

Maternal Physical Activity and Birth Outcomes

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ABSTRACT

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(under the direction of Anna Maria Siega-Riz)

Background: Information on physical activity (PA) during pregnancy and subsequent maternal birth outcomes (such as cesarean rate, labor duration) is plentiful in the literature, but consensus among studies is lacking. Poor exposure analytic methods may be a source of conflicting results. **Objective:** To estimate associations between PA during pregnancy and maternal birth outcomes using appropriate statistical methods.

Methods: Detailed 7-day PA recalls were administered to pregnant women at two time points: 17-22 and 27-30 weeks' completed gestation. Covariables and labor outcomes were obtained by a combination of self-administered questionnaires and medical record abstraction. Physical activity was treated in analyses as a continuous, non-linear variable. We analyzed separately 8 different exposures: total hours/week PA at each time point, hours/week moderate-to-vigorous PA (MVPA) at each time point; total hours/week recreational PA at each time point, and finally hours/week recreational MVPA at each time point. Outcomes included induction, labor duration, augmentation, operative vaginal delivery (OVD), cesarean birth, episiotomy, and laceration severity. Covariables for each model were selected using directed acyclic graphs (DAGs); variables in final models were chosen through backwards stepwise selection using analysis of deviance. Sensitivity analyses explored the effects of excluding women reporting extremely large PA volumes and of excluding women reporting zero hours/week PA. **Results:** Physical activity during pregnancy was associated with a

decreased risk of induction. Recreational PA at the second time point only was associated with a decreased risk of augmentation. PA during pregnancy was associated with longer labor durations, but our measure of labor duration was crude and we do not consider this result definitive. PA was not associated in these data with episiotomy, OVD, or cesarean. PA may be associated with increased laceration severity, but effects were quite small. **Conclusions:** Lack of consensus in the literature on the associations between PA and maternal birth outcomes may be partially because of categorical treatment of the exposure and lack of attention to gestational age at time of exposure.

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LIST OF ABBREVIATIONS

ACOG, American College of Obstetricians and Gynecologists

B/C, because

BMI, body mass index

BW, birthweight

CDC, Centers for Disease Control and Prevention

CI, confidence interval

CM, centimeters

CL, confidence limits

CS, cesarean section

DAG, directed acyclic graph

DM, diabetes mellitus

ED, education

ENDUR, endurance training

EXP, exposure

G, grams

GA, gestational age

HELLP, hemolysis, elevated liver enzymes, low platelets

HR, heart rate

HTN, hypertension

HX, history

INT, interval training

IQR, inter-quartile range

IRB, institutional review board

L&D, labor and delivery

LBW, low birth weight

LTPA, leisure-time physical activity

MVPA, moderate-to-vigorous physical activity

NICU, neonatal intensive care unit

NIH, National Institutes of Health

NS, non-significant

OB/GYN, obstetrics and gynecology

OR, odds ratio

OVD, operative vaginal delivery

PA, physical activity

PEH, pre-eclampsia, eclampsia, or HELLP syndrome

PIN3, third Pregnancy, Infection, and Nutrition study

PRAMS, Pregnancy Risk Assessment Monitoring System

PT PREF, patient preferences for labor and delivery

RCT, randomized controlled trial

RR, risk ratio

SD, standard deviation

SES, socio-economic status

STR, strength training

UNC, University of North Carolina

US, United States

VBAC, vaginal birth after cesarean

YO, years old

INTRODUCTION AND SPECIFIC AIMS

The American College of Obstetricians and Gynecologists (ACOG) issued the most recent update to their guidelines for exercise during pregnancy in January of 2002.(1) They recommend “30 minutes or more of moderate exercise on most, if not all, days of the week”—an exercise prescription which corresponds closely to what the Centers for Disease Control and Prevention (CDC) suggested for all adult Americans at that time.(2) Of note, ACOG's use of the word "exercise" is probably a misnomer, as the guidelines do discuss non-exercise physical activity; however, ACOG does intentionally limit its recommendations to moderate exercise (rather than moderate or vigorous, as the CDC suggested), noting that little research had been done on strenuous exercise during pregnancy. They caution all pregnant women to limit exercise intensity and duration; to avoid competitive, injury-prone, and supine-position activities; to be aware of the physiologic changes that accompany pregnancy and which therefore present heightened risks; and not to exercise at all if women have any of a number of pregnancy complications (placenta previa, pre-eclampsia, unexplained late bleeding, incompetent cervix, signs of preterm labor, etc.) While ACOG does not state that exercise benefits pregnancy *per se*, they do note the lack of apparent harm as well as the benefits of exercise enjoyed by all relatively healthy adults, regardless of pregnancy status.

Many maternal benefits have been postulated to follow physical activity during pregnancy, mostly based on the assumption that an active woman's body is better able to withstand the rigors of labor and birth. These claims are largely unsubstantiated by the scientific literature because of lack of consensus among published reports. This lack

of consensus is likely because of a number of methodological difficulties, including inadequate sample sizes and lack of appropriate statistical techniques. This study examined the associations between physical activity during pregnancy and maternal birth outcomes. Data came from the third Pregnancy, Infection, and Nutrition (PIN3) cohort and from the University of North Carolina at Chapel Hill's Department of Obstetrics and Gynecology's clinical Perinatal Database. This study represents an improvement over previous efforts because of the large sample size, extensive prospective exposure ascertainment, and large number of available covariables.

The aims were:

- **To determine whether women who report more hours/week of physical activity (PA), or those who report more hours/week of moderate-to-vigorous PA (MVPA), at either 17-22 weeks or at 27-30 weeks, have a different pattern of delivery modes than do women who report less activity.**

Hypotheses: Women reporting more hours/week will have fewer primary urgent/emergent cesareans than women reporting fewer.

- **To describe the patterns of labor for women who report different volumes of PA and MVPA at 17-22 weeks and 27-30 weeks.**

Hypotheses: When excluding women who had cesarean births, women with higher volumes of physical activity during pregnancy will require fewer inductions, have shorter labors, require less augmentation, have fewer operative vaginal deliveries, fewer episiotomies, and less severe perineal lacerations.

LITERATURE REVIEW

Previously-Reported Associations Between Maternal PA and Pregnancy Outcomes

Active women have slightly smaller babies, but there is no change in the percent of babies falling into the low birth weight category (LBW, <2500 g).(3-4) Activity during pregnancy does not appear to increase rates of preterm birth.(3-5) A woman who is active during her pregnancy has a reduced risk of developing gestational diabetes,(3-4,6) pregnancy-induced hypertension,(6) and pre-eclampsia.(3-4,6) Active women gain less weight during their pregnancies (3,6)—a bad prognostic factor in developing countries where adequate maternal nutrition is scarce, but a good sign in the US, where many women gain above the Institute of Medicine's recommendations.(7-8) Women who are active during their pregnancies have fewer physical complaints (nausea, leg cramping, backache) than do less active women.(6,9) Pregnant women who exercise regularly may also have fewer depressive symptoms.(6) However, there is still debate regarding the effects, if any, that physical activity during pregnancy may have on maternal birth outcomes such as delivery mode, pain, labor duration, perineal lacerations, episiotomy, and need for induction or augmentation of labor.

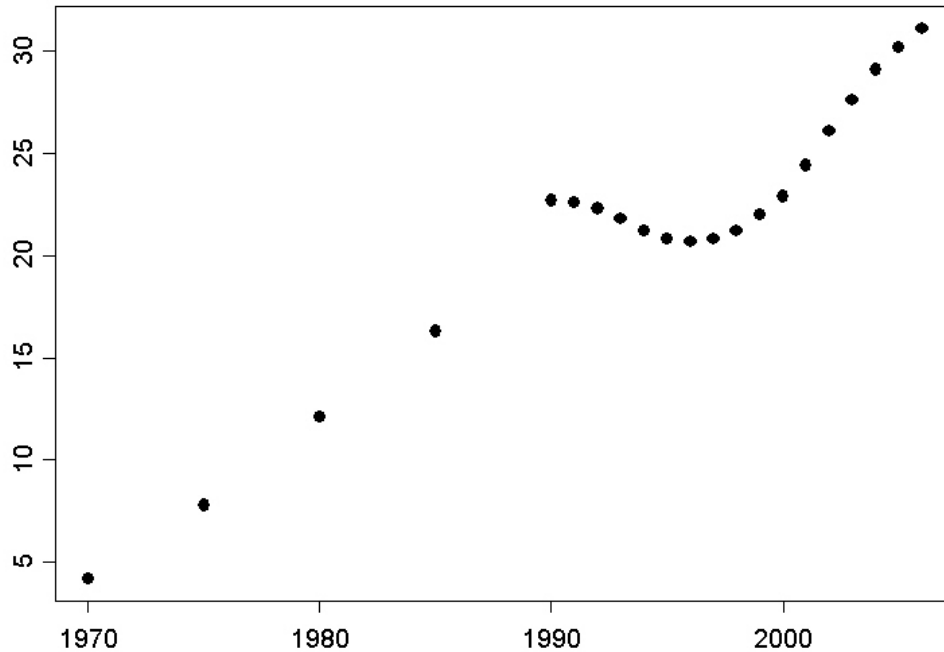
A systematic search of the English-language literature indexed by the National Library of Medicine was conducted on 19 October 2008 by searching the keyword terms (exercise or physical activity) and (maternal or pregnancy or pregnant or antepartum or antenatal or prenatal); limiting the results to those studies involving research on human subjects retrieved 4229 articles. All titles were read, and 286 studies identified that may have a bearing on this topic. Of the 286, abstracts were read where available (if not, full text was pulled); the end result was that 93 full-text articles were pulled and searched for

relevant results. The systematic search was repeated on 15 April 2009, this time searching the English-language literature indexed by the National Library of Medicine using the medical subject heading (MeSH) terms (athletic performance or exercise tolerance or exercise or physical exertion or physical fitness or exercise therapy or exercise test or sports or exercise movement techniques or muscle stretching exercises or resistance training) and (parturition or labor,obstetric or pregnancy outcome or delivery,obstetric or oxytocin); when limited to human and female, 344 articles were identified. Of these, abstracts for 84 were read, and 55 original research articles identified for full-text searching. Of these 55, 27 were duplicates from the earlier search, leaving 28 new original research articles, and a total of 121 studies identified. This search was repeated on 15 Dec 2009, and an additional 2 studies were identified.

Physical Activity During Pregnancy and Cesarean Birth

Rates of cesarean delivery in the US have risen steadily since 1970 (see Figure 2.1), prompting the US Department of Health and Human Services to make reduction in the number of cesareans among low-risk mothers one of the goals of Healthy People 2000, 2010, and 2020.⁽¹⁰⁾ Unfortunately, during the last decade the cesarean rate has in fact not declined, but rather has risen as sharply as ever, and is currently over 31%.⁽¹¹⁾ This is of concern from a public health perspective because cesareans are not risk-free; they also cost substantially more than vaginal deliveries.⁽¹²⁾

Figure 2.1. Rates of cesarean birth in the US, 1970-2006. Data from the CDC.



Delivery by cesarean section is associated with increased risk of hysterectomy, postpartum pain, neonatal respiratory morbidity, neonatal seizures, maternal ureteral tract injury, accidental laceration of the newborn, infection, and postpartum hemorrhage.(13-17) Additionally, cesareans increase a woman's risk for uterine rupture, unexplained fetal death, and placental problems in subsequent pregnancies, not to mention drastically increase her risk for future deliveries by cesarean.(15) Cesareans are associated with increases in both neonatal (RR 3.0) and maternal (reported RRs range from 2.6-7.0) mortality.(15,18-21) Finally, cesarean deliveries cost more than vaginal births,(12) and are associated with increased lengths of stay and lower patient satisfaction.(22)

Available evidence suggests that while some of the recent increase in cesarean deliveries results from the corresponding increase in maternal obesity,(23) the increase

in cesareans cannot be attributed entirely to a worsening of maternal or fetal risk profiles.(24-26) This implies that some of the cesareans performed each year in the U.S. may be medically unnecessary, exposing women and babies to risks without proven benefit.(27-29) Interventions aimed at reducing cesarean delivery rates should thus be a public health priority.

Many researchers have examined whether or not physical activity during pregnancy is associated with cesarean delivery; however consensus has not been reached. Many studies show a reduced risk of cesarean, but methodologic limitations are a concern. From the 121 articles identified through the systematic search described above, 23 were found to report an association between physical activity during pregnancy and cesarean delivery.(30-52) Twenty-two studies present results for cesarean vs. all vaginal deliveries, and one reports results for cesarean/operative vaginal vs. spontaneous vaginal births. Characteristics of these studies are summarized in Table 2.1.

Table 2.1. Characteristics of studies reporting maternal birth outcomes. Abbreviations: LTPA, leisure-time physical activity; CS, cesarean section; RCT, randomized controlled trial; yo, years old, HR, heart rate; str, strength training; int, interval training, endur, endurance training; hx, history; b/c because; PA, physical activity; OVD, operative vaginal delivery; PRAMS, pregnancy risk assessment monitoring system

Author (year)	design	location	n	inclusion criteria	exposed	control	results
Baciuk (2009)	RCT	Brazil	71	<20 weeks, singleton, no complications, early prenatal care, sedentary, no contraindications to exercise during pregnancy, ≤1 previous cesarean	water aerobics, moderate intensity, 50 minutes 3/week, 70% max HR (women wore HR monitors)	told "not to carry out any regular physical activity during the entire pregnancy"	no significant differences in labor duration or delivery mode
Beckmann (1990)	prospective cohort; questionnaire and record review		100		n=50 attending prenatal exercise classes, includes str, flexibility, toning, did not include endur; 1 hour 2/week, ≥12 weeks	n=50 from same OB practices, not attending the classes	shorter labor, fewer augmentations, fewer OVD, fewer CS among exposed
Botkin (1991)	telephone interview postpartum, record review	Iowa	44	delivery ≤6 months ago	n=19, LTPA ≥20 minutes, ≥2 times per week, ≥20 weeks of pregnancy	n=25	fewer forceps, shorter stage 2 labors among exposed
Bovbjerg (2009)	cross-sectional	North Carolina	1955	PRAMS participant in 2004-2005	during last 3 months of most recent pregnancy, exercise for ≥30 minutes, 1-4 times (n=750) or ≥5 (n=143) times/week	<1 / week (n=1062)	fewer CS among exposed, preterm births only
Bungum (2000)	cohort; retrospective exposure data via questionnaire before delivery; delivery data via telephone interview postpartum	South-western US	137	nulliparous, non-smoking, singleton, 17-40 yo, no complications	pilot-tested checklist; check activities ≥20 min, 3/week during 1 st or 2 nd trimester; n=44	n=93	fewer CS among exposed; no difference in labor duration

Clapp (1990)	cohort		131	recreational runners or aerobic dancers	n=87 who continued at $\geq 50\%$ maximal capacity, ≥ 30 min ≥ 3 /week	n=44 did not continue pre- conception levels of activity	fewer CS, fewer OVD, faster labor, fewer augmentations among exposed
Collings (1983)	intervention; first 5 not random, rest random		20		n=12; 50 min 3/week at 65-70% capacity	n=8, did not report regular LTPA	longer labors, fewer CS among exposed
Dale (1982)	retrospective cohort, prospective cohort (results reported together)		44		n=21 delivered in last 5 years and ran during pregnancy; n=12 currently running during pregnancy	n=11 not currently running during pregnancy	more CS among exposed
Erdelyi (1962)	case series	Hungary	172	athlete under author's care	athletes	---	fewer CS, faster labor among exposed; no difference in OVD
Hall (1987)	intervention	Florida	845	recruited from private OB clinics	tailored exercise prescription, 45 min 3/week n=82 attended 10- 20 sessions n=309 attended 21- 59 sessions n=61 attended ≥ 60 sessions	n=393 attended ≤ 10 sessions	fewer CS among exposed; no difference labor duration
Horns (1996)	cohort; questionnaire before delivery for exposure, postpartum record review and telephone interview		101	nulliparous, 20-30 yo, >31 weeks' gestation, no medical conditions	checklist, which for 15-30 minutes continuously ≥ 3 /week	n=53	fewer CS among exposed; no difference labor duration
Jarrett (1983)	retrospective cohort; questionnaire	Chicago	67		n=48 self-reported jogging during pregnancy	---	fewer CS among exposed than national rate
Kardel (1998)	intervention, not randomized	Norway	42	elite athletes, non- smokers, low-risk, <20 weeks' gestation, no medications, no alcohol	n=21 high intensity: 72 min str 2/week, 35 min int 2/week, 150 min endur 2/week	n=21 medium intensity: 72 min str 2/week, 25 min int 2/week, 90 min endur 2/week	more OVD among exposed; no difference in CS

Kulpa (1987)	RCT, block stratified by parity; exposure info captured via prospective diary	Michigan	37 primips, 48 multips	18-34 yo, non-smoker, within 15% of ideal body weight, no pregnancy complications/ medical problems, interest in recreational sports	n= 34 given an exercise prescription following an exercise test, target HR 75% maximum, NFIG	n= 47 maintained target HR <20 minutes per week	no difference in OVD, CS, lacerations; shorter 1 st stage, primiparas only
Lynch (2003)	intervention		23	sedentary 1 st 4 months pregnancy; nulliparous	40 min swimming, 3/week; HR < 140	---	fewer CS among exposed than national rate
Magann (1996)	cohort; validated exposure questionnaire, LTPA and occupational	Australia	2743	≥18 yo, English-speaking, singleton, prenatal care, 16-18 weeks' gestation	group 4, n=608: expend 2701-2900 kcal/day group 5, n=172: expend >2900 kcal/day	group 1, n=359: expend ≤2300 kcal/day group 2, n=545: expend 2301-2500 kcal/day group 3, n=1059: expend 2501-2700 kcal/day	more OVD, more inductions, more CS, longer labor (primiparas only) among exposed
Magann (2002)	retrospective cohort	California	750	active duty Navy	4 groups based on voluntary and mandatory activity (group 4 had the most activity)	group 1	more CS, longer labor, more induction, more augmentation, among exposed; no difference OVD
Marquez-Sterling (2000)	RCT	Florida	15	low-risk, sedentary ≥1 year pre-pregnancy	n=9 1 hour str & endur, 3/week	n=6	no difference CS
Melzer (2009)	cohort	Switzerland	44	low-risk, no history of CS	≥30 minutes, ≥3 times during 7 days of accelerometry	did not accumulate that amount of activity	fewer OVD, fewer CS, shorter 2 nd stage among exposed women
Narendran (2005)	non-randomized intervention	India	335	18-35 yo, singleton, 18-20 weeks' gestation, no illness, no yoga training	walk 30 min 2/day	1 hour yoga/day	fewer elective CS but more emergent CS among exposed

