.07	No effect estimates presented, cortisol is higher in women that deliver PT, cortisol predicts placental CRH

Table 12. Summary of maternal and pregnancy characteristics associated with growth restriction.

First author, year	Exposure classification	Effect Estimates	Comments
Preeclampsia/Hypertension			
Zeitlin, 2001		OR (p<.01)	Estimates are for SGA/PTB which were much higher (p<.001) than the estimates for non-SGA/PTB.
	No diagnosis	1	
	Hypertension		
	w/out proteinuria	5.34	
	w/proteinuria	17.51	
Plouin, 1983	Diastolic BP	%SGA (p<.01)	1996 singleton pregnancies, all mothers had documented BP <85 mmHg before 16th wk
	<85 mm/Hg	3.2	
	85-94	6.3	
	>94	8.5	
Previous pregnancy outcome			
Heinonen, 2000		OR	History of stillbirth n=92 Controls:11,818 Birth registry in Finland
	History of stillbirth	1.38 (.665, 2.88)	
	Controls	1	
Jivraj, 2001	Recurrent miscarriage	%SGA 13	Patients at a recurrent (≥3) miscarriage clinic, case notes from delivery retrieved Controls: all hospital deliveries
	Control	2.1 (p<0.01)	
Age			

Fraser, 1995		RR (SGA)	Babies born in Utah
	≤17 yrs	1.2 (1.1, 1.2)	1970-90
	18-19	1.0 (1.0, 1.1)	
	20-24	1	
Jacobsson, 2004		OR (SGA)	Swedish Medical
	20-29 yrs	1	Birth Register,
	40-44	1.9 (1.8, 2.1)	~1,000,000 births
	>45	2.7 (2.0, 3.5)	Point estimates increase slightly if PTB is defined as <34 or <32 weeks
Body Mass Index			
Zeitlen, 2001	BMI	SGA/PTB	Compared with term
	<18.3	(p<.01)	birth, ORs were
	18.3-28.8	1.69	significantly higher
	>28.8	1	than those of non-
		1.58	SGA PTB
Abenhaim, 2007	Pre-pregnancy	SGA	McGill Obstetrical
	BMI	1.5 (1.4, 1.7)	and Neonatal
	≤19.9	1	Database
	20-24.9	1.01 (0.6, 1.7)	SGA: birthweight
	25-29.9	0.9 (0.7, 1.1)	ratio using hospital-
	30-39.9	1.2 (0.6, 2.2)	based distribution
	≥40		
SES			
Parker, 1994	Poverty level	OR, White	p<0.05
	Poor	moms	No association for
	Near poor	1.48	black mothers
	Above near poor	1.45	
		1	
Parker, 1994	Paternal	Black couples	p<0.05
	Education	2.36	Weaker
	<12 yrs	1.92	associations among
	12	1.65	white couples
	13-15	1	Data from National
	≥16		Maternal & Infant Health Survey, ~6500 births
Smoking			
Cliver, 1995	Cigarettes /day	BWT (g)	Adjusted for GA
	0	3235	Multiparous women
	1-19	3074	at U of Alabama,
	≥20	3014	1205 births
Alcohol			
Windham, 1995	Alcohol intake		N=1233
	None	1	Weighted average
	3+ drinks/wk	2.3 (1.2, 4.6)	of weekly intake

Sokol, 2003	Review of FAS		FAS is associated with growth restriction
Henderson, 2007	Low-moderate prenatal alcohol exposure	Systematic review	There is no strong evidence, but there are limitations in the research, so an effect cannot be ruled out
Multiple Gestations			
Alexander, 1998		%SGA	U.S. Natality Data Files
	Singletons	9.4	SGA: 10%ile of
	Twins	35.6	BWT for GA using
	Triplets	36.6	U.S. 1991 reference curve
Garite, 2004	Singletons Twins	Presented in a figure	Twins are smaller at each gestational age, but it is because one twin is smaller than the other, the large twin is similar to a singleton

Appendix D: Informal Assessment of Recreational Activity and Preterm Birth and Growth Restriction Literature

Table 13. Summary of research investigating exercise or recreational physical activity and preterm birth.

Author	Exposure	Effect Estimates	Findings	Covariates
Studies finding no association				
Hall, 1987	Personalized exercise prescription based on measured fitness, asked to perform exercises 3x/wk, 4 categories of exercise based on # of completed sessions	(No significance test presented)	No differences in gestational age	No adjustment
	Control	39.9		
	Low	40.1		
	Medium	40.1		
	High	40.4		
Botkin, 1991	Exercise for >=20 minutes, 3x/wk, for 20 wks of preg (vs not)	None presented Mean GA: 40.5 wks (exer) 40.1 wks (non)	No differences in # wks gestation	None
Lokey, 1991	Meta-analysis	Mean GA, SD	No association w/length of gestation	
	Exercise	39.8 wks (1.1)		
	None	39.9 wks (0.2)		
Rice, 1991	'Active' (continuous aerobic activity 3x/wk for 30 min)	Mean GA, SD 39.9 (1.4)	No differences in gestational length	Women were "rejected" due to "smoking habits" or planned C-section No multivariate analysis?
	Sedentary	39.5 (1.4) p=0.2		
Rose, 1991	"usual amount of physical activity" (All activities? Not clear what's included)	None Presented	No significant differences in PTB (data not shown)	None?
	Light			
	Moderate			
	Vigorous			
Horns, 1996	Physical Activity Index for cardiovascular endurance (type, x/wk collected, activity must be performed for at least 15-30 minutes) 3x/wk = active	Mean GA (SD)	No effect on gestational length	No multivariate analysis?
	Sedentary	39.9 (1.4)		

		39.2 (4.3)		
Alderman, 1998	Moderate/Vigorous PA >2hrs/wk in any month of 2nd trimester	PTD: OR:0.7 (0.3, 1.6)	No effect on gestational length	Age, marital, race, eth, educ, employ, income, prepreg wt, ht, genital anomalies, myomas, chronic dx, HPT, prior poor preg outcome, PNC, inf gender…more!
Sternfield, 1998	Used frequency, duration, and mode of exercise to define a 4-level variable Aerobic exercise >=3x/wk for 20min/session (excluding walking) >=3x/wk, 20min/session (including walking) aerobic exercise ≥1x/week (but not enough for Levels I and II) No aerobic exercise, <1x/week	None presented	No associations found between exercise level and gestational age.	Unclear?
Leiferman, 2003	Exercise >=3x/wk before preg (conditioned), >=3x/wk after pregnant (exerciser), Conditioned exerciser Conditioned nonexerciser Unconditioned exerciser Unconditioned nonexerciser	 1 1.01 (0.83, 1.33) 0.73 (0.53, 1.02) 1.12 (0.74, 1.69)	No association with timeliness of delivery	Race, age, marital status, education, income, smoking, BMI
Duncombe, 2006	# of sessions >=30min, and HR >50% of age-adjusted max, >=3x/wk (Bell) 5+ 3-4 1-2 All criteria not met No aerobic exercise No exercise >=3x/wk, >=15 continuous minutes, at HR >140 BPM (ACOG) Did not exceed all criteria	Means reported, ANOVA F test p-value =0.46 39.5 40.1 39.8 39.6 39.8 39.0 ANOVA p=0.40	No significant differences in gestational age at birth	Tobacco, alcohol, cannabis, medication

	Did other exercise	39.7		
	No exercise	39.7		
		39.6		
		39.0		
Orr, 2006			No significant differences in risk of lbw or ptb for exercise vs none, before or during pregnancy	The study pop is low-income, urban, Black women
Haas, 2005	Exercised during the month before pregnancy	1	No association with exercise, but there was an association with "poor physical function"	Age, country of birth, race, education, parity, site, BMI, physical function, depression, medical conditions, smoking
	No	1.21 (0.79, 1.86)		
Mixed results				
Klebanoff, 1990	Light work/exercise, heavy work/exercise (refers to an entire day, not just job)	OR	No assoc of heavy work w/PTB, small negative association between light work and PTB	Excluded women <16 yrs old, diabetes, hyperten, hrt dx, renal dx, multiple preg, Rh sens, corticosteroid use, and more
	Heavy work, 0 hours	1		
	1-3 hr	0.94 (0.75, 1.18)		
	>=4hr	1.04 (0.76, 1.42)		
		p for trend:1.0		
	Light work, 0 hr	1		
	1-3hrs	0.74 (0.48, 1.14)		
	4-7hrs	0.69 (0.44, 1.07)		
	>=8hrs	0.59 (0.38, 0.93)		
		p for trend: 0.02		
Hatch, 1998	Types of leisure-time activities, time/wk, kcal/wk trichotomized:	RR	Low-moderate exercise had no assoc w/gestational length, Heavier exercise reduced risk of PTB, conditioned heavy exercisers deliver faster postterm	Age, parity, prepregnant wt, 1st trimester bleeding, income
	None	1.11 (0.88, 1.39)		
	Low-Moderate ($\leq$1000kcal/wk)			
	Heavy (>1000kcal/wk), conditioned	0.11 (0.02, 0.81)		
	Heavy, not conditioned	0.72 (0.24, 2.15)		
	Postdates (Week 43):			
	Heavy, conditioned	5.62 (1.41, 22.47)		