10	Penttinen (1997)	retrospective cohort, questionnaire— exposed only! and record review	Finland	60	primiparous	n=30 elite endurance athletes	n=30 next woman delivering at same hospital— <i>assumed</i> did less exercise than elite athletes	more CS among exposed; no difference labor duration
	Pomerance (1973)	cross-sectional	California	41	wives of Naval officers, low-risk, no history of CS	fitness test results	---	higher fitness assoc. with shorter labor, multiparas only
	Rice (1991)	cross-sectional	Kentucky	23		≥30 minutes, ≥3/week aerobic exercise	do not meet exposed definition	longer 2 nd stage among exposed, but more primiparas in exposed group; no difference 1 st stage
	Zeanah (1993)	retrospective cohort, pilot-tested questionnaire	national physical fitness conferences	173		high-intensity (n=18) long-duration (n=37) <i>above groups not mutually exclusive</i>	moderate- or low-intensity medium- or short-duration	more CS among exposed

Summary of Previous Literature on Cesarean/Physical Activity (PA)

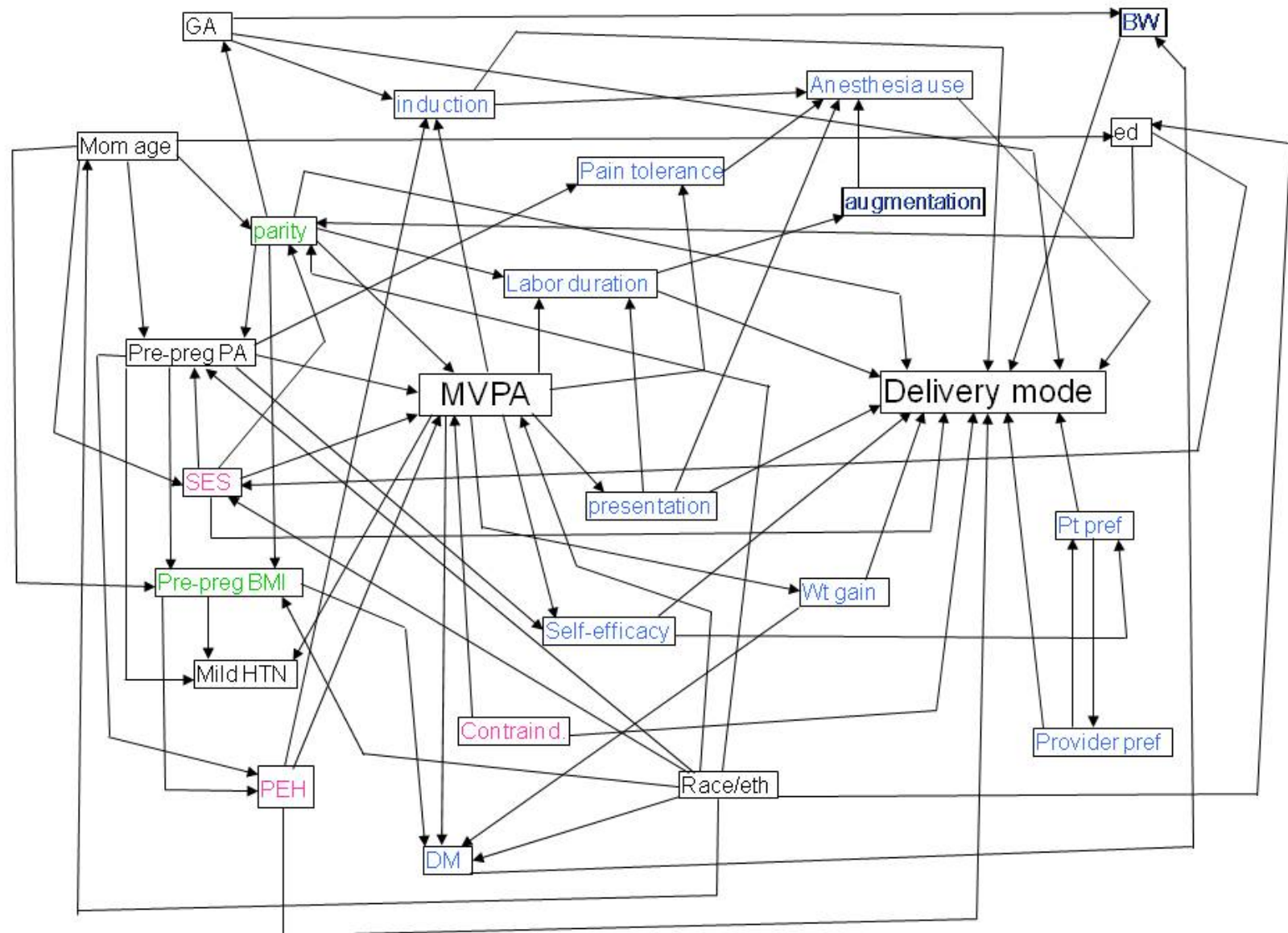
Botkin (32) and Kulpa (43) found "no difference" in cesarean rates between the exercising women and control women. In the Kardel study (42), one woman in each equally-sized group had a cesarean; in the Marquez-Sterling study (47), 3/9 exercising women and 2/6 control women (33% each) delivered via cesarean.

Three studies did not have control groups.(38,41,44) The Jarrett and Lynch studies were conducted in the U.S. and reported cesarean rates of 17% and 5.1% among active women; the U.S. cesarean rates for those years were 22% and 20%, respectively. Erdelyi reported that 2.19% of his 172 athlete-patients delivered abdominally, while the national average in Hungary at that time was 4.1%. Though the women participating in these studies are almost certainly not representative of the American or Hungarian childbearing populations as a whole, the numbers lend some credence to the hypothesis that physical activity during pregnancy is associated with reduced cesarean delivery rates.

Eight studies report that women who were active vs. sedentary, or women who exercised more rather than less, were *less* likely to deliver via cesarean. Bungum (34) reported an odds ratio of 4.48 (95% CL: 1.23-16.23, $p = 0.02$) for cesarean delivery if a woman was sedentary during pregnancy, controlling for age, weight gain, epidural use, place of delivery, induction, labor duration, and pre-gravid exercise. Confounder control is important; however based on the causal diagram shown in Figure 2.2, Bungum et. al. may well have controlled for variables on causal pathways, and thus their reported result may be biased. In the Clapp study (35), 6% of women who continued exercising at pregravid levels delivered via cesarean, compared to 30% of women who did not, chi-square $p = 0.01$. In the Collings study (36), 2 control women had cesareans but no exercising women did (Fisher's exact test $p = 0.2$). Hall and colleagues (39) report that

28% of controls, 23% of low-level exercisers, 10% of medium-level exercisers, and 7% of high-level exercisers delivered by cesarean (p for trend < 0.001). In the Horns study (40), 32% of sedentary women had cesareans compared to 25% of active women (p = 0.6). Baciuk et. al. reported 36% cesareans in the 34 women randomized to water aerobics and 46% in the 37 women randomized to the non-exercising group (X^2 p = 0.6).(30) However, this study was small and randomization did not work well; the control group had both more nulliparous women and more women with a history of cesarean delivery, either of which could explain the discrepancy in cesarean rates between the groups. Melzer et. al. reported an odds ratio of 7.65 (95% CI 1.27-45.84, adjusted for parity, gestational weight gain, and birth weight), indicating that active women in their sample had fewer cesarean births.(48) Finally, Bovbjerg et. al. reported fewer cesareans among women reporting at least one 30-minute exercise session per week during the last 3 months of the most recent pregnancy, compared to those reporting less than 1 such session per week (OR 0.65 [0.38, 1.13] for 1-4/week, 0.62 [0.29, 1.33] for ≥ 5 /week, compared to <1/week; adjusted for gestational age, parity, and hypertensive disorders of pregnancy), but among women delivering preterm only.(33) Given the text of the question used in the Bovbjerg study (exercise during the last 3 months), it is unclear whether preterm births themselves, or merely the timing of the exercise in relation to the gestational age of the fetus, is driving this association.

Figure 2.2 (on next page): Directed Acyclic Graph showing the causal relationships between minutes of moderate to vigorous physical activity (MVPA) and delivery mode. Abbreviations: GA, gestational age; SES, socio-economic status; DM, diabetes mellitus (pre-existing or gestational); PEH, pre-eclampsia, eclampsia, HELLP syndrome; Pt pref, patient preferences for labor and delivery; ed, education; BW, birth weight, contraind, contraindications to activity during pregnancy, includes incompetent cervix, 3rd trimester bleeding, placenta previa or abruption, and undelivered preterm labor; mild HTN, mild hypertension, includes chronic and pregnancy-induced hypertension; pre-preg PA, amount of physical activity prior to the index pregnancy. The double arrows between Pt pref and provider pref indicates uncertainty in the direction of the association; the DAG was analyzed with each arrow separately and the results did not change. Variables in blue are on causal pathways; variables in pink and green represent a minimally-sufficient adjustment set.



Four studies report that women who are active vs. sedentary, or who are more active vs. less active, are *more* likely to deliver via cesarean. In the Dale study (37), 15% of runners and 11% of controls delivered via cesarean (Fisher's exact test, $p = 0.9$). In Magann (1996) (45), primiparous women in group 5 (who expended the most energy) had more urgent/emergent cesareans than did women in other groups, though these subgroups analyses were performed *post hoc*. In Magann (2002) (46), 15% of women in group 1 (the least active women), 13% of women in group 2, 15% of women in group 3, and 22% of women in group 4 had cesareans. This increase for group 4 was not statistically significant, and was driven by an increase in urgent/emergent operations. In the Zeanah study, women in the low- and moderate-intensity groups had fewer cesareans than did women in the high-intensity group, $p < 0.05$.(52)

The Narendren study reported mixed results. Women in the yoga group had more elective cesareans than did those women in the walking group (22% vs. 16%, $p = 0.4$) but fewer urgent/emergent cesareans (23% vs. 33%, $p = 0.2$). (49)

Finally, Beckmann et. al. reported the results of combined forceps/cesarean deliveries compared to spontaneous vaginal deliveries.(31) The exercising group had 5/50 operative deliveries, whereas the non-exercising group had 22/50 (Fisher's exact test $p = 0.002$; the paper reports the result of a chi-square test).

To summarize the cesarean results, which are too heterogeneous for formal meta-analysis, the studies indicate that physical activity during pregnancy may decrease a woman's risk of delivering by cesarean. Half of the papers reporting this association were statistically significant, despite smaller average sample sizes; the papers (especially the 2 Magann studies) showing a trend towards a detrimental effect of exercise tended not to be significant and yet had large samples. Additionally, the three

studies without control groups add a bit of weight to the argument, with the caveat that the question is far from resolved.

Physical Activity During Pregnancy and Induction of Labor

The *Listening to Mothers II* survey estimated that 41% of women in the US currently have their labors induced.(53) This is of concern from a public health perspective because while induction is a necessary intervention in some scenarios, it carries risks for both mother and baby, including increased risk of uterine hyperstimulation (which in turn can lead to fetal distress or non-reassuring fetal heart rate, fetal acidosis, meconium aspiration, postpartum hemorrhage, and uterine rupture), placental abruption, uterine infection, respiratory distress/transient tachypnea of the newborn, operative delivery, lacerations, and maternal hypotension; increased use of regional anesthesia because augmented contractions are more painful; increased neonatal intensive care unit (NICU) admissions; longer labor duration, and possible gastrointestinal side effects or fever if prostaglandins are used.(54-58) One also runs the risk of iatrogenic prematurity.(59) Inductions cost between 15-20% more than do deliveries subsequent to spontaneous labor.(60)

The systematic review of the literature described above found five studies reporting an association between physical activity during pregnancy and induction of labor. Unfortunately only one of the 5 studies reporting associations between prenatal physical activity and labor induction specified indication for induction: Lynch et.al. report that 1 of 23 women in the intervention group was induced at 34 weeks' gestation for pre-eclampsia.(44) However, as the Lynch study did not include a control group, it is difficult to interpret this number. The Bungum study specified that there were no differences between groups for "other medications"—a category which may or may not include pharmacologic induction.(34)

Results vary across the remaining 3 studies. Clapp et. al. report that 13% of women continuing pre-pregnancy training were induced compared to 14% of controls, a non-significant difference.(35) The Magann (1996) study reported that there were more inductions in group 5 (who expended the most energy per day), $p = 0.04$.(45) The other Magann (2002) study reported RR 1.84 (95% CL: 1.05, 3.20) for requiring induction if a woman was more active (46); however this calculation cannot be replicated using numbers reported in the paper. From Table 3 in the Magann paper, 8% of women were induced in group 1 (the group engaging in the least amount of activity), 14% in group 2, 13% in group 3, and 15% in group 4, $\chi^2_3 = 6.2$, $p = 0.10$, suggesting that perhaps being somewhat sedentary is associated with lower risk of induction but there is a low threshold for activity above which a woman's risk increases but not in a dose-response fashion.

The data reported in the literature for an association between physical activity during pregnancy and labor induction are sparse and inconclusive, though currently they trend towards a higher risk of induction if a woman is physically active during pregnancy. If indeed physically active women are less likely to experience spontaneous onset of labor, it is unclear what the clinical and public health implications would be. Risks from more inductions may be offset by known benefits of physical activity, but this would be a difficult issue to settle. At the least, results would have patient counseling implications.

Physical Activity During Pregnancy and Labor Duration

Duration of labor has important consequences for patients. Labor duration is strongly associated not only with the use of medical interventions (which themselves may be important patient-oriented outcomes, such as episiotomy or operative delivery) but also with patient satisfaction.(61-64) Labor duration is also associated with neonatal outcomes such as Apgar scores and NICU admissions.(63) Duration of labor also has billing, staffing, and patient volume implications for clinicians and hospitals.

The systematic review of the literature described above found sixteen studies that reported associations between duration of labor and physical activity during pregnancy.(30-32,34-36,38-40,43,45-46,48,50-51,65) It is difficult to synthesize the results of these studies because of markedly different outcomes (duration of 1st stage, total duration of labor, etc) and varying definitions within a single outcome (does the second stage start at full dilatation or with pushing? does it end with birth of the baby or with cutting the cord? does total labor duration include stage 3 or not?). A summary of results is shown table 2.2.

Table 2.2: Summary of labor duration studies. Data are mean \pm SD unless otherwise noted; if definition of labor duration is not specified, or if exact numbers are not given, none were stated in the paper.

	significantly shorter among active women	NS shorter	no difference	NS longer	significantly longer
Stage 1 (hours)	Clapp ^{1,2} : 3.72 \pm 2.23 vs. 5.03 \pm 3.18, p = 0.01	Horns: 11.5 \pm 5.8 vs. 12.6 \pm 10.3 Rice: 6.1 \pm 2.3 vs. 6.7 \pm 3.1, t-test p = 0.2	Botkin	Collings: 9.2 \pm 4.3 vs. 7.2 \pm 2.5 Penttinen: 10.43 \pm 5.53 (range 1.67-27.0) vs. 9.6 \pm 5.37 (range 0.67-26.25)	Magann(1996): primiparous women who expended the most energy had longer stage 1 labors: median 7.4 hours vs. 6.0-6.5 hours for other groups, controls for maternal age
Stage 2 (minutes)	Botkin ³ : 27 \pm 20 vs. 59 \pm 48, t-test p = 0.004	Horns ⁶ : 120 \pm 186 vs. 132 \pm 252 Kulpa ⁷	Hall ⁹ Penttinen: 27.9 \pm 17.8 (range 4-62) vs. 27.8 \pm 27.2 (range 5/125)	Collings: 46.6 \pm 35.7 vs. 41.7 \pm 41.3 Rice ¹⁰ : 38.2 \pm 32.8 vs. 19.9 \pm 10.3, p = 0.09	
Stage 3 (minutes)			Botkin		
Total (hours)	Clapp ^{2,4} : 4.40 \pm 2.48 vs. 6.37 \pm 4.58, p = 0.01 Pomerance ⁵ : higher physical fitness associated with shorter labor duration, R = -0.65, p = 0.04	Erdelyi ⁸ Horns: 13.4 \pm 6.6 vs. 14.6 \pm 10.6	Baciuk Botkin Bungum Hall ⁹	Kardel ¹¹ : 9.4 \pm 5.9 vs. 6.7 \pm 5.5 ¹² ; 11.7 \pm 3.4 vs. 8.0 \pm 2.6 ¹³	Magann (2002): RR for most active group vs. least active group 1.38 (95% CL: 1.16-2.60)

¹ 4 cm to 10 cm; ² explicitly limited to women delivering vaginally; ³ complete dilation to birth of the baby; ⁴ stage 1 + stage 2; no definition given for end of stage 2 among multiparas only; ⁶ these seem unusually long—perhaps this includes stage 3? unclear from the paper

⁷ "The primigravid group in the exercise group appeared to have a shortened active phase in the second stage of labor when compared with the primigravid women in the control group. No differences were seen for multiparas." No numbers were reported. It is unclear to which stage of labor this is referring—active labor (i.e. mid- to late stage 1) or stage 2.

⁸ Erdelyi reports that 150 of the 172 athletes under his care "delivered their babies faster than the established average." He also mentions that stage 2 lasted about half the duration as expected from non-athletes. No explicit comparison group.

⁹ Primiparas only, because parity not evenly distributed among the groups

¹⁰ Based on 18 vaginal deliveries; would be significant if not underpowered

¹¹ stage 1 + stage 2, defined as contractions 5 minutes apart until birth of the baby

¹² spontaneous deliveries only; ¹³ operative vaginal deliveries

In summary, some studies report longer total labors, stage 1, or stage 2 labors in exercising women; others report shorter labors. Many report no significant differences, though in many cases power is an issue. Only 4 studies report differences separately for primiparous vs. multiparous women (39,43,45,51), and for the latter 2 of those it appears to be an unplanned *post hoc* comparison. Controlling for primiparity should be automatic when reporting labor duration results, as the course of labor is so markedly different for these women. Only 2 studies explicitly limit the population to women delivering vaginally—presumably all studies did this, but this is uncertain.(35,42)

It is difficult to synthesize these results because of heterogeneity of exposures, outcomes, and reporting methods; however when taken as a whole there does not seem to be a consensus of the relation between PA during pregnancy and labor duration. Studies to date have not used rigorous PA ascertainment methods or standardized labor duration definitions; many have also been underpowered and none used appropriate statistical techniques (though as discussed above, a few controlled for parity or operative vaginal delivery (OVD)—though OVD is inappropriate to include as a confounder).

Physical Activity During Pregnancy and Labor Augmentation

Augmentation of labor is closely tied to labor duration; conceivably if women who are more active have either shorter or longer labors then use of labor augmentation for these women would also vary. It is also possible that physical activity during pregnancy may be related to labor augmentation directly, if an active woman's body works more efficiently.

Labor augmentation, though often required and used successfully to avoid operative deliveries (and their sequelae) resulting from poor progress or maternal fatigue, is associated with a number of adverse outcomes for both the mother and the

baby, and therefore should be used judiciously in clinical practice.(66) Adverse outcomes associated with labor augmentation include increased risk of uterine hyperstimulation (which in turn can lead to fetal distress or non-reassuring fetal heart rate tones, fetal acidosis, meconium aspiration, postpartum hemorrhage, and uterine rupture), placental abruption, uterine infection, respiratory distress/transient tachypnea of the newborn, operative delivery, lacerations, and maternal hypotension; increased use of regional anesthesia because augmented contractions are more painful; increased NICU admissions; and longer labor duration.(54-58) Some of these associations are the result of the augmentation itself (hyperstimulation, increased epidural use), some (labor duration, operative delivery) are probably confounded by upstream factors such as dystocia. In some cases the causal relationship may be unclear; for example the increase in perineal lacerations may be secondary to increased vaginal operative deliveries or it may be that oxytocin during the second stage causes the baby to be born so quickly that the perineal tissue does not have a chance to stretch.

The systematic review of the literature described above found three studies that report an association between physical activity during pregnancy and labor augmentation, and one additional study that may report such an association. Beckmann et. al. reported that 2/50 women attending prenatal exercise classes required labor augmentation compared with 8/50 women not attending such classes (Fisher's exact test $p = 0.09$; paper reports a chi-square test).(31) The Clapp study reports that 13% of women who continued pre-gravid levels of training required labor augmentation compared to 20% of women who did not ($p = 0.01$). (35) The Magann (2002) study in Active Duty Navy women reports that women who were in the highest of 4 levels of prenatal exercise were more likely to require oxytocin for induction or augmentation than were women in the lowest level of prenatal exercise (RR 1.53, 95% CL: 1.19, 1.97).(46)

Finally, in the research presented by Bungum et. al., "No significant differences were found between active and sedentary women for the use of epidural anesthesia, other medications..." (p. 261).(34) It is unclear from the text whether or not this category of "other medications" might include oxytocin, or whether it merely includes other forms of analgesia.

In summary, consensus has not been reached regarding PA during pregnancy and need for labor augmentation. Previous efforts have been hampered partly by their non-generalizeable study populations and poor exposure ascertainment (see Table 2-1), but also by the lack of appropriate confounder control. None of the studies presented in this section conducted any adjusted analyses for this association.

Physical Activity During Pregnancy and Operative Vaginal Delivery

Vaginal operative deliveries (OVD), though associated with less overall maternal morbidity than cesarean deliveries, are nonetheless associated with increased risks of perineal laceration, episiotomy, anal sphincter injury, neonatal trauma, maternal hemorrhage, urinary incontinence, and cervical laceration when compared with spontaneous vaginal deliveries.(67-75) They are also associated with lower APGAR scores and increased need for neonatal resuscitation.(69,72) Some risk factors for OVD are not modifiable, or not easily modifiable: parity, fetal gender, and fetal presentation.(75-77) However, several modifiable risk factors are known, including labor duration, epidural use, birth weight, and maternal overweight or obesity (63,76-79)—each of which may in turn be affected by physical activity during pregnancy. Increasing women's physical activity during pregnancy could have an impact on rates of OVD, thus reducing maternal and neonatal morbidity.

The systematic review of the literature described above found eleven studies reporting an association between PA during pregnancy and OVD.(31-32,34-35,37-38,42-

43,45-46,50) Of these, nine present results for spontaneous vaginal vs. operative vaginal, one reports results for cesarean/operative vaginal vs. spontaneous vaginal, and one reports use of "obstetric interventions," a category which includes use of forceps. These studies are summarized in Table 2.1.

Both Bungum (34) and Kulpa (43) report "no significant differences"; Erdelyi (38) reports that the athletes under his care had a forceps delivery rate of 6.0%, which is nearly identical to the 6.1% reported in Hungary as a whole at that time. As mentioned above in the discussion on cesarean delivery, Beckmann et. al. (31) reported the results of combined forceps/cesarean compared to spontaneous vaginal deliveries. The exercising group had 5/50 operative deliveries, whereas the non-exercising group had 22/50 ($p = 0.002$). Botkin et. al. reported that 19/25 (76%) non-exercising and 8/19 (42%) exercising women ($p = 0.06$) had an "obstetric intervention", a category which included forceps, oxygen resuscitation, or use of a fetal monitor.(32)

Clapp et. al. reported OVDs at the rate of 9/31 (29%) in the women who reduced their exercise as pregnancy progressed, and 5/82 (6%) in the women who continued exercising at their pre-conception levels ($p = 0.003$). (35) Dale reported 5/10 (50%) operative vaginal deliveries in controls and 8/28 (29%) in runners ($p = 0.26$). (37) Kardel found 3/20 operative vaginal deliveries in the medium-intensity group, and 2/20 in the high-intensity group ($p = 0.9$). (42) Penttinen found 8% vaginal operative deliveries in the exposure group and 11% in the control group, a non-significant difference. (50)

Magann (1996) found fewer operative vaginal deliveries only among multiparous group 1 women (who expended the least amount of energy per day). (45) In the Magann (2002) study, 16% of women in group 1 (who were the least active) had forceps or

vacuum extraction, compared to 19% in group 2, 22% in group 3, and 17% in group 4 ($p = 0.6$ for trend).(46)

It is difficult to draw firm conclusions about the relationship, if any, between physical activity during pregnancy and OVD based on currently-published studies.

Physical Activity During Pregnancy, Episiotomy, and Perineal Lacerations

Episiotomy and perineal lacerations are important patient-oriented outcomes of delivery. Sequelae to episiotomy include increased risks of maternal hemorrhage, infection, antibiotic use, anal sphincter injury, severe perineal laceration, and neonatal trauma; decreased patient satisfaction; and longer durations of both catheter use and hospital stay.(67,80-81) Increasing severity of perineal laceration is associated with increased maternal hemorrhage, infection, urinary incontinence, fecal incontinence, dyspareunia, rectovaginal fistula, and pain; and decreased pelvic floor muscle strength and sexual functioning postpartum.(67,73,82-83) Interventions with the potential to reduce rates of episiotomy and laceration would be of great interest to patients, and also of interest to payers, clinicians, and patients' families.

The systematic review of the literature described above revealed three studies that reported associations between physical activity and perineal lacerations and two studies that reported associations between episiotomy use and physical activity during pregnancy; characteristics of these studies are presented in Table 2.1.

Bungum reported no significant differences in episiotomy between women who had exercised throughout their pregnancies and those who hadn't; exact numbers were not reported.(34) Clapp et. al. reported that 38/82 (46%) women who maintained a high level of activity during pregnancy had episiotomy compared to 25/31 (81%) women who did not.(35) Firm conclusions about such associations cannot be drawn merely from

these studies, especially given the practice trend towards decreased routine episiotomy use since they were conducted.(84)

For perineal lacerations, the Kulpa study reported no differences between groups, but with no further details.(43) The Penttinen study reported no "vaginal or perineal ruptures" in either group.(50) The Magann (2002) study classified active duty Naval women into 4 groups based on voluntary and mandatory activity; group 1 had the least amount of total activity during pregnancy and group 4 had the most.(46) There were no differences in severity of lacerations across these 4 groups, $\chi^2_6 = 6.6$, $p = 0.4$. At this time, one cannot say for certain whether or not physical activity during pregnancy is associated with perineal lacerations.

Summary

Research on maternal birth outcomes following PA during pregnancy is plentiful for some outcomes (delivery mode, labor duration) and sparse for others (episiotomy, lacerations, induction, augmentation). This literature suffers from small non-population-based samples, retrospective exposure ascertainment, poor outcome characterization, and little or no confounder control. At this point it is unclear what associations, if any, exist between physical activity during pregnancy and these maternal birth outcomes. If causal, these would be complex relationships—perhaps the most important methodologic improvement that could be made in future studies is appropriate confounder control.

From a public health perspective, if PA during pregnancy were indeed associated with fewer adverse maternal birth outcomes, then encouraging women, especially pregnant women, to be physically active would represent a low-risk, low-cost potential intervention that could conceivably reduce not only maternal and fetal/neonatal morbidity but also health care costs. If, on the other hand, physical activity during pregnancy were

associated with more adverse maternal birth outcomes, the public health implications would be less clear. Perhaps the increase in adverse birth outcomes would be "worth it," given the many known benefits of physical activity, both in general and during pregnancy—but perhaps it would not. In this scenario, it may be more of an individual choice, with each pregnant woman weighing the pros and cons herself or in conjunction with her health care provider—in which case results of research on this topic would have important patient counseling implications. Either way, resolving the uncertainty surrounding the relationship between physical activity during pregnancy and maternal birth outcomes via well-designed, appropriately-analyzed studies is a wise use of limited research resources.

RESEARCH DESIGN AND METHODS

The vast majority of the methods are detailed in the two papers resulting from this dissertation project, which can be found in later chapters. Here the basic methods are reiterated and the logic behind the methods decisions is discussed.

This study was a secondary data analysis of a pregnancy cohort study, designed to assess the associations, if any, between physical activity (PA) during pregnancy and maternal birth outcomes such as delivery mode, episiotomy, perineal lacerations, labor duration, induction, and augmentation. Exposure data came from the third Pregnancy, Infection, and Nutrition (PIN3) cohort, and included detailed 7-day PA recalls during two windows in pregnancy: the first at 17-22 weeks, the second at 27-30 weeks. The bulk of the outcomes data came from a clinical database kept by the Obstetrics department at UNC, which is populated from medical records.

Paper 1 explored the association between maternal PA and cesarean delivery, among women without a history of cesarean. One objective of this paper was to determine if in fact PA predicts cesarean birth, but the other was to explore the characteristics of the association, if any: was there a dose-reponse relationship? If yes, was it linear? Did the association change depending on gestational age at time of exposure? To address these questions analytic methods new to this topic area were used (made possible by the excellent and extremely detailed PA data available in the PIN3 dataset). These included leaving PA exposure data continuous, allowing it to

depart from linearity in the log risk as necessary to ensure adequate model fit, and using data from the two time points separately.

Restricted cubic splines were used for all non-linear models. This method was chosen over other ways of relaxing the linearity assumption (namely polynomials) for four reasons. First, polynomials require the model to be fit with all lower-order terms included—i.e. if adding a quadratic term, the non-squared exposure term must be included as well. As one would expect, these terms are collinear, which can lead to instability in the predicted estimates. Second, spline terms are able to capture function shapes which are not exact polynomials. With no previous studies using continuous exposure data, no prior guess as to the shape of an association was available. Third, restricted splines are so-named because they are restricted to be linear in the tails (outside of the outermost knots). This decreases the influence of data points at the extremes of exposure, though in this case it did not work perfectly (see Paper 1). Lastly, restricted splines generally use fewer degrees of freedom than their corresponding polynomial term.

Biostatisticians agree that when using restricted splines, the important parameter is the number of knots, with results being much less dependent on knot location.⁽⁸⁵⁾ Common advice is to use four knots, preferably five should the sample size be adequate ($n=400$ or so). However, as mentioned in Paper 1, using either five or four knots with these data resulted in overfitting in the exposure ranges of 0-5 hours/week, presumably because this is where the bulk of the data lie. It seemed highly implausible that the risk of cesarean truly increased, then decreased, then increased, then decreased again, all within the 0-5 hours/week span—using 3 knots solved this problem, and biologically-plausible smoother curves resulted. For knot location, given that location is of

secondary importance, evenly-spaced percentiles were used, as recommended by a prominent text on the subject.(85)

Models were built using a backwards step-wise variable selection process, selecting covariables for retention using a model fit criterion based on Analysis of Deviance. Deviance is equivalent to two times the log likelihood; the software used for this project happens to report deviance and not the log likelihood, but conclusions would be identical from either method. A change-in-estimate criterion was not employed because many PA exposures were expected to be non-linearly related to the outcomes. Effect estimates in such cases have less meaning, being so highly dependent on exactly which two exposure levels one compares.(86)

Paper 2 explored labor patterns for women accumulating varying amounts of PA. The methods used in Paper 2 built on the conclusions from Paper 1. First, in Paper 1 results sometimes varied depending on which exposure time point was used, 17-22 weeks vs. 27-30, implying a potential effect of gestational age (GA) at time of exposure ascertainment. However, including more finely-measured GA at time of exposure (i.e. GA in days at time of the telephone interview) did not improve the fit of any of the models in Paper 1, and therefore it was not included in Paper 2.

Likewise, Paper 1 explored whether or not PA at 17-22 weeks should be included as a covariable in models using PA at 27-30 weeks as the main exposure. This was intended to isolate the effects of activity at the second time point, though collinearity was a potential threat to validity. However, in no case did including the earlier estimate of PA improve model fit, and so this exercise was not repeated for Paper 2. Analysis elements from Paper 1 which were carried over included allowing for non-linear effects and dropping women reporting volumes of PA in the upper 2.5% of a given exposure. The

proposal discussed looking at indication for induction; however, given the poor data quality for indication for cesarean (see Paper 1), this aspect of the analysis was not pursued.

Missing data was a problem for the data set used in Paper 2; three variables were missing more than 5% of the data. Multiple imputation was used to address this concern. The imputed data sets were generated using the `aregImpute()` function in the `Hmisc` library for `S-Plus` (87), using 3 burn-in repeats followed by 10 iterations that were then used as the imputed data sets. The model which generated the imputed data included all exposure and outcome variables, race, marital status, maternal age, maternal education, percent poverty, pre-gravid BMI, gestational diabetes, chronic hypertension, pre-existing diabetes, Bishop's score on admission, parity, pre-conception PA, PA during the first trimester, history of OVD, contraindications to PA during pregnancy, gestational age at birth, and birthweight. For all subsequent analyses, models were fit using the `fit.mult.imput()` function (also from `Hmisc`); this function fits each model 10 times, once with each of the imputed data sets, averages the coefficients, and reports standard errors inflated to account for multiple model fittings.

One topic unique to Paper 2 is the decision to limit the sample to women who had a vaginal birth. For some outcomes, such as operative vaginal delivery (OVD), episiotomy, and laceration severity, restricting to women who had a vaginal birth is obviously the correct choice. For labor duration, however, arguably one could also include women who had a cesarean birth. After much thought, they were not included, for three reasons. First, it was unclear whether their labor durations should be right-censored or not. On the one hand, if a woman is laboring at 6 cm, and her membranes rupture and her cord prolapses, leading to a cesarean, then she did not experience the whole of labor, and so her duration should be right-censored. But on the other hand, the

"end" of labor is defined in all obstetrics and midwifery texts as either "birth of the baby" or "birth of the placenta"—both of which occur during cesarean delivery. So in that case the 6 cm woman's labor duration should NOT be right-censored. Which is it? One can easily argue either way, and neither, perhaps, is entirely correct.

The second reason labors ending in cesarean were not included is that even more so than vaginal births, cesarean births are a heterogeneous group. If the woman described above had five hours of labor before her cesarean at 6 cm, can she really be grouped with a woman who got to 10 cm and had a vaginal birth, all within five hours? Otherwise, can she be grouped legitimately with a woman who had 22 hours of labor, including 4 hours of pushing, and a cesarean at the end for maternal exhaustion? Whether censored or not, one or the other of these comparisons would be made, and again, neither is quite correct.

Finally, the public health/patient education message to be gleaned is unclear. Suppose that, among labors destined to end in cesarean, women reporting more hours/week of PA had shorter labors than those reporting fewer hours. What, then, to do with this information? At this time we are entirely unable to predict which labors will end in cesarean, so having ready advice on how to behave during pregnancy for those women is moot.

In Paper 2, the proportional odds model was used to examine PA and laceration severity. In the graphical results for that outcome, the odds of at least mild severity were subtracted from the odds of at least severe to obtain the odds of mild alone. This was not detailed in the methods section of that paper, given that the target audience is clinicians. Additionally, because the proportional odds model was used for laceration severity, logistic regression was used for all dichotomous outcomes in Paper 2.

Binomial regression would have been a better choice for most of the outcomes, given that they were relatively common, but the results are much clearer if they always refer to odds and odds ratios (OR) when discussing models, rather than ORs in some cases and risk ratios in others.

PAPER 1

Physical Activity During Pregnancy and Cesarean Birth

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Abstract

Background: Studies of physical activity during pregnancy and cesarean birth report inconsistent results. *Methods:* Physical activity data were collected from 1205 North Carolina pregnant women without prior cesarean, between 2001-2005. Data were collected via 7-day recalls, at 17-22 weeks' and 27-30 weeks' completed gestation, and included recreational, occupational, transportation, care-giving, and indoor/outdoor household activities. Outcome data are from medical records. We analyzed physical activity as a continuous variable using binomial regression. Multivariable models controlled for primiparity, contraindications to exercise during pregnancy, pre-eclampsia, BMI, and percent poverty. *Results:* In unadjusted analyses, physical activity during pregnancy is associated with cesarean if all intensities of activity are included, but not if exposure is limited to moderate /vigorous activity. This association is non-linear and reverses direction when one considers exposure at 17-22 weeks versus 27-30 weeks. However, the strong unadjusted effect is largely attenuated when controlling for confounders, when exposure is limited to recreational activity only, or when women reporting volumes of activity in the upper 2.5% are dropped. This pattern of results suggests that the association may be spurious secondary to residual or unmeasured confounding. *Conclusions:* There is no overall association between physical activity and cesarean birth. Future studies using maternal physical activity as an exposure should treat it as a continuous variable, allow it to depart from linearity at least in preliminary analyses, and give careful consideration to all potential confounders, including gestational age at time of exposure.

Introduction

Cesarean rates have risen dramatically in the U.S., and are currently over 32%.⁽⁸⁸⁾ Cesareans, though sometimes life-saving procedures, are not risk-free. Interventions which reduce the cesarean rate could improve both neonatal and maternal outcomes as well as control costs.^(12,16,19)

One proposed intervention is physical activity (PA) during pregnancy, the theory being that an active woman is better able to withstand the rigors of labor and birth. Twenty-two previous studies examined the association between PA or exercise during pregnancy and risk of cesarean.^(30-49,51-52) Effect estimates are not consistent across studies, with results split among those showing no effect ^(32-33,42-43,47), an increased risk ^(37,45-46,49,52), and a decreased risk ^(30-31,33-36,38-41,44,48-49,51) of cesarean with higher levels of PA or exercise.