	Heavy, not conditioned	1.20 (0.47, 3.07)		
Negative association				
Berkowitz, 1983	Leisure-time PA in hours/wk, before pregnancy: Yes No During pregnancy Yes No First trimester 0 hrs/wk 1-2 3-5 6+ (Second trimester shows similar pattern)	 0.67 (0.46, 0.97) 1 0.53 (0.36, 0.78) 1 1 0.55 0.50 0.74 p<0.01 (any PA v none)	Logistic regression included yes/no variable? Participation in exer during preg led to lower odds of PTB when measured as any vs none and when divided into hours per week, although association was weaker for highest level. Also, the proportion of cases who participated in 'high' exertion PA was higher than in controls for all 3 trimester	Race, SES, pregravid weight, weight gain, infertility history, previous induced abortion, vaginal spotting/bleeding, alcohol consumption, negative attitudes towards pregnancy. Adjustment had little effect on point estimates.
Magann, 1996	Kilocalories in work and leisure <2300kcal/day 2301-2500 2501-2700 2701-2900 >2900	% preterm birth 10 10.3 8.1 8.1 8.1 p=0.006	Medium energy expenditure→ fewer incidences of prelabor rupture of membranes. Lower energy group has higher risk of PTB.	Socioeconomic score, parity, weight gain
Misra, 1998	Moderate/strenuous exer >=60 total days in the 1st 2 trimesters (~3x/wk), stair climbing, walking to work/store, etc. <60	 0.51 (0.27, 0.95) 1	Low-income women: climbing stairs + odds of PTB, purposive walking + odds, leisure-time ex – odds of PTB, adjustment doesn't change point estimate	Race, age, use of illicit drugs, prenatal care, maternal height, smoking, insurance, prior fetal losses, prior LBW, hypertension, bleeding, fever, hospitalization
Kardel, 1998	Highly active women recruited, asked to participate in a medium or high-intensity	Mean GA (among girls)	Earlier onset of labor for women who had	Excluded daily drinkers, smokers,

	exercise program (strength, interval, endurance training)	difference:-1.2 (-2.2, -0.2)	girls, but mean for both groups is >=39 weeks	women on meds, or other risks
	Medium	40.2		
	High	39.0		
Evenson, 2002	Any participation in vigorous leisure activity:		No statistically significant association, but tendency toward protective association	Smoking, age, BMI, marital status, education race, parity, energy intake, bedrest
	First trimester	0.80 (0.48, 1.35)		
	Second trimester	0.52 (0.24, 1.11)		
	First trimester, hours/week			
	0	1		
	0.1-2.9	0.75 (0.36, 1.56)		
	3+	0.85 (0.44, 1.66)		
Badr, 2005		Reg Coefficient	p-value=0.01, women w/preterm births exercised less	Comparison of Mexican-Am., Lebanese, Egyptian, White
	1-unit change in a 5-level variable where 1=never and 5=always (It isn't totally clear how they modeled this exposure?)	1 -1.80 (0.90)		

Table 14. Summary of research investigating exercise or recreational physical activity and fetal growth.