Several methodological issues arise when examining the body of work on this issue, including small samples, varying exposure definitions, inadequate methods for ascertaining exposure, questionable generalizeability, and inadequate statistical methods. Only three studies conducted multivariable analysis ^(33-34,48), all 22 categorized the exposure, and only one explicitly accounted for timing of activity in relation to gestational age of the fetus.⁽³³⁾

This study had two objectives. The first was to explore the associations between maternal PA and cesarean risk, noting the shape of a possible dose-response curve and timing of PA in relation to gestational age. The second was to conduct a rigorous multivariable analysis, based on results from the first objective.

Methods

The aims were addressed by merging two data sources. The first was the third Pregnancy, Infection, and Nutrition (PIN3) cohort, an ongoing study of pregnancy in central North Carolina that provided PA exposure data. The PIN3 Study recruited women, January 2001 through June 2005, from prenatal clinics affiliated with the University of North Carolina (UNC) Hospitals. Women were eligible if they presented for antenatal care before 20 weeks' gestation, intended to deliver at a UNC hospital, were carrying a singleton fetus, were ≥ 16 years old, read and spoke English, and had access to a telephone. Complete details about the data collection protocols can be found at the PIN3 website (http://www.cpc.unc.edu/pin/design_pin3.html).

The PIN3 Study collected 7-day PA recalls by telephone interview at 17-22 weeks' and 27-30 weeks' gestation. These detailed interviews collected information about occupational, recreational, indoor and outdoor household, care giving, and transportation activities. Women were asked to list the specific activities, the frequency and average duration for each, and to rate the intensity of the activity as "fairly light," "somewhat hard," or "hard or very hard." Expert review of selected taped interviews ensured consistency among interviewers. The entire questionnaire, along with evidence demonstrating reliability and validity in pregnant women, is available elsewhere.⁽⁸⁹⁾

Based on the recall data, women were assigned values for total hours/week of PA, and hours per week of moderate-to-vigorous PA (MVPA—anything rated as at least "somewhat hard"). These calculations were conducted separately for each recall, and also for recreational activity only.

PA data were examined for outliers. Paper records for women who reported more than 21 hours/week for a given activity, women who reported more than 70

hours/week of total PA (or more than 40 hours of MVPA), and women whose average duration for a given bout of PA exceeded 1 hour were reviewed. Data entry errors were corrected, and unreasonable values were set to missing.

The second data source, which provided outcomes data, was the Perinatal Database maintained by the UNC Hospitals Department of Obstetrics and Gynecology. Data were collected by labor and delivery (L&D) nurses, who review medical records for all admitted women and fill out a 12-page Perinatal Record form containing information on demographics, obstetrical history, prenatal care, comorbidities, assessment on admission to L&D, the course of labor, and any complications arising during L&D. Monthly validity checks allow correction of impossible or inconsistent values.

The outcome for this paper was primary cesarean birth. We considered a woman to have a cesarean delivery if her delivery mode was recorded as primary planned cesarean or primary emergent/urgent cesarean. Though we did not address reliability or validity of the outcome for this study, delivery mode is typically accurately and prominently recorded in medical records because of patient care needs, liability concerns, and billing requirements.

These data sources were merged on mother's medical record number and baby's date of birth. Following electronic merge, additional matches were made by hand. 3203 women were eligible for PIN3; of these 2006 agreed to participate (63%). Of the 2006, 2% became ineligible (4 multiple pregnancies, 43 pregnancy losses), 9% were lost to follow-up (126 did not complete any questionnaires or interviews; 48 asked to be dropped later in the study), and 121 (7%) were participating for the second or third time, leaving 1654 participants. Of these, 1488 (90%) were successfully merged with the Perinatal Database. For this analysis, all women with previous cesarean deliveries

(n=282) were excluded because the repeat cesarean rate was over 95%. Finally, we excluded one woman with extreme PA values, leaving 1205 women. Both this project and the PIN protocols were approved by the Institutional Review Board (IRB) at UNC; this project was also approved by the IRB at Oregon State University. Women gave written informed consent to participate in PIN.

Covariables

Women self-reported their race, marital status, education, and household information, including income, number of adults, and number of children. From these data one can calculate the percent of the 2001 poverty level (90): a score of 100 indicated a household living exactly at the poverty line.

Women were asked about previous pregnancies, including both live births and still births, which were combined to define parity. Parity was collapsed into primiparous vs. multiparous, as there is a clear difference in labor pattern and outcome between these two groups, but fewer differences are observed between higher order labors. Maternal height was measured by study staff; pre-gravid weight was self-reported. Pre-gravid body mass index (BMI) was calculated from these values. Gestational age (GA) at birth was estimated using ultrasonography if the test was performed prior to 22 weeks, and on date of last menstrual period otherwise. Birthweight was abstracted from the medical record.

Information about pregnancy complications came from the Perinatal Database. Complications considered as covariables were contraindications to exercise during pregnancy as defined by the American College of Obstetricians and Gynecologists (includes incompetent cervix, cerclage, placenta previa/abruption, undelivered

premature labor)(1) and severe hypertensive disorders of pregnancy (includes pre-eclampsia, eclampsia, and HELLP [hemolysis, elevated liver enzymes, low platelet count] syndrome).

Data analysis, objective 1

The first objective was to explore the associations between maternal PA and cesarean risk, particularly in regards to the shape of a possible dose-response curve and timing of activity in relation to GA. We used 4 different exposure measures for this objective: hours/week of total PA at 17-22 weeks and 27-30 weeks; and hours/week MVPA at 17-22 weeks and 27-30 weeks. In unadjusted binomial regression analyses, we either forced the exposure to be linear in the log risk or allowed it to depart from linearity via restricted cubic splines with 3 knots, placed at quantiles 0.10, 0.50, and 0.90.(85) We initially used 5 knots, and then 4, but both of these choices resulted in over-fitting at the lower end of PA where most of the data occurred.

Data analysis, objective 2

The second objective was to conduct a multivariable analysis of the association between maternal PA and primary cesarean risk, basing exposure assumptions on results from the first objective. We used binomial regression to account for covariables, which were chosen based on a directed acyclic graph (DAG).(91) Based on our understanding of the causal relationships involved, we *a priori* decided to include primiparity and pre-gravid BMI in the final models regardless of model testing results because these variables were likely to be strongly associated with both PA and cesarean risk. Additionally, primiparity was included in the initial models as a possible effect modifier because of the large differences between first labor and higher order

labors; however, no evidence of effect modification by parity surfaced for any of the exposures, so interaction terms were dropped. All other DAG-identified covariables were tested only as possible confounders. These included percent poverty, contraindications to exercise during pregnancy, severe hypertensive disorders of pregnancy, primiparity, GA at time of exposure ascertainment (in days), and BMI. Initial models testing exposures from the 27-30 week time point also included the corresponding exposure from 17-22 weeks as a possible confounder, and dropped women who delivered prior to 27 weeks (n=9). Exposure variables were, based on our findings from objective 1, initially entered as restricted cubic splines with 3 knots.

We then reduced the models to more parsimonious final versions via backwards stepwise selection (using a criterion of $p \leq 0.10$ on a nested analysis of deviance X^2 test), but with the caveat that all four final models should contain the same confounders. This criterion was intended to reduce type I error in model building; given that we were fitting 4 separate models, each with either 6 or 7 covariables, the chances of finding (erroneous) statistically significant contributions to model fit were increased. By requiring that all 4 final models have the same structure, we reduced the likelihood that we would adjust for a variable that was not acting as a confounder in our data but which contributed "significantly" to the fit of one of the models merely by random chance. We used analysis of deviance instead of a change in estimate criterion because we allowed the associations to be non-linear; effect estimates would therefore vary depending on chosen cutpoints.

The final assessment of model fit tested whether or not allowing the exposure to depart from linearity in the log risk contributed substantially to model fit. This was

accomplished again with nested analysis of deviance, but using a criterion of $X^2 p \leq 0.20$ for keeping the spline term.

We then re-ran the final models restricting the exposures to recreational PA only (rather than PA from all modes), using the same four exposure categories: hours/week total recreational PA at 17-22 weeks and 27-30 weeks; hours/week recreational MVPA at 17-22 weeks and 27-30 weeks. We did not repeat the entire model building process, but we did assess whether or not the spline terms were necessary. For all analyses using recreational PA as the exposure, we controlled for PA from all other modes.

Because PA data were severely right-skewed, we also ran a sensitivity analysis in which we excluded the top 2.5% of women for each of the 4 main exposures. We also explored models excluding women who reported no PA or no MVPA. All analyses were conducted using S-Plus version 8.1 for Windows (Tibco Spotfire, Inc., Palo Alto, CA), with the Hmisc and Design libraries enabled.(85,87)

Results

Demographics are shown in Table 4.1. Women in this study were largely White, married, and well-educated. Fourteen percent delivered preterm; 10% had a low birthweight baby. Women decreased total volume of PA slightly between 17-22 weeks and 27-30 weeks. Twenty-four percent had a primary cesarean birth.

Objective 1

We analyzed the data with PA as a continuous exposure, but assuming linearity in the log risk; we then allowed the exposures to depart from linearity. These unadjusted

results are shown together, with the linear effect estimate superimposed on the non-linear, in Figure 4.1.

Several trends are evident from this Figure. First, PA was highly right-skewed, with the vast majority of participants reporting levels of activity within a fairly narrow range near the lower end of the spectrum. This limits interpretation of these figures at higher levels of activity. In Figure 4.1 (and all figures in this paper), a green vertical line denotes the 90th percentile of exposure; above this line confidence limits are wide and estimates unstable. We therefore restrict firm conclusions to women reporting levels of PA below the 90th percentile. Second, for total hours/week of PA both at 17-22 weeks and 27-30 weeks (first two panels), the splined curve differs substantially from the curve estimated by assuming linearity in the log risk, implying that the linearity assumption may not be valid in these analyses. However, the linear approximation may be sufficient for exposures in this data set involving MVPA (second two panels). Third, for both exposures (total PA, MVPA) at the 17-22 week time point, the association is an inverse J-shape, whereas the trend for both exposures at the 27-30 week time point is J-shaped. This reversal of the shape at 27-30 weeks remained even when controlling for activity at the 17-22 week time point (data not shown). This inverting of direction supports the hypothesis that timing of exposure ascertainment may be important in this relationship.

Objective 2

The final adjusted models controlled for primiparity, severe hypertensive disorders, contraindications to exercise during pregnancy, percent poverty, and BMI. The exposures measuring total hours/week of PA at 17-22 weeks, and at 27-30 weeks, had models which fit best when allowing the exposure to depart from linearity in the log risk; however, consistent with the results from objective 1, the MVPA exposures at the

two time points had adequate fit with a linear term. In each of the 4 model building processes, GA (in days) at time of exposure ascertainment was removed early in the fitting process, yet direction of association consistently changed from 17-22 weeks to 27-30 weeks. The two 27-30 week exposure models initially included the corresponding exposure at 17-22 weeks, but removing the earlier exposure did not affect model fit.

Results from the final multivariable models for the four main exposures are shown in Figure 4.2 and in Table 4.2. The four graphs in Figure 4.2 show adjusted predicted risk of cesarean plotted against each of the four exposures, for a primiparous woman without severe hypertensive disorders or contraindications to exercise, and with percent poverty and BMI set at the sample median (386% 2001 poverty, 23.7 kg/m²). Table 4.2 shows the predicted maximum or minimum point on the curve (or the intercept, for MVPA exposures) for women in other strata. The shapes of the curves shown in Figure 4.2 apply to all women; the curves move up and down the y-axis depending on subgroup.

After controlling for BMI, percent poverty, severe hypertensive disorders of pregnancy, primiparity, and contraindications to exercise during pregnancy, we saw the same curve direction-change that was present in the unadjusted results shown under Objective 1. However, in adjusted analyses, MVPA was not associated with cesarean birth at either 17-22 weeks or 27-30 weeks. Hours/week total PA was not associated with cesarean birth at 17-22 weeks, but was 27-30 weeks. This association was weak when compared to the associations between the 5 covariables and the outcome. Regression coefficients, standard errors, and test statistics from the final models for the four main exposures are shown in Table 4.3.

We then restricted the exposures to recreational PA; results are shown in Figure 4.3. These associations did not reverse direction at the 27-30 week time point when compared to the 17-22 week time point. Additionally, the linear approximation provided a sufficient fit to the data for all four recreational PA exposures. The strength of association between recreational PA and cesarean is weaker than for PA from all modes. Both total recreational PA and recreational MVPA were very weakly associated with cesarean risk at 17-22 weeks (Wald χ^2 p-values 0.18 and 0.19), but not associated at 27-30 weeks (0.34 and 0.79).

Next, we repeated the analysis dropping women in the upper 2.5% for each of the four main exposures; this completely attenuated any associations between PA and cesarean (Figure 4.4). We also dropped women reporting 0 hours/week total activity, or 0 hours/week MVPA. Excluding these women did not change the results, either with or without the women in the top 2.5% (data not shown).

Discussion

Nearly two dozen previous studies have published results associating PA during pregnancy and cesarean birth; however, no consensus has been reached about the magnitude or even the direction of the association. Our results suggest that three contributing factors to the lack of consensus could be use of cutpoints in the exposure, lack of attention to GA at exposure assessment, and lack of appropriate confounder control. Based on the graphs shown in Figures 4.1 and 4.2, a modest, non-linear dose-response relationship may exist between total PA (but not MVPA) during pregnancy and primary cesarean birth, though most of the association was attenuated when controlling for pre-gravid BMI, severe hypertensive disorders of pregnancy, contraindications to exercise during pregnancy, percent poverty, and primiparity. These relationships may

vary markedly depending on GA at exposure, and in fact reversed direction between 17-22 weeks and 27-30 weeks. They are, however, weaker if exposure is limited to recreational PA, and disappear entirely if women who reported extremely large volumes of PA were dropped.

Our results suggest that, at least for preliminary analyses, researchers should not assume that PA during pregnancy is linear in the log risk (or log odds) of cesarean. Perhaps preliminary analysis would indicate that linearity is a reasonable assumption, but in some cases departures from linearity would be sufficient to require relaxation of the assumption in order to yield a valid result.

Second, researchers should consider analyzing PA as a continuous variable. Categorization schemes by definition do not retain all of the available information, and can harbor residual confounding if categories are not sufficiently homogenous. Categorizing a continuous variable can therefore adversely affect a study's internal validity.⁽⁸⁵⁾⁽⁹²⁾ Categorization could also adversely affect precision.⁽⁸⁶⁾ Furthermore, if the underlying association is non-linear, choice of cut points will affect the estimated effect measure.⁽⁸⁶⁾ Given that all 22 previous studies on this topic used categorized exposure data, then these methods issues probably explain a good deal of the variation seen among reported results.

Our graphical results showed that for some exposures, timing of exposure was an important determinant of the shape of the association between PA and cesarean. We saw the curve reverse direction when comparing 17-22 weeks vs. 27-30 weeks for some exposures; however, including exact GA (in days) at time of exposure ascertainment did not contribute to model fit in multivariable analysis. We interpret this to mean that while 20 weeks vs. 30 weeks may be important as far as physiologic effects

of PA, effects of GA are substantially smaller when comparing, say, 27 weeks to 30 weeks.

Because maternal and fetal physiologies change progressively during pregnancy, it is possible that this influence of GA is a true biological effect. In our previous work analyzing data from the Pregnancy Risk Assessment Monitoring System (PRAMS) we also found an effect of gestational age, but we could not discern whether the important piece was GA at time of exposure, or GA at birth.(33) This is because the PRAMS questionnaire asks about PA during the last 3 months of pregnancy—so for women delivering preterm this period falls earlier in gestation than for women delivering at term. It is possible that other studies will find GA to be irrelevant (as we did when limiting exposure to recreational PA); however, given that we have found a possible association of GA using two different study populations, we would recommend that future analyses using maternal PA account for GA at time of exposure ascertainment at least in preliminary analyses. Gestational age *at delivery* could be a confounder or modifier, but this is a different matter.

We found an association, when using all modes of activity, for total hours/week at 27-30 weeks, but not when exposure was limited to MVPA or for total hours/week at 17-22 weeks. Additionally, we found very weak associations when restricting exposure to recreational PA. This could explain why some previous studies have not found an association, as several of them enrolled athletes or other groups that one would expect to obtain substantial amounts of recreational MVPA. Our data could be interpreted to suggest that if light intensity activities—i.e. household chores, childcare activities, transportation, occupational PA—are not included, then an association could be missed.

An alternative explanation could be that our data have residual or unmeasured confounding.

Given the results of our sensitivity analysis—that when dropping the women reporting the most extreme upper values of PA, associations are completely attenuated—it seems more likely that residual or unmeasured confounding is the culprit, and that there is actually no overall association between maternal PA and cesarean. We believe that at least most of these upper 2.5% of women reported valid values (all impossible values were set to missing during data cleaning), but they did exert undue influence on the model fit despite our use of restricted cubic splines. This suggests that either both light intensity activities *and* large volumes of activity are important components of this association, or that confounding is present.

A different interpretation is that the true “exposure” is overall cardiovascular fitness. We did not measure fitness *per se*, we measured self-reported PA during two 7-day windows during pregnancy. It is, however, a reasonable assumption that women who report large volumes of PA during pregnancy also accumulate large volumes of PA when not pregnant—so it is possible that the upper 2.5% of women would be those who were more fit. It could be that it is this habitually-active lifestyle—and hence “fitness”—which drives the association between maternal PA and cesarean. However, this very pattern also supports the idea that there is an unmeasured confounder at work, since women who lead a more active lifestyle would also have other characteristics which may influence their birth outcomes.

Our study has several limitations. First, the PIN3 study sample was likely not generalizeable to all childbearing women in the US. Women in our study were wealthier, better educated, and more likely to be white and married; they also by definition received

early antenatal care. The extent to which these characteristics might affect any association between maternal PA and cesarean is unclear. Second, half of our exposures included all activities reported by the women as feeling "fairly light." However, the interview text asked women to report activities that "caused an increase in breathing or heart rate"; therefore, light intensity activities were likely under-reported. If reporting light intensity activities was differential by any predictor of cesarean birth, then confounding could result.