Author	Exposure	Effect estimates	Findings	Covariates
Studies suggesting babies of exercising mothers are bigger				
Hatch, 1993	Types of leisure-time activities, time/wk, kcal/wk trichotomized	BW differences (g) (During pregnancy)	Beneficial for fit, low-risk patients, exercise + correlated with growth (mean BWT) No effect if women were unconditioned or had a history of adverse outcome, also looked by trimester, but no clear patterns emerged	Gestational age, gestational age squared, parity, log of prepregnant weight, average weekly weight gain, smoking, nausea, income
	Non-exercisers	1		
	Low-moderate	124 (-6, 255)		
	Heavy	276 (54, 497)		
	Changing pattern	32 (-54, 117)		
Magann, 1996	Kilocalories in 5 categories, work & leisure combined	BW differences (p-values)	Medium energy expenditure→ higher BWT, lower energy→ lower BWT, all groups in the normal range	Gestational age, smoking, infant sex, height, pre-pregnancy weight, parity
	<2300			
	2301-2500	-73 (0.01)		
	2501-2700	-60 (0.02)		
	2701-2900	1		
	>2900	-23 (0.33)		

		-22 (0.52)		
Collings, 1983	3x/wk at 65% MVO2 for ~13wks, biking	BW (grams) 3596.3 (479.8)	Exercise group: + BWT, +Blength, + placental weight, not significant	(Mostly) randomized trial
	Control	3353.8 (415)		
		Birth Length		
	Exercise	52.6 (2.9)		
	Control	50.6 (2.7)		
Hall, 1987	Personalized exercise prescription based on measured fitness, asked to perform exercises 3x/wk, 4 categories of exercise based on # of completed sessions	BW (grams)	Controls had lower BWTs than exercise groups (p=0.06). No SDs reported	No adjustment
	Control	3359		
	Low	3471		
	Medium	3445		
	High	3510		
Leiferman, 2003	Exercise >=3x/wk before preg (conditioned), >=3x/wk after pregnant (exerciser), 4 categories	Very LBW	Unconditioned, non-exercisers more likely to have VLBW infants, but not LBW, conditioned non-exercisers more likely to have VLBW/LBW than conditioned exercisers	Race, age, marital status, education income smoking, BMI
	Conditioned exerciser	1		
	Conditioned nonexerciser	1.94 (1.60, 2.36)		
	Unconditioned exerciser	1.20 (0.80, 1.58)		
	Unconditioned nonexerciser	1.47 (1.03, 2.11)		
Studies finding no association				
Botkin, 1991	Exercise for >=20 minutes, 3x/wk, for 20 wks of preg	BW (grams, SD) 3663.8 (318.4)	No differences in BWT or BLength	None
	Nonexercise	3523.3 (351.0)		
		Birth Length		
	Exercise	52.4 (2.3)		
	Nonexercise	51.6 (1.7)		
Duncombe, 2006	# of sessions >=30min, and HR >50% of age-adjusted max, >=3x/wk (Bell)	Mean BWT (SD)	No significant differences in BWT	None
	5+	3324 (526.1)		
	3-4	3528.2 (395.6)		

	1-2	3548.6 (435.6)		
	All criteria not met	3518.2 (558.0)		
	No aerobic exercise	3593.1 (673.4)		
	No exercise	3482.6 (538.2)		
	>=3x/wk, >=15 continuous minutes, at HR >140 BPM (ACOG)	3435.2 (428.5)		
	Did not exceed all criteria	3524.3 (505.5)		
	Did other exercise	3445.5 (559.4)		
	No exercise	3482.6 (538.2)		
Kardel, 1998	Highly active women recruited, asked to participate in a medium or high-intensity exercise program (strength, interval, endurance training)	BW (SD)	No difference between med and hi exercise grps in BWT (no nonexercisers)	Excluded daily drinkers, smokers, women on meds, or other risks
	Medium	3590.5 (532)		
	High	3650.7 (515.8)		
Klebanoff, 1990	Light work/exercise, heavy work/exercise (refers to an entire day, not just job)	BW (trend p=0.29)	No assoc w/gestational-age adjusted BWT	Excluded women <16 yrs old, diabetes, hyperten, hrt dx, renal dx, multiple preg, Rh sens, corticosteroid use, and more, adjusted for age, education parity, marital status, income, smoking, alcohol, insurance, employment
	Heavy work, 0 hours	3210		
	1-3 hr	3187		
	>=4hr	3261 (trend p=0.25)		
	Light work, 0 hr	3182		
	1-3hrs	3250		
	4-7hrs	3217		
	>=8hrs	3226		
Lokey, 1991	Meta-analysis	BW (kg) (SD)	No association with BWT	
	Exercise	3.4 (2.1)		
	None	3.5 (1.8)		
Rice, 1991	'Active' (continuous aerobic activity 3x/wk for 30 min)	Fetal weight (lbs) 7.7 (0.7)	No difference in fetal weight	Women were "rejected" due to "smoking habits" or planned C-section,
	Sedentary	7.6 (0.99)		

				exercise not associated with GA No multivariate analysis?
Horns, 1996	Physical Activity Index for cardiovascular endurance (type, x/wk collected, activity must be performed for at least	BW (SD)	No effect on BWT (N=53 sedentary, 48 active, power?)	No multivariate analysis?
	15-30 minutes) 3x/wk = active	2496 (486)		
	Sedentary	3467 (434)		
Rose, 1991	"usual amount of physical activity" (All activities? Not clear what's included)		No significant differences in BWT, LBW was more common in the "light" group but not significantly	None?
	Light	3443		
	Moderate	3460		
	Vigorous	3429		
Alderman, 1998	Moderate/Vigorous PA >=2hrs/wk in any month of 2nd or 3rd trimester	OR	- risk of LGA No sig effect on SGA	Age, marital, race, eth, educ, employ, income, prepreg wt, ht, genital anomalies, myomas, chronic dx, HPT, prior poor preg outcome, PNC, inf gender…more!
		0.8 (0.3, 2.3)		
	No	1		
		LGA		
	Yes	0.3 (0.2, 0.7)		
	No	1		
Nieuwenhuijsen, 2002	Hours spent swimming/week, at 18-20 weeks	BW difference (g)	No effect of swimming on BWT	Parity, smoking, education, housing tenure, age, cannabis, hard drugs, alcohol, gestational age, ethnicity
	Never	0		
	<1hr/week	7.84 (-10.36, 26.05)		
	2+	16.74 (-11.4, 44.9)		

Studies suggesting babies of exercising mothers are smaller

Perkins, 2007	48hr accelerometer readings at 20/32 wks gestation, used to calculate METs METs/day (average of 20/32 wks)	Beta (from least squares regression of FGR) -0.13 (-.21, -.02)	Fetal growth ratio (BWT/median BWT for gest wk, adjusted for gender/race/parity) inversely assoc w/average PA at both time points, mostly in taller mothers, all infants were of healthy weight	Maternal weight gain, maternal height
Campbell, 2001	Structured exercise 0-2x/wk 3-4x/wk >=5x/wk	3rd trimester 2.18 (1.15, 4.13) 1 3.96 (1.66, 9.44)	>=5 and <3x/wk structured exercise in 3rd trimester were related to + odds of SGA No interaction w/prepreg wt or age, also looked at leisure activity	Stress, ethnicity, parity, educ, ht, prepreg wt, wt gain, alcohol consump, smoking, hyperten, infections, prepreg fitness
Clapp, 1990	Runners & aerobic dancers (vs. conditioned women) who maintained their exer level at >=50% of preconcept level Control Exercise Control Exercise	BW (SD) 3691 (348) 3381 (322) p=0.01 BW %ile 65 (19) 45 (22) p=0.01	Lower BWT, BWT %ile, ponderal index, PI %ile, fetoplacental wt ratio, most due to lower fat mass, no diff in crown-heel length or head circumference	Controls matched to exercisers on general health, physical fitness, education income, age, parity, contraceptive use, pregravid weight, job type, dietary intake, sleep-avtivity cycles, smoking, alcohol

Appendix E: Summary of the Pregnancy, Infection, and Nutrition 3 Study Physical Activity Questionnaire (administered at 17-22 and 27-30 weeks gestation)