Finally, as did nearly all previous studies, we treated cesarean birth as a dichotomous outcome. Narendren (49) and Magann (45-46) both separated urgent/emergent from planned/elective cesareans, but these are still heterogeneous groups; a pregnant woman might have a cesarean birth for any one of a large number of indications. If PA is associated with cesarean, it is unlikely that all such pathways are involved. Lumping all cesareans into one global outcome variable could mask a true association, if one exists. We had planned to address this concern; however, our outcomes data come from medical records. Medical records have some known limitations, one of which is that data are selectively recorded to ensure adequate clinical care, without thought to future research projects. Thus, absence of a given condition does not imply that it was not present, merely that it was not recorded. Such errors would make results of a mediation analysis somewhat suspect.

Conclusion

In this study, we found in unadjusted analyses that PA during pregnancy was predictive of cesarean birth if all intensities are included, but not if exposure is limited to MVPA. Furthermore, this association is non-linear and reverses direction when one considers exposure at 17-22 weeks vs. 27-30 weeks. The strong unadjusted effect is

largely attenuated when controlling for percent poverty, pre-gravid BMI, contraindications to exercise during pregnancy, severe hypertensive disorders, and primiparity; when exposure is limited to recreational activity; or when women reporting volumes of activity in the upper 2.5% are dropped. The pattern of our results suggests that any associations may be spurious secondary to residual or unmeasured confounding. It is possible that there is an association for a subgroup of women, or that PA is acting through only one of the many pathways to cesarean (and thus our dichotomous outcome is masking the true association), but given our results we conclude that there is no meaningful association between maternal PA and cesarean birth. We do, however, recommend that future studies using maternal PA as an exposure analyze it as a continuous variable, allow it to depart from linearity at least in preliminary analyses, consider GA at time of exposure as a covariable, and give careful consideration to all other potential confounders.

Table 4.1. Characteristics of 1205 women from the third Pregnancy, Infection, and Nutrition cohort (PIN3) who were at risk for primary cesarean during the index pregnancy. Data collected prospectively in North Carolina between 2001-2005.

	mean	stdev ^a	median	IQR ^b
birthweight (grams)	3273	742	3311	2970-3653
gestational age (completed weeks)	38.3	2.4	39	38-70
maternal age at conception	28.5	5.7	29	24-32
% 2001 household poverty level	401	231	386	193-596
hours/week PA ^c (any intensity) reported at 17-22 weeks	7.0	8.9	4.2	1.8-8.7
hours/week PA ^d (any intensity) reported at 27-30 weeks	6.1	7.6	3.8	1.5-8.0
	n	%		
married	863	72		
Caucasian	826	69		
maternal education:				
completed at least high school	1108	92		
completed at least 4 years college	697	58		
primiparous	670	56		
preterm birth (<37 weeks)	168	14		
low birth weight (<2500 g)	118	10		
contraindication to exercise during pregnancy ^e	81	7		
pre-eclampsia	67	6		
cesarean birth	291	24		

^a standard deviation

^b interquartile range

^c physical activity

^d 12 women delivered prior to 27 weeks

^e incompetent cervix, cerclage present, undelivered preterm labor, placental abruption, complete or partial placenta previa. Third trimester bleeding was not included because the exposures were assessed prior to 30 weeks. Carrying multiples is also a contraindication in the later gestational ages but women carrying multiples were excluded from PIN3.

Table 4.2. Maximum and minimum predicted adjusted risks associated with different participant characteristics, 1205 women from the third Pregnancy, Infection, and Nutrition cohort (PIN3) who were at risk for primary cesarean during the index pregnancy. Data collected prospectively in North Carolina between 2001-2005. Rows representing the curves shown in Figure 2 are in **bold**.^a

exposure	number of women in category	primiparous?	contraindications?	severe hypertensive disorders?	predicted MAXIMUM risk	pointwise 95% CL ^b around max risk	exposure level at predicted MAXIMUM risk
total	466	no	no	no	11.4%	8.5, 15.4	
hours/week	591	yes	no	no	27.8%	22.0, 35.1	
physical	43	no	yes	no	23.1%	14.7, 36.3	10.7 hours/week
activity	36	yes	yes	no	56.0%	36.3, 86.4	
17-22 weeks	25	no	no	yes	22.3%	14.2, 35.1	
	42	yes	no	yes	54.2%	36.6, 80.3	
					predicted MINIMUM risk	pointwise 95% CL around min risk	exposure level at predicted MINIMUM risk
total	431	no	no	no	8.3%	6.0, 11.4	
hours/week	560	yes	no	no	20.8%	16.2, 26.8	
physical	40	no	yes	no	15.3%	9.4, 25.0	8.4 hours/week
activity	33	yes	yes	no	38.4%	24.1, 61.3	
27-30 weeks	21	no	no	yes	17.1%	10.5, 27.9	
	36	yes	no	yes	42.9%	27.9, 65.8	
					predicted MAXIMUM risk (intercept)	pointwise 95% CL around max risk	exposure level at predicted MAXIMUM risk
hours/week	466	no	no	no	10.5%	8.0, 13.9	
MVPA ^b	591	yes	no	no	25.1%	20.8, 30.2	
17-22 weeks	43	no	yes	no	20.1%	13.3, 30.6	0 hours/week
	36	yes	yes	no	48.0%	32.6, 70.6	
	25	no	no	yes	20.8%	13.3, 32.4	
	42	yes	no	yes	49.6%	34.1, 72.0	
					predicted MINIMUM risk (intercept)	pointwise 95% CL around min risk	exposure level at predicted MINIMUM risk
hours/week	431	no	no	no	9.2%	6.9, 12.3	
MVPA	560	yes	no	no	23.5%	19.3, 28.5	
27-30 weeks	40	no	yes	no	17.6%	11.3, 27.6	0 hours/week
	33	yes	yes	no	45.1%	29.9, 68.0	
	21	no	no	yes	18.7%	11.7, 29.9	
	36	yes	no	yes	47.7%	32.1, 71.1	

^a The curve shapes are shown in Figure 2; this table is intended as a supplement to those pictures. The models did not include interaction terms, so the shape of the curve will remain the same but will move up or down the y-axis depending on participant characteristics; the maxima and minima listed here provide the reader with an anchor point to assess predicted risk for each type of woman. All models also included percent poverty and BMI; these variables were set to the median. Categories with both contraindications=yes and hypertensive disorders=yes are not shown because only 1 primiparous and 1 multiparous woman fell into these categories and thus predicted risks were unstable; ^b CL, confidence limits; MVPA, moderate-to-vigorous PA

Table 4.3. Final model coefficients and test statistics for each of the four physical activity exposures, n=1205 women at risk for primary cesarean, North Carolina, 2001-2005. The outcome is primary cesarean birth.

	coefficient	standard error	Wald X^2	p-value
hours/week total physical activity, 17-22 weeks	β_1 : 0.052 ^a	0.033	2.6	0.28
	β_2 : -0.085	0.055		
primiparous	0.89	0.15	33.8	<0.001
with contraindications to exercise during pregnancy ^b	0.70	0.20	12.7	<0.001
with a severe hypertensive disorder of pregnancy ^c	0.67	0.19	12.1	<0.001
pre-gravid BMI ^d	0.041	0.008	27.5	<0.001
percent poverty	0.0009	0.0003	8.6	0.003
hours/week total physical activity, 27-30 weeks	β_1 : -0.064	0.034	5.8	0.05
	β_2 : 0.11	0.051		
primiparous	0.92	0.16	31.9	<0.001
with contraindications to exercise during pregnancy	0.61	0.21	8.4	0.004
with a severe hypertensive disorder of pregnancy	0.72	0.20	12.5	<0.01
pre-gravid BMI	0.041	0.008	23.8	<0.01
percent poverty	0.001	0.0003	11.6	<0.01
hours/week MVPA^d, 17-22 weeks	-0.008	0.012	0.47	0.49
primiparous	0.87	0.15	32.7	<0.001
with contraindications to exercise during pregnancy	0.65	0.20	11.2	<0.001
with a severe hypertensive disorder of pregnancy	0.68	0.19	12.6	<0.001
pre-gravid BMI	0.04	0.008	26.3	<0.001
percent poverty	0.0008	0.0003	9.0	0.003
hours/week MVPA, 27-30 weeks	0.009	0.01	0.79	0.37
primiparous	0.94	0.16	33.4	<0.001
with contraindications to exercise during pregnancy	0.65	0.21	9.8	0.002
with a severe hypertensive disorder of pregnancy	0.71	0.20	12.1	<0.001
pre-gravid BMI	0.042	0.008	25.4	<0.001
percent poverty	0.001	0.0003	10.0	0.002

^a If two coefficients are given, the exposure was modeled as a restricted cubic spline with 3 knots.

Otherwise

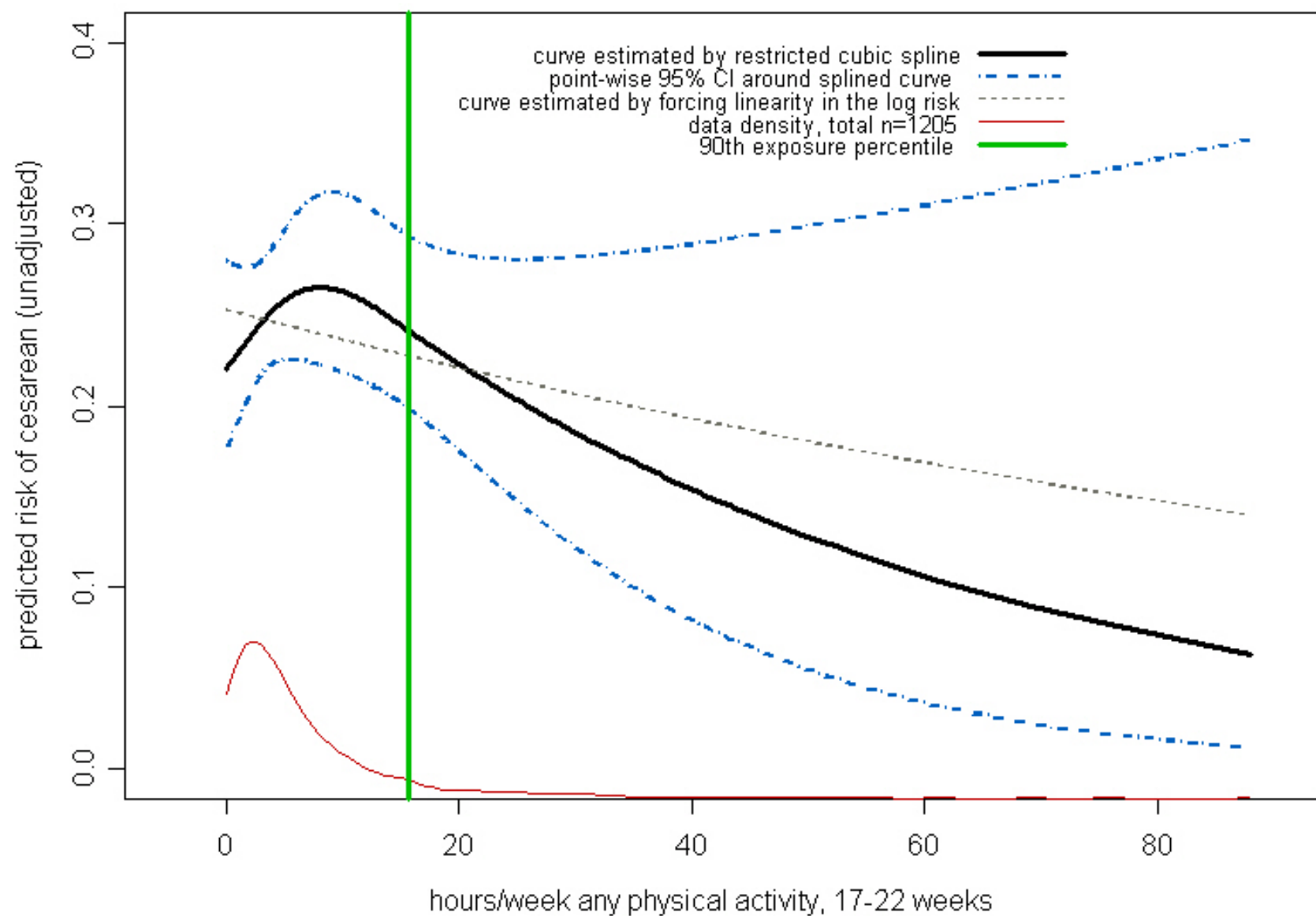
linear approximations were used. BMI and poverty were always treated as linear terms.

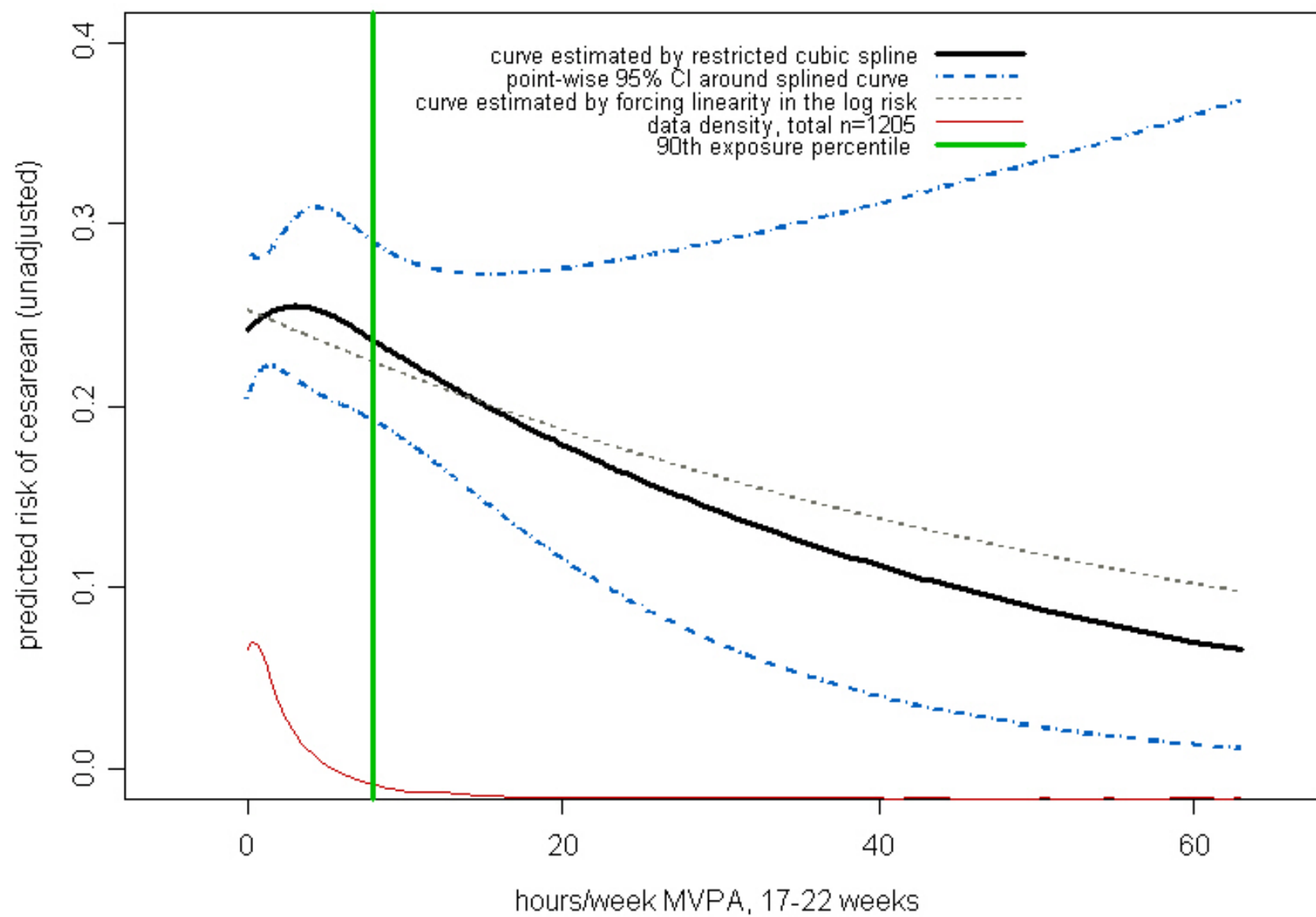
^b incompetent cervix, cerclage present, undelivered preterm labor, placental abruption, complete or partial placenta previa. Third trimester bleeding was not included because the exposures were assessed prior to 30 weeks. Carrying multiples is also a contraindication in the later gestational ages but women carrying multiples were excluded from PIN3.