	Question	Type	Frequency	Duration	Intensity*
Recreational	In the past week, did you participate in any non-work recreational activity or exercise, such as walking for exercise, swimming, or dancing that caused at least some increase in breathing and heart rate?	What type of recreational activities did you do during the past week? For certain activities: on average, how far did you usually (activity)?	How many times in the past week did you (activity)?	On average, for how many minutes or hours did you usually (activity) at a time?	Thinking about your breathing and heart rate, how hard did this usually feel to you? Fairly light / Somewhat hard / Hard or very hard
Outdoor household activities	In the past week, did you participate in any outdoor household activities such as gardening, mowing, or raking that caused at least some increase in breathing and heart rate?	What type of outdoor household activities did you do during the past week? For lifting, carrying, or shoveling: On average, how much did the objects weigh that you (activity)?	How many times in the past week did you (activity)?	On average, for how many minutes or hours did you usually (activity) at a time?	Thinking about your breathing and heart rate, how hard did this usually feel to you? Fairly light / Somewhat hard / Hard or very hard
Indoor household activities	In the past week, did you participate in any indoor household activities such as scrubbing floors, mopping, or vacuuming that caused at least some increase in breathing and heart rate?	What type of indoor household activities did do during the past week? For lifting or carrying: On average, how much did the objects weigh that you (activity)?	How many times in the past week did you (activity)?	On average, for how many minutes or hours did you usually (activity) at a time?	Thinking about your breathing and heart rate, how hard did this usually feel to you? Fairly light / Somewhat hard / Hard or very hard
Child and adult care – lifting	Child and adult care activities … would be activities such as playing with children, pushing a stroller or wheelchair, carrying, or lifting a child or adult that you may do in your home or as a volunteer. In the past week, did you	What type of child or adult care activities did you do during the past week? For lifting or carrying: On average, how much did the objects weigh that you (activity)?	How many times in the past week did you (activity)?	On average, for how many minutes or hours did you usually (activity) at a time?	Thinking about your breathing and heart rate, how hard did this usually feel to you? Fairly light / Somewhat hard / Hard or very hard

	participate in any child or adult care activities that caused at least some increase in breathing and heart rate?				
Transportation - walk	In the past week, did you walk for transportation, such as to work or to the store, which caused at least some increase in breathing and heart rate?	WALK On average, how far did you usually walk one-way?	How many one-way trips did you walk in the past week?	On average, for how many minutes or hours did a one-way walking trip usually take?	Thinking about your breathing and heart rate, how hard did this usually feel to you? Fairly light / Somewhat hard / Hard or very hard
Transportation - bike	In the past week, did you bike for transportation, such as to work or to the store, which caused at least some increase in breathing and heart rate?	BIKE On average, how far did you usually bike one-way?	How many one-way trips did you bike in the past week?	On average, for how many minutes or hours did a one-way biking trip usually take?	Thinking about your breathing and heart rate, how hard did this usually feel to you? Fairly light / Somewhat hard / Hard or very hard
Work and school activities	In the past week, did you participate in any work activities such as walking, lifting, or carrying objects, that caused at least some increase in breathing and heart rate?	What type of work activities did you do during the past week? For carrying or shoveling: On average, how much did the objects weigh that you (activity)?	How many times in the past week did you (activity)? For walking: On average, how far did you usually walk?	On average, for how many minutes or hours did you usually (activity) at a time?	Thinking about your breathing and heart rate, how hard did this usually feel to you? Fairly light / Somewhat hard / Hard or very hard
Other activity	Before we move on to another section, I want to be sure you had a chance to tell me about all the activities you did in the past week that caused at least some increase in breathing and heart rate. Can you think of any other activities, including lifting, you did in the past week that we have not talked about?	What other activities did you do during the past week? For some activities: On average, how far did you usually (activity)?	How many times in the past week did you (activity) at a time? For lifting, carrying, or shoveling: On average, how much did the	On average, for how many minutes or hours did you usually (activity) at a time?	Thinking about your breathing and heart rate, how hard did this usually feel to you? Fairly light / Somewhat hard / Hard or very hard

			objects weigh that you (activity)?		

Note: The lead in question described the questionnaire in this way: "Now I am going to ask you some questions about physical activities you might do at work, at home, for recreation, and about activities involving child or adult care. I want you to tell me about activities you did that “caused at least some increase in breathing and heart rate”. The questions ask about the past week, meaning the last 7 days not including today, so that would mean from last <*day*> to yesterday or <*day*>."

*Intensity was defined as not hard = did not feel any increase in breathing or heart rate and thus not recorded; fairly light = at least some increase in breathing and heart rate; somewhat hard = moderate increase in breathing and heart rate; nad hard or very hard = large increase in breathing and heart rate.