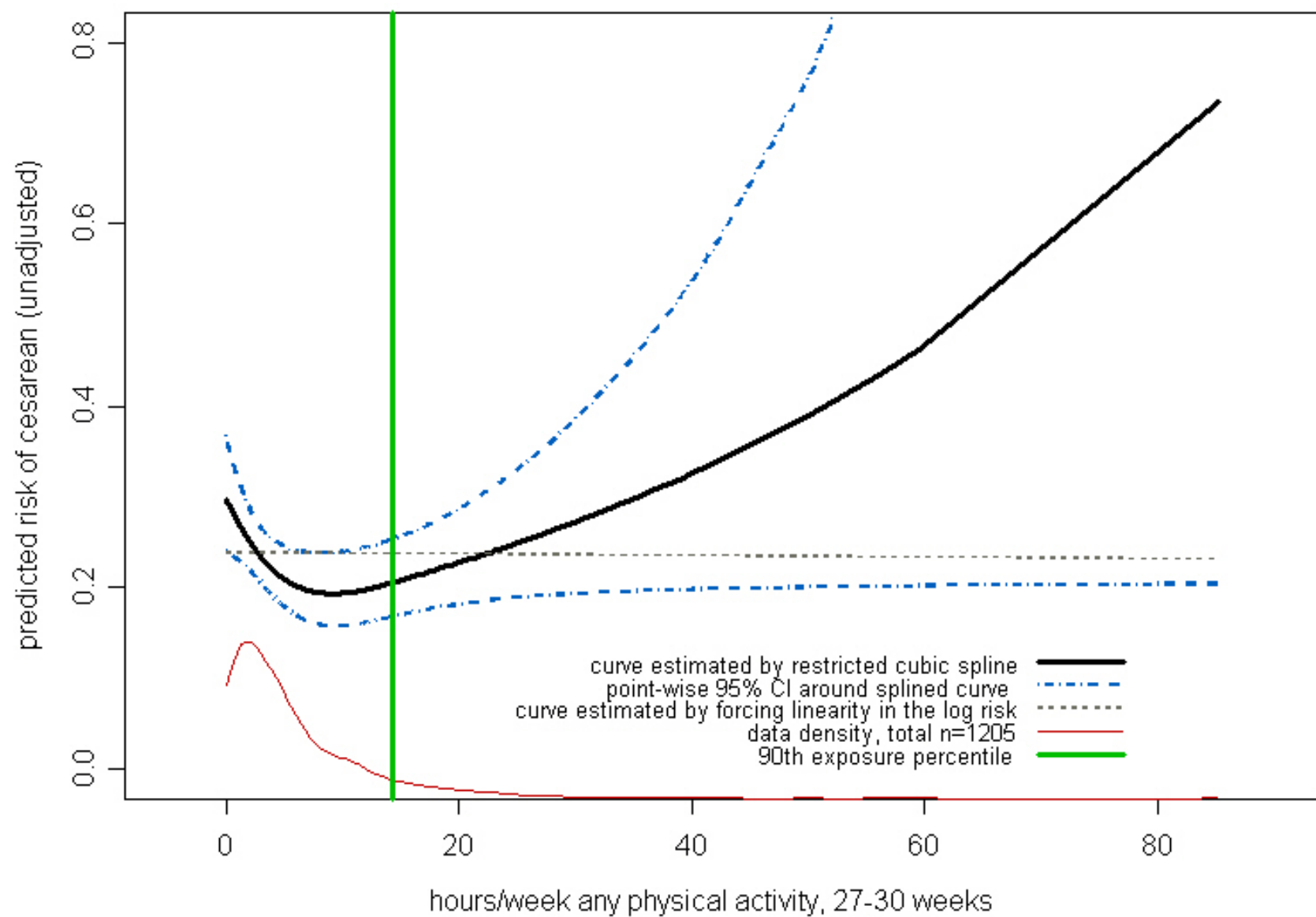
^c pre-eclampsia, eclampsia, HELLP syndrome

^d BMI, body mass index; MVPA, moderate-to-vigorous physical activity

Figure 4.1 (shown on next 4 pages). Unadjusted predicted risk of cesarean by 4 maternal physical activity exposures: total activity at 17-22 weeks' and 27-30 weeks' gestation; moderate-to-vigorous activity at 17-22 weeks and 27-30 weeks. Physical activity was self-reported via 7-day recall; data were collected prospectively in North Carolina between 2001-2005. The curves estimated by assuming linearity in the log risk (shown as gray dotted lines) are correct as shown; these curves are very shallow and difficult to differentiate from a line when shown on this scale. The green vertical lines indicate the 90th percentile of each exposure; above this point estimates are unstable.







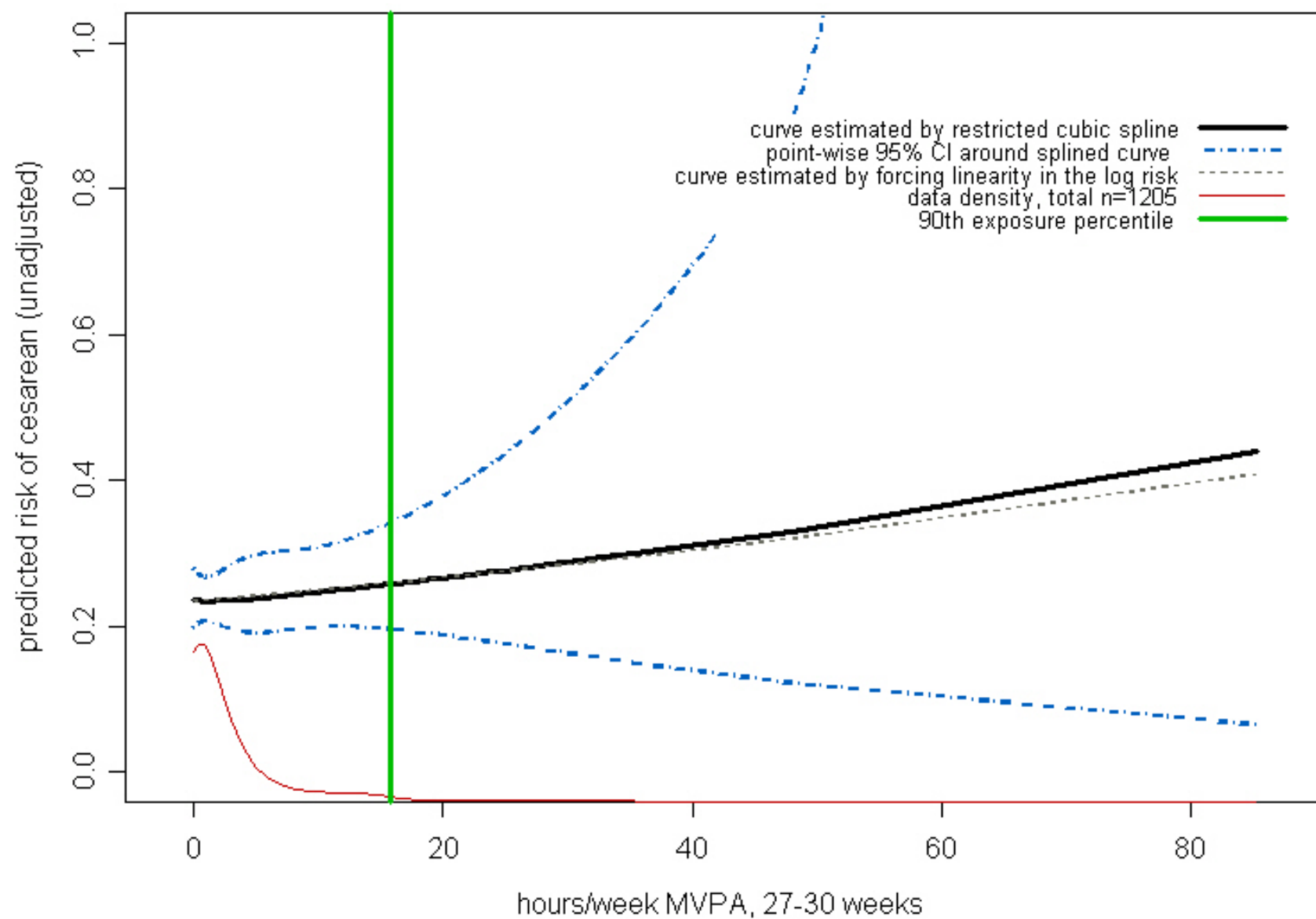
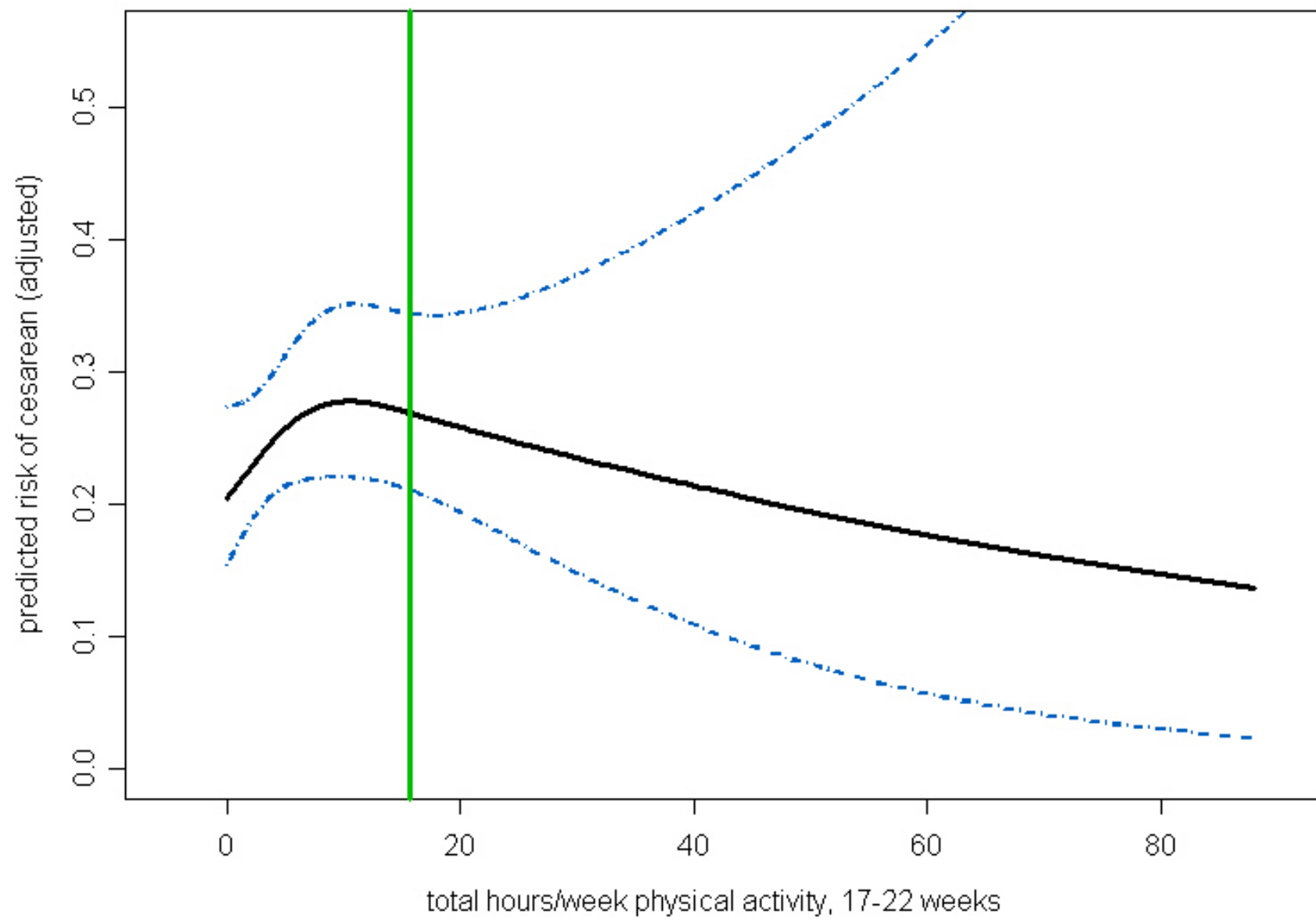
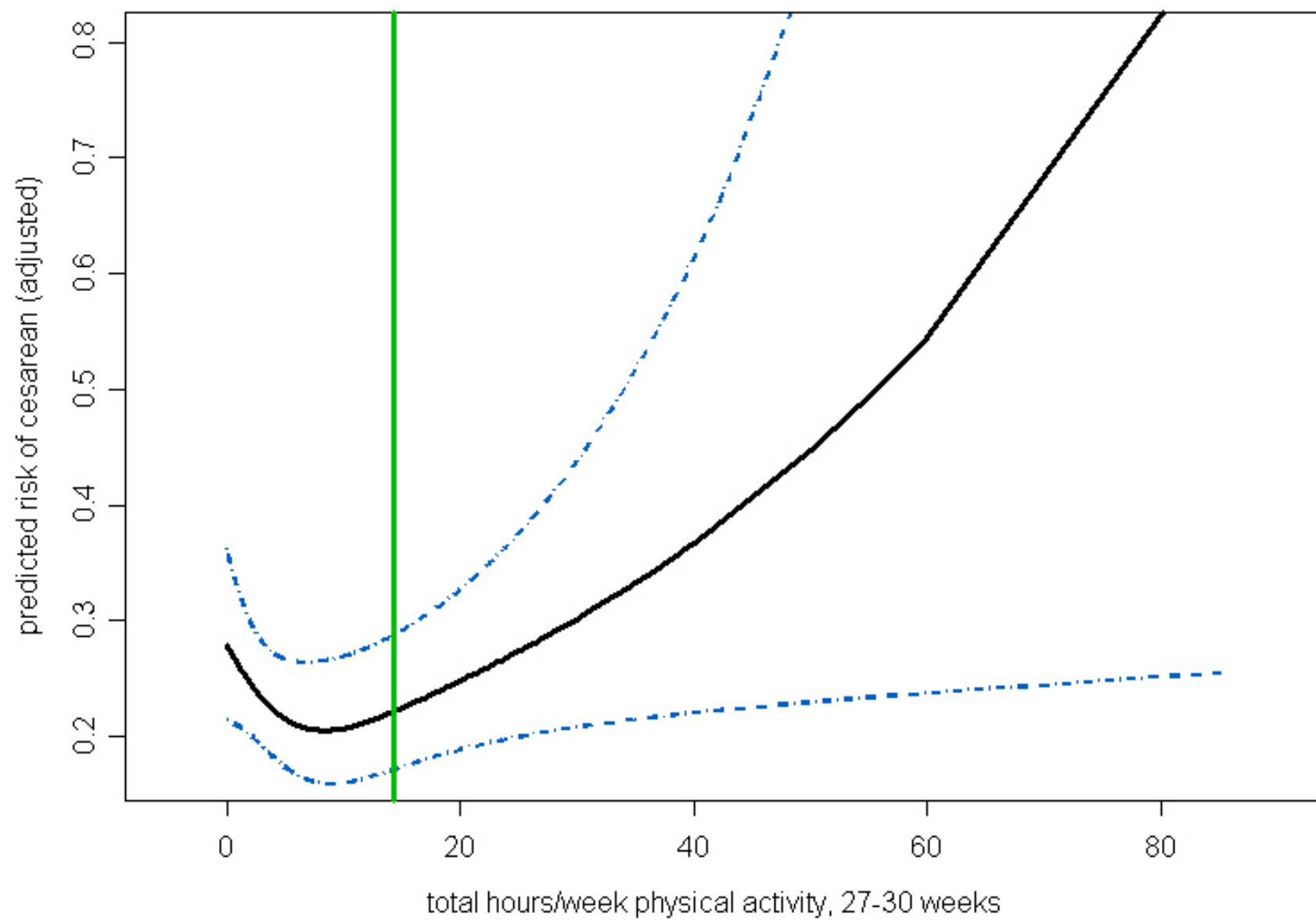
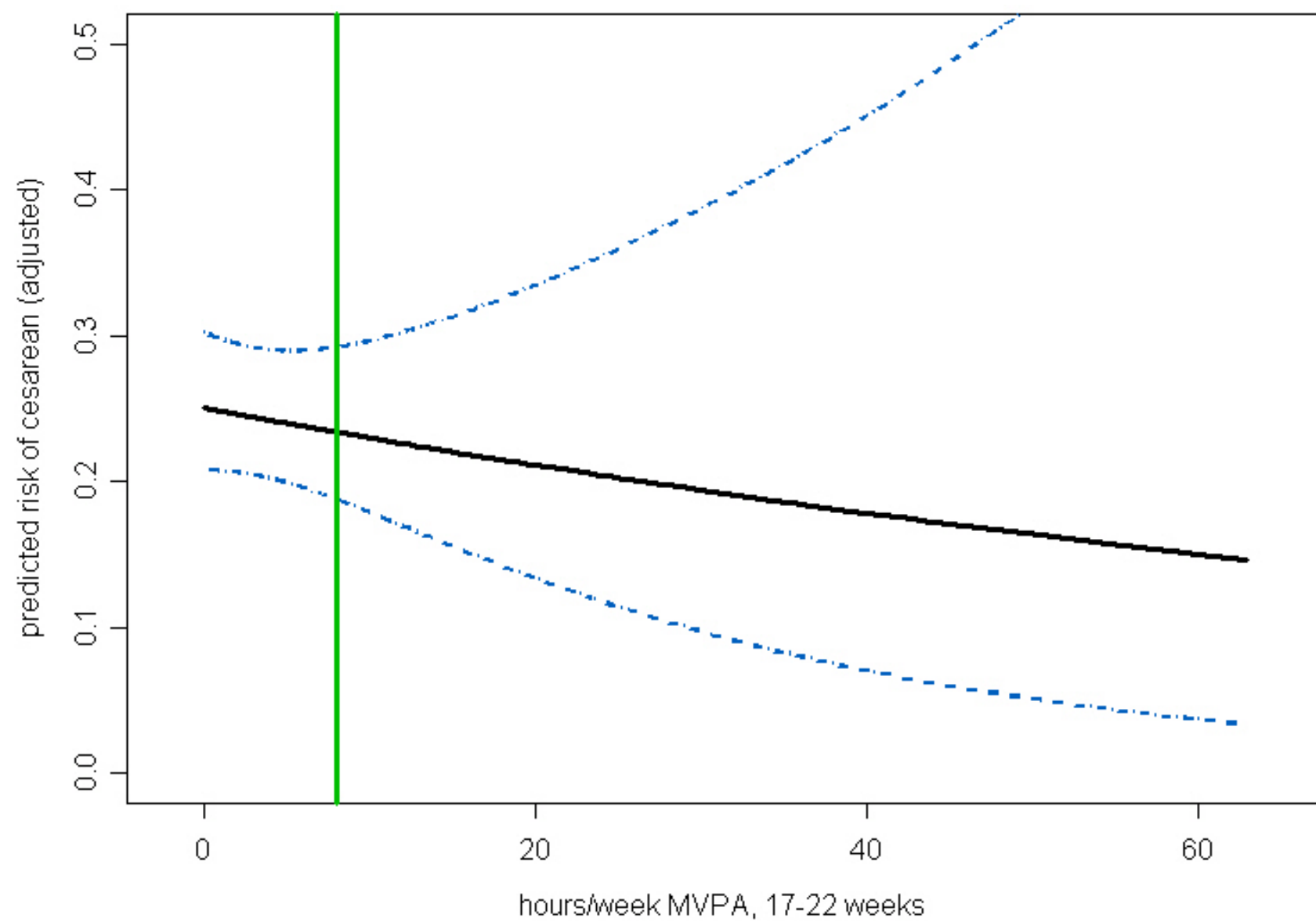


Figure 4.2 (shown on next 4 pages). Adjusted predicted risk of cesarean following physical activity during pregnancy. These graphs show predicted risk for a primiparous woman with no contraindications to exercise during pregnancy; without pre-eclampsia, eclampsia, or HELLP syndrome; and with BMI and percent poverty set to the sample median (23.7 kg/m² and 386% 2001 poverty level). Predicted risks for other subgroups can be found by moving the curve along the y-axis to align the maximum or minimum point to the values shown in Table 2.