Appendix F: Right From the Start Vigorous Physical Activity Questionnaire

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 recreational 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 outdoor household activities, like working in the yard or indoor household activities, 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 child or adult care 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 work activities 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 G: Directed Acyclic Graphs

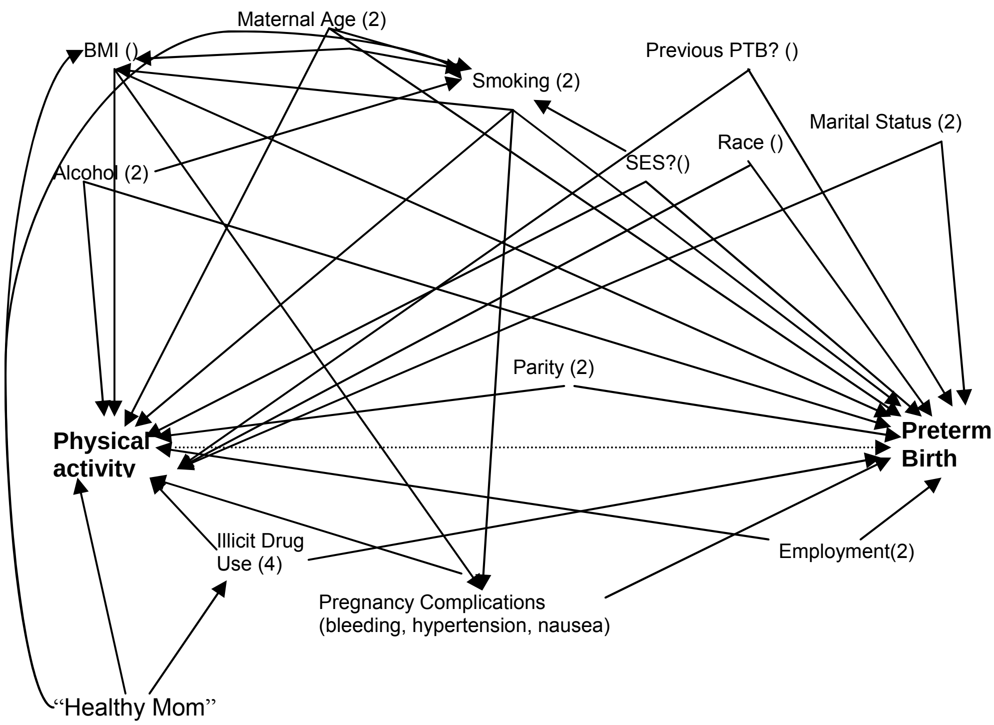

Diagram of the hypothesized associations between risk factors for preterm birth and physical activity for the assessment of confounding. Dashed arrow represents the association under investigation in this analysis.