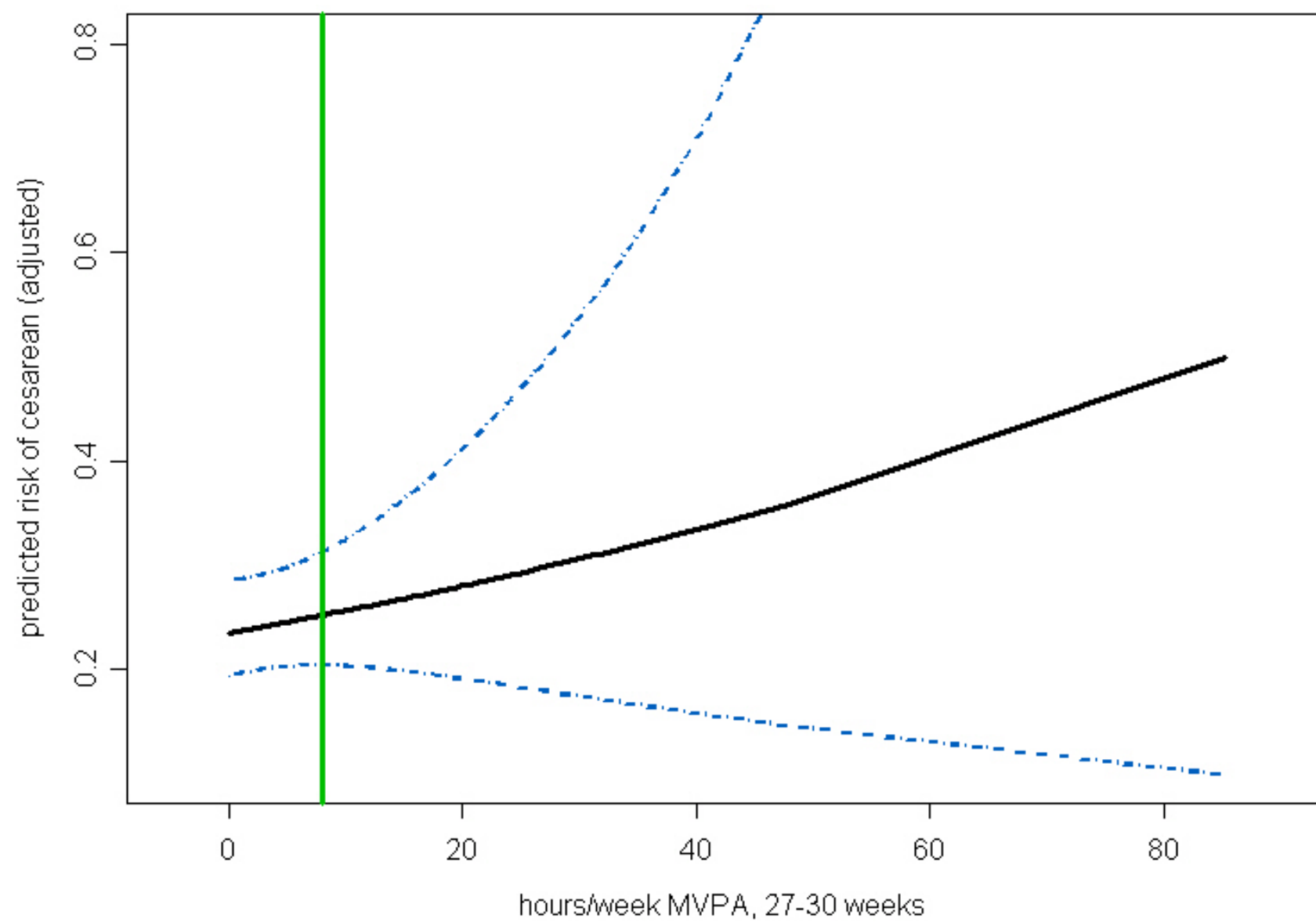
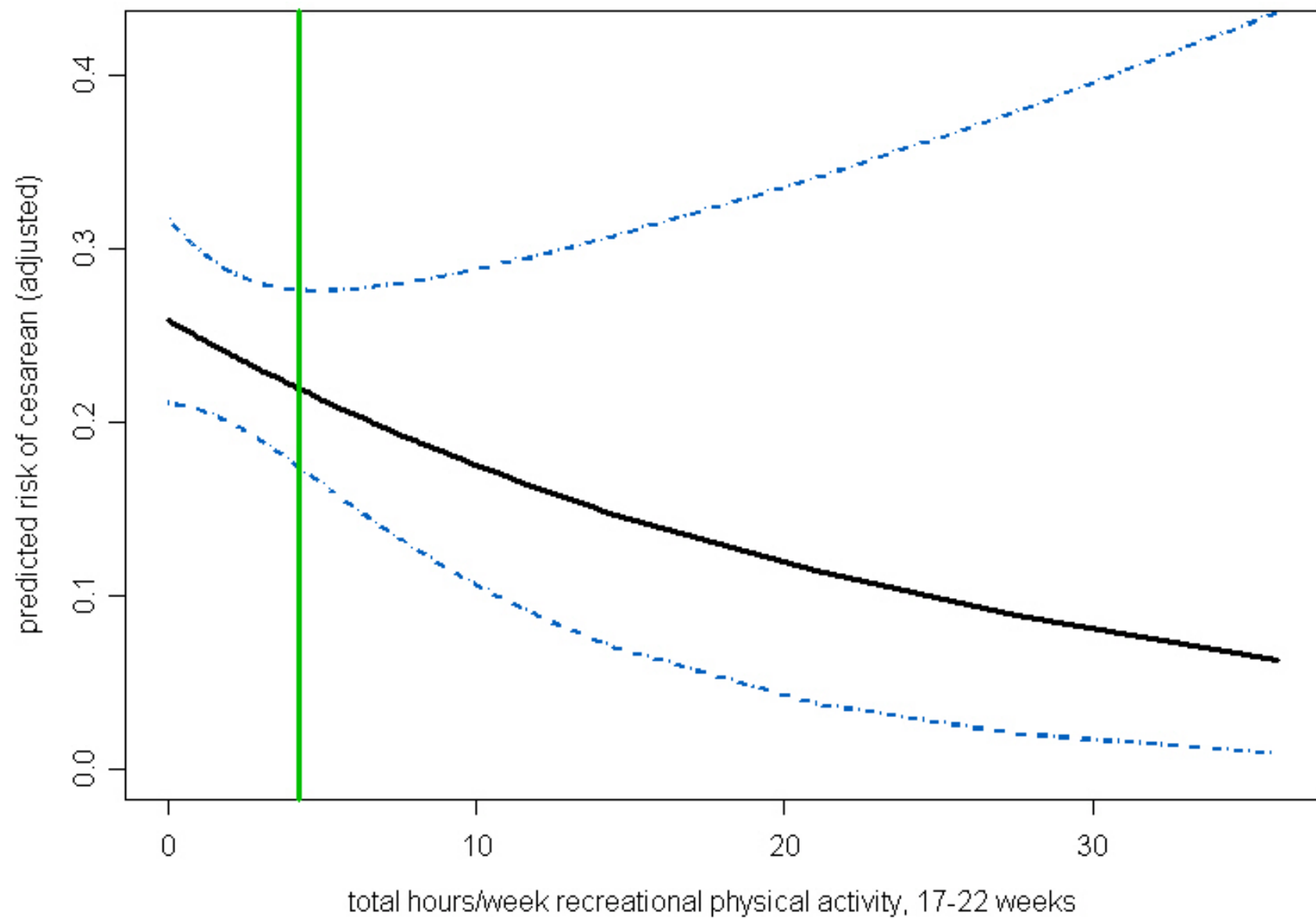
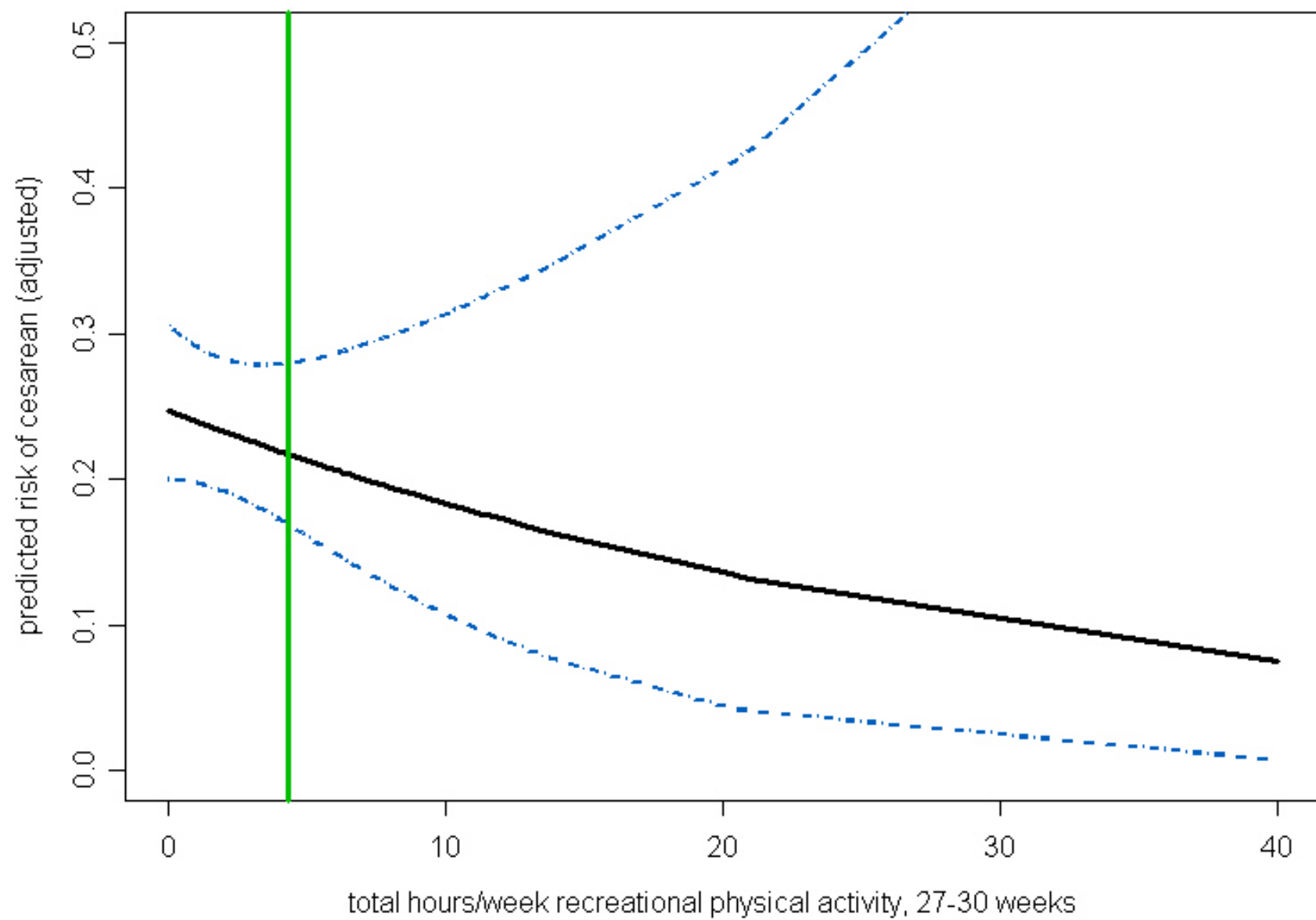
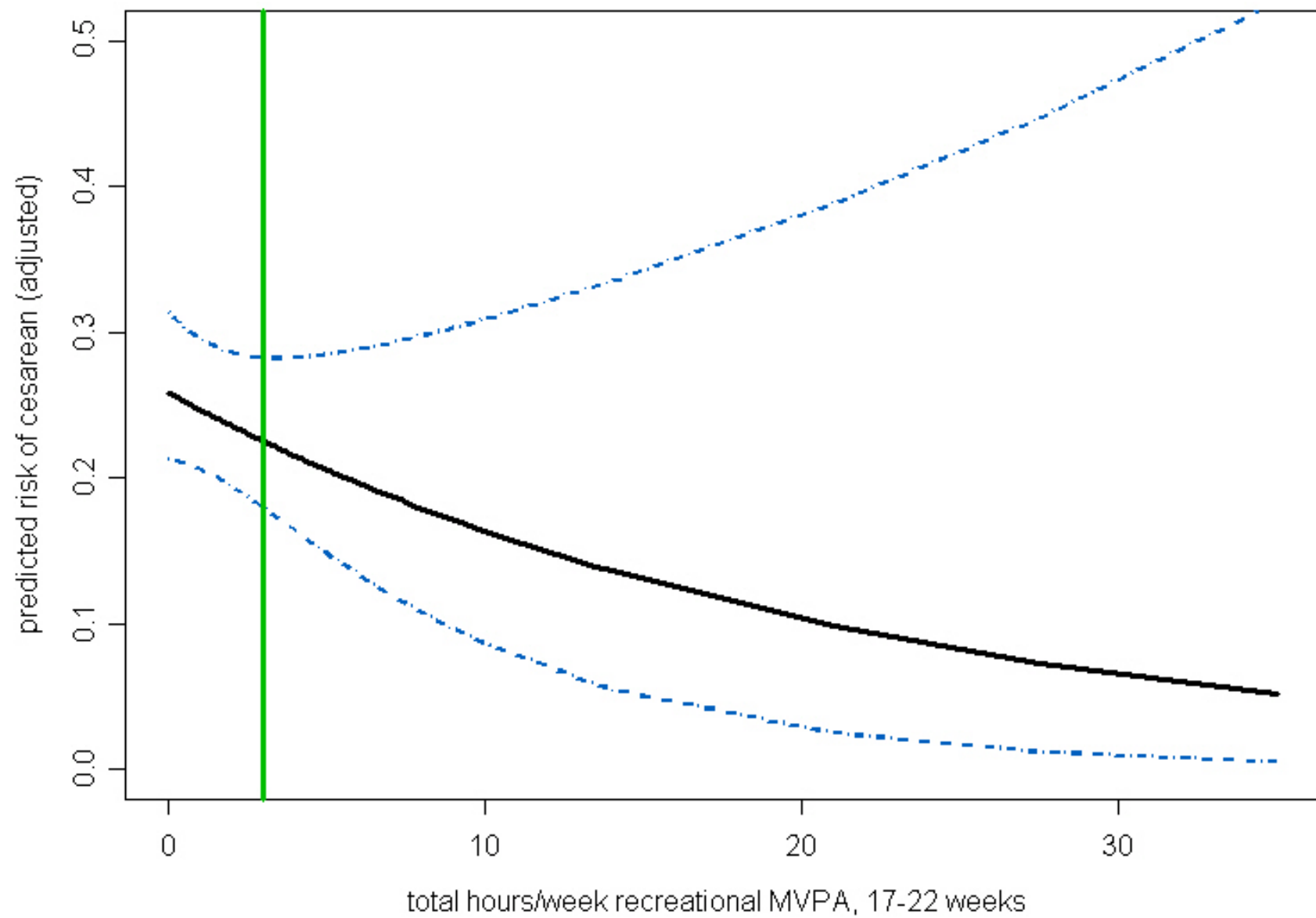


Figure 4.3 (shown on next 4 pages). Adjusted predicted risk of cesarean, limiting exposure to recreational physical activity. The graphs shown show predicted risk for a primiparous woman with no contraindications to exercise during pregnancy; without pre-eclampsia, eclampsia, or HELLP syndrome; and with BMI and percent poverty set to the sample median (23.7 kg/m² and 386% 2001 poverty level).