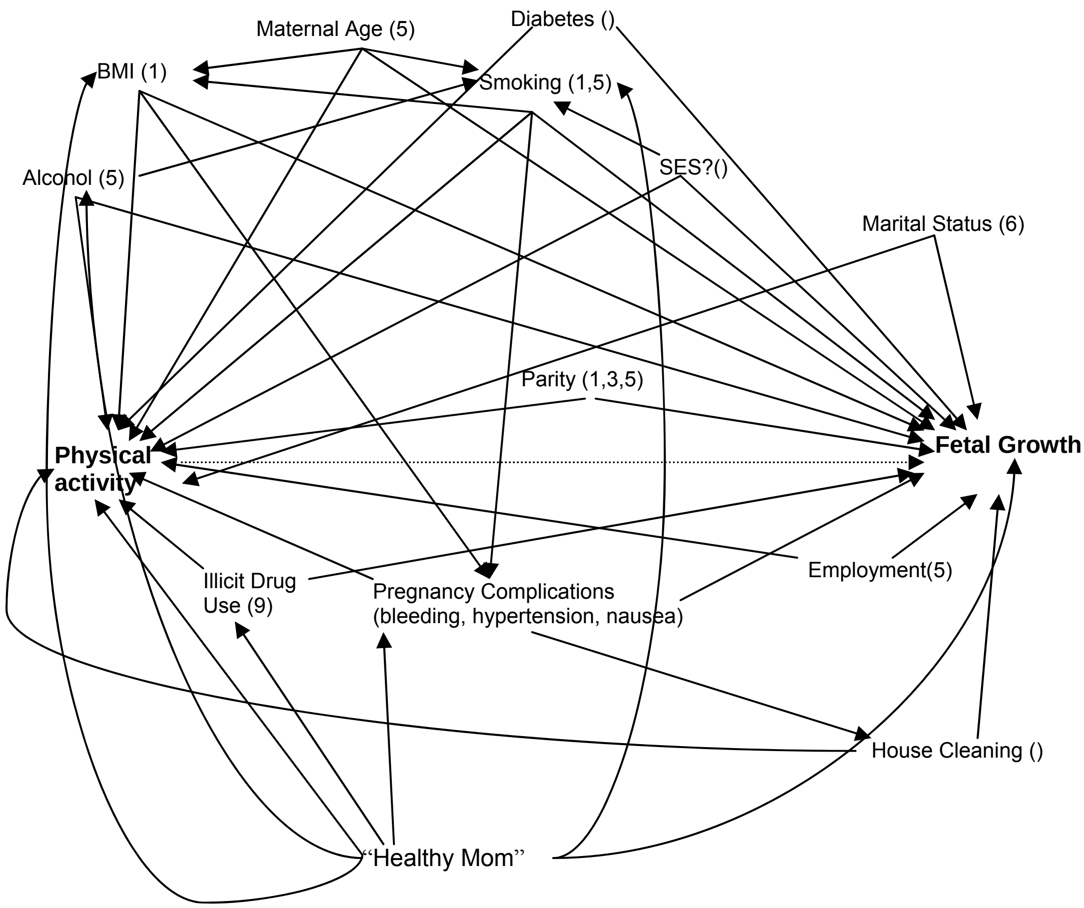

Diagram of the hypothesized associations between factors related to fetal growth and physical activity for the assessment of confounding. Dashed arrow represents the association under investigation in this analysis.

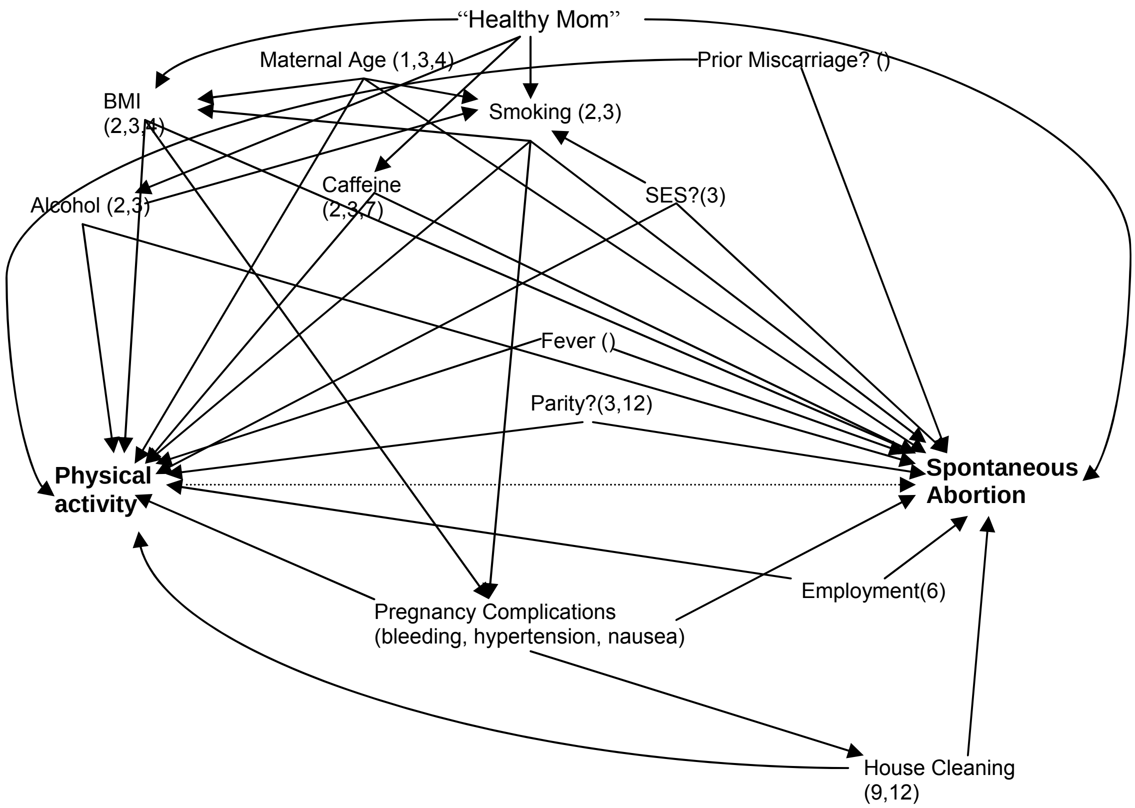

Diagram of the hypothesized associations between factors related to spontaneous abortion and physical activity for the assessment of confounding. Dashed arrow represents the association under investigation in this analysis.

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