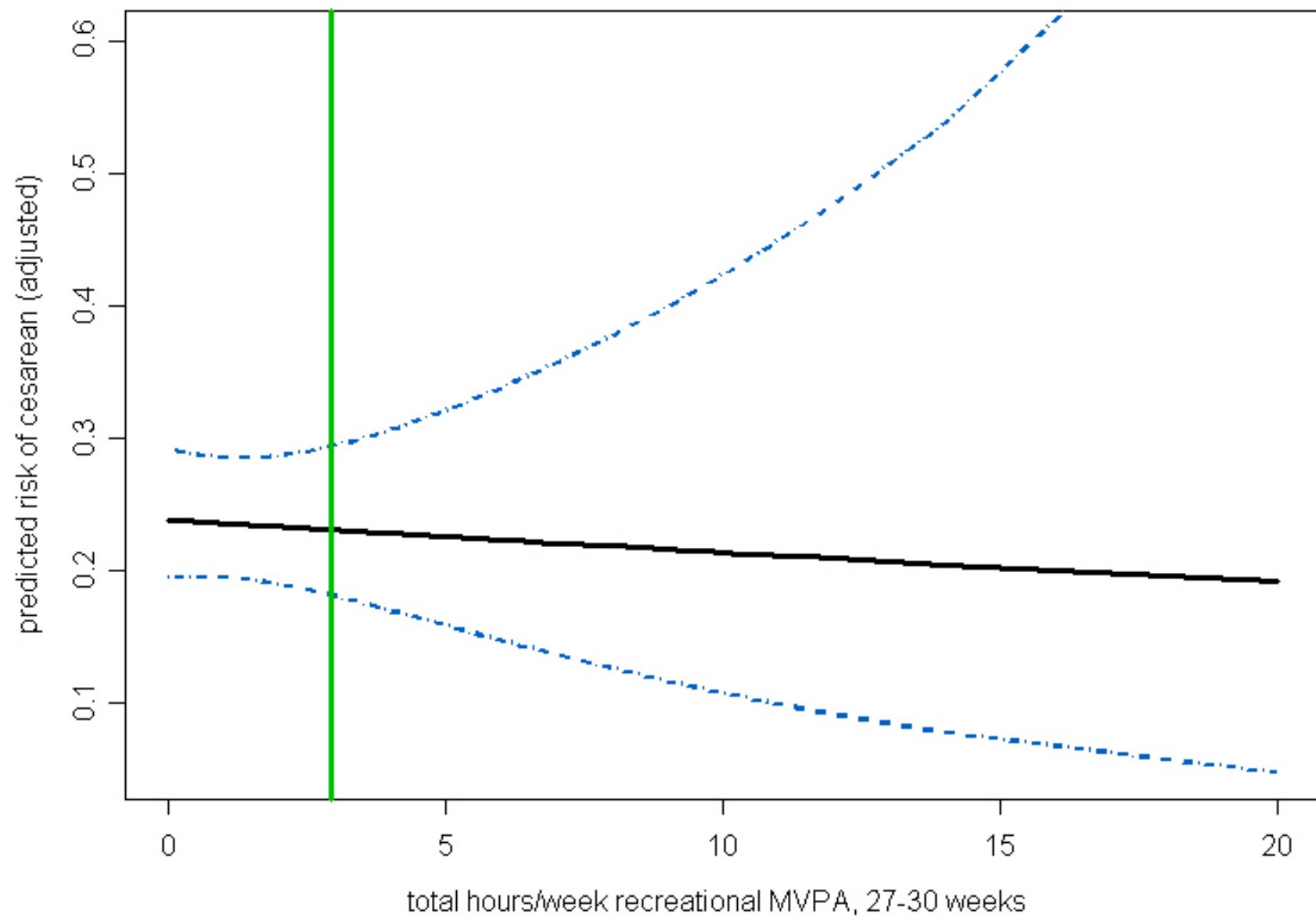
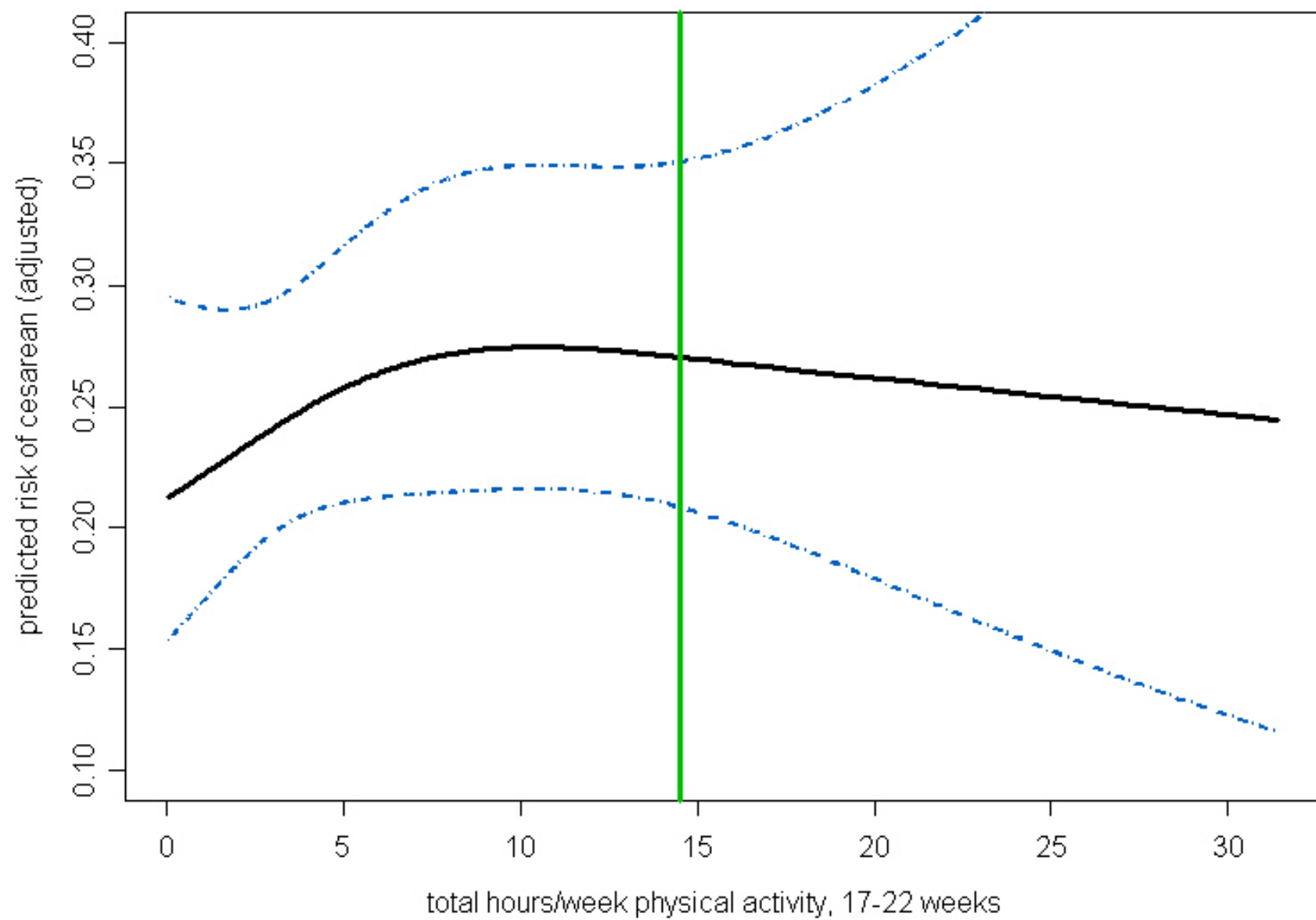
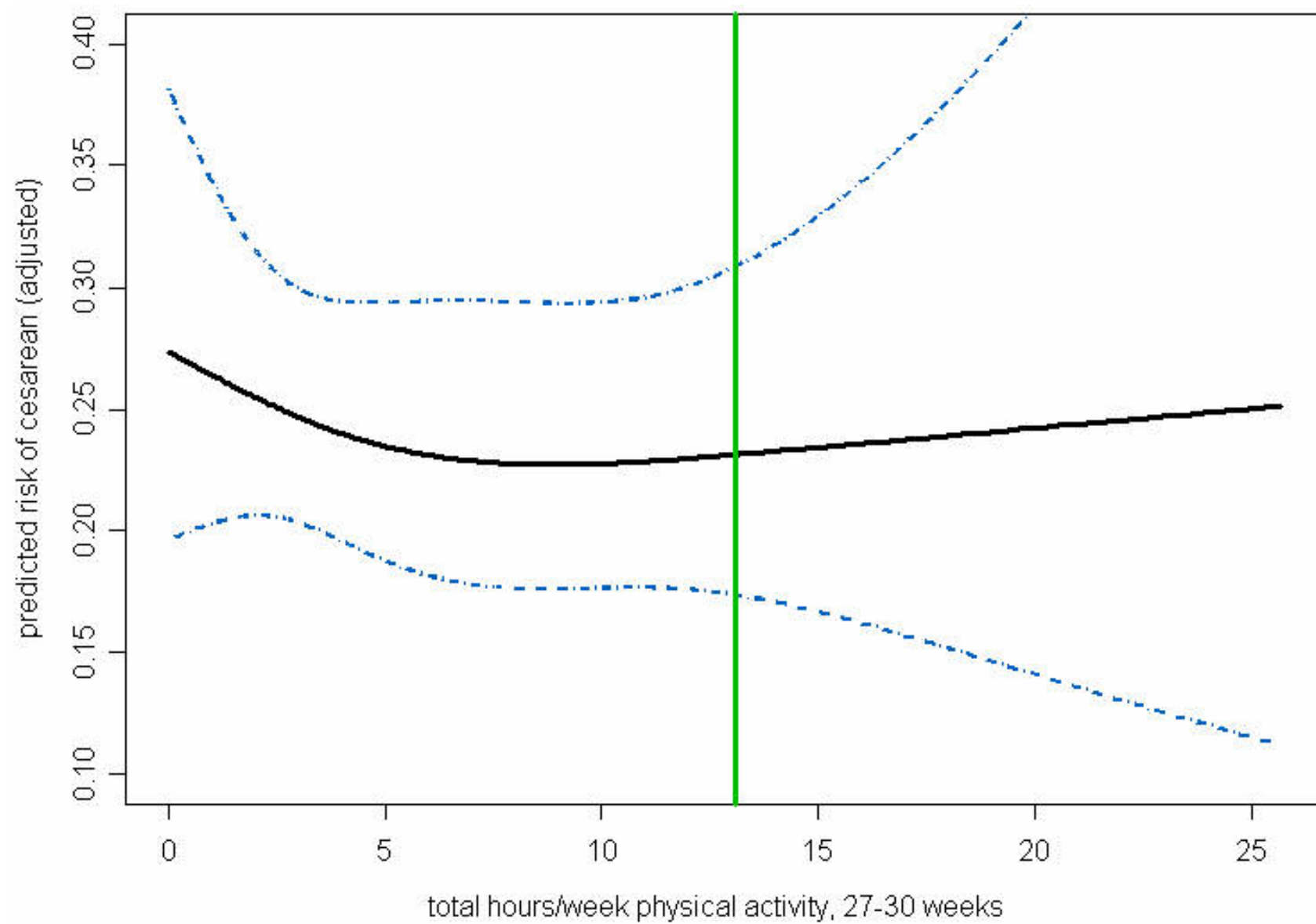
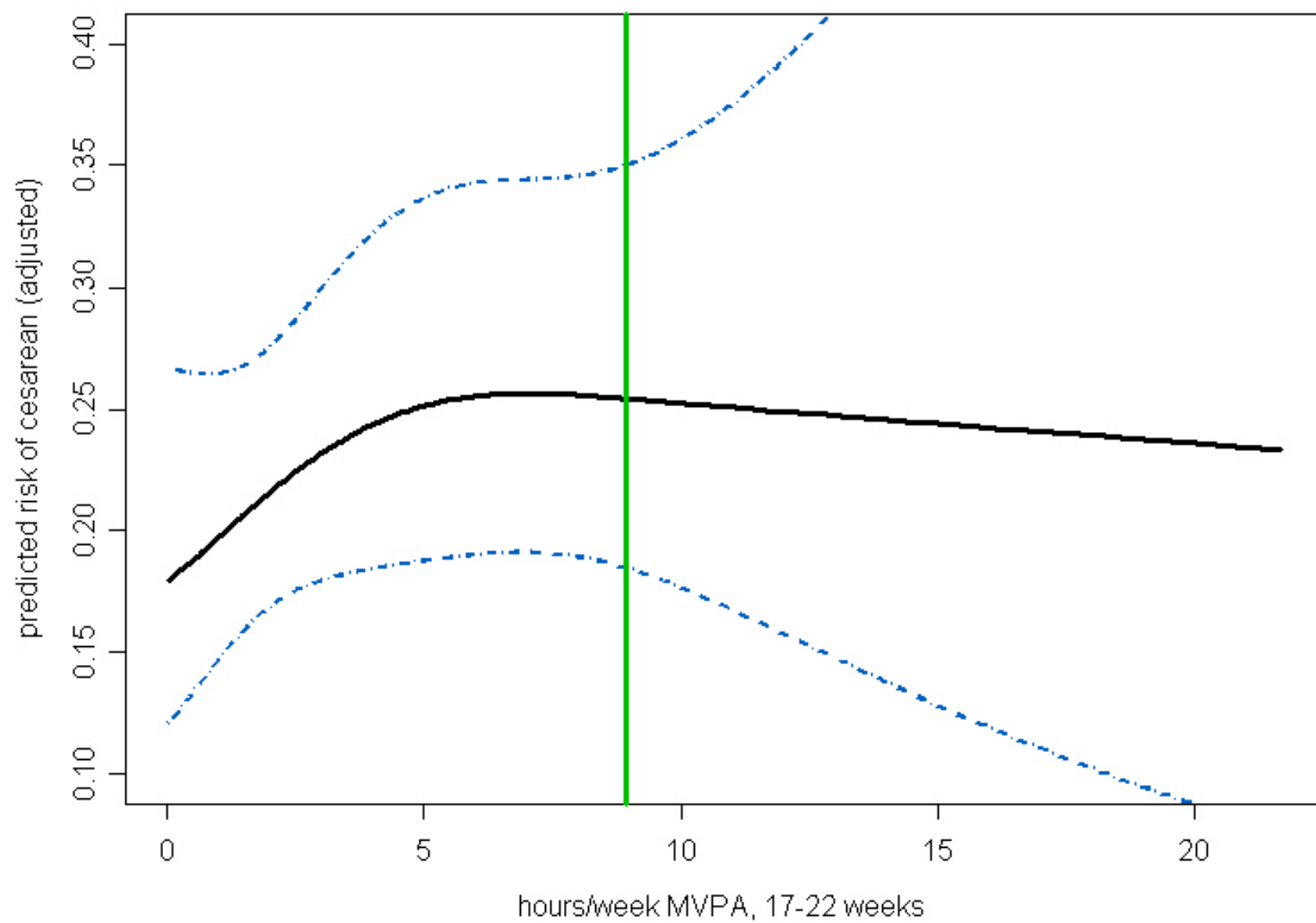
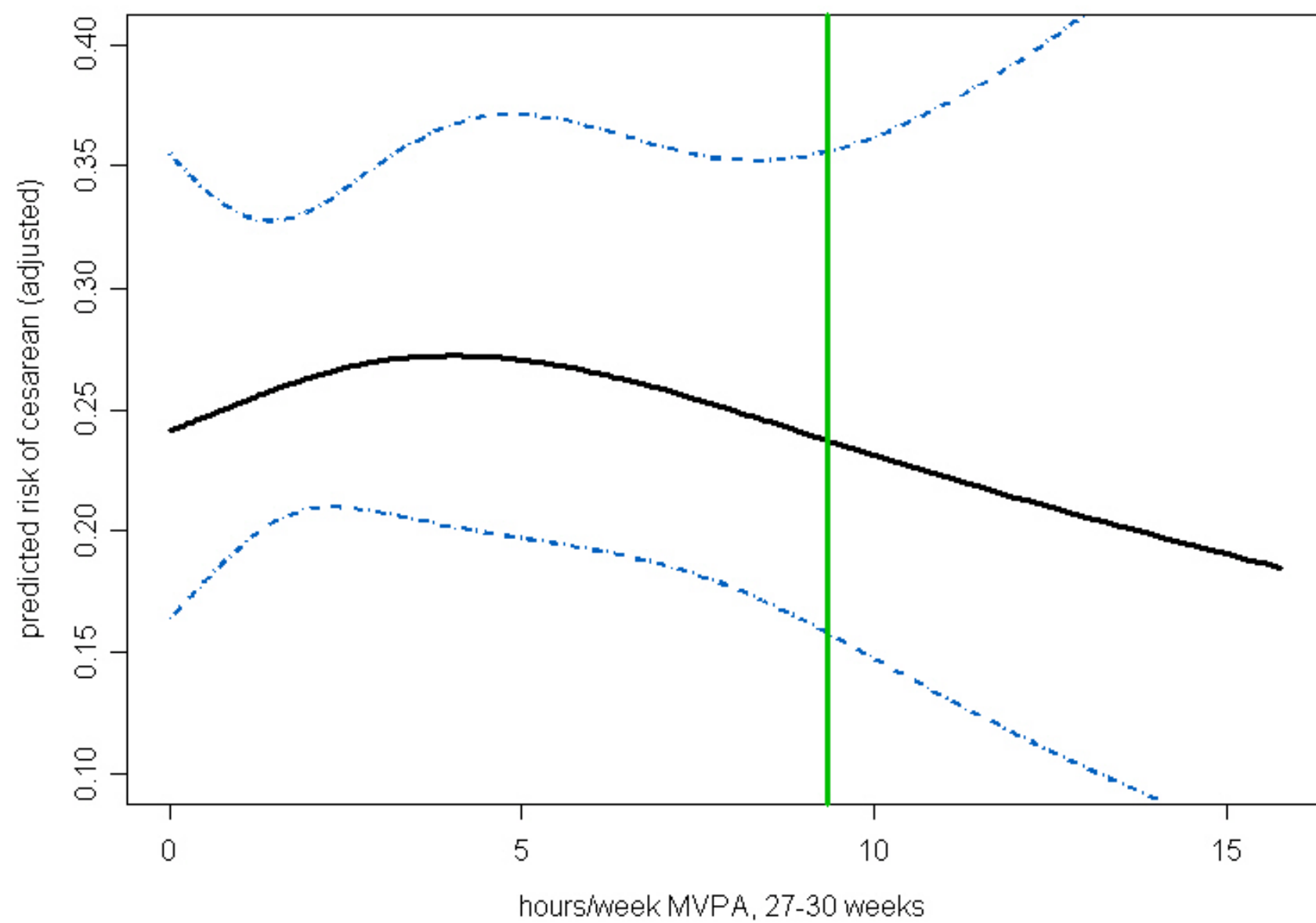


Figure 4.4 (shown on next 4 pages). Adjusted predicted risk of cesarean, using the same exposures as in Figures 1 and 2, but dropping the women who reported activity volumes in the upper 2.5%. The graphs shown show predicted risk for a primiparous woman with no contraindications to exercise during pregnancy; without pre-eclampsia, eclampsia, or HELLP syndrome; and with BMI and percent poverty set to the sample median (23.7 kg/m² and 386% 2001 poverty level).









PAPER 2

Physical Activity During Pregnancy: associations with vaginal birth outcomes

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Abstract

Background: Published reports on the association between physical activity (PA) during pregnancy and maternal birth outcomes are inconsistent. This analysis was undertaken to clarify the relationship between PA and vaginal birth outcomes, including induction risk; labor duration; risk of augmentation, operative vaginal delivery, and episiotomy; and laceration severity. Methods: During a prospective cohort study of pregnant women, detailed 7-day recalls of PA were collected at 17-22 weeks and again at 27-30 weeks completed gestation, and linked to medical records for 945 women who had a vaginal birth. Exposures included total PA, moderate-to-vigorous PA (MVPA), recreational PA, and recreational MVPA, each assessed at both time points in hours/week. Results: Women who reported more hours/week of PA were less likely to be induced. Women who reported more hours/week of recreational PA at 27-30 weeks required less labor augmentation. Women who reported more hours/week of PA had longer labor durations; however, our labor duration measure was crude, so this result should not be interpreted definitively. All associations remained unchanged after excluding women who reported large amounts of PA. PA during pregnancy was not associated with operative vaginal delivery or episiotomy; our results were inconclusive for laceration severity. Conclusions: PA during pregnancy may be associated with clinically-significant reductions in induction and augmentation risk but increases in labor duration.

Introduction

Despite extensive study, associations between physical activity (PA) during pregnancy and vaginal birth outcomes remain unclear. For example, ten studies have reported associations between maternal PA and operative vaginal delivery (OVD)—five reported decreased risk (31,35,37,42,50), four no difference (34,38,43,46), and one an increased risk (45). A definitive conclusion from the current literature is lacking, partly because of methodological limitations such as small sample sizes, incomplete exposure ascertainment, and lack of confounder control.

For labor duration the current state of the literature is even more unclear, in part because of the varying definition of duration. Some studies report total labor duration, whereas others report the three stages separately, or total duration of just the first and second stages, or some other combination entirely. Furthermore, though fourteen studies report associations with PA and labor duration, there is no clear consensus.(32,34-36,38-40,42-43,45-46,50-51,65) Some report longer stages or total durations with increased PA (36,42,45-46), some shorter (32,35,38,40,43,50-51)—one even reports shorter first stage but longer second.(65)

Other vaginal birth outcomes have not been studied as extensively. One study found no differences in risk of induction for physically active vs. control women (35), whereas two studies found significantly more inductions as women accumulated more PA.(45-46) Two studies reported that sedentary women required more labor augmentation than did active women (31,35), whereas one reported the reverse.(46) Two studies reported no difference in risk of perineal lacerations when comparing active to sedentary women (43,50), but one reported elevated risks for active women for both 1st/2nd degree and 3rd/4th degree lacerations.(46) Finally, one study reported more episiotomies in the control group compared to the exercising group (35), and one reported no difference.(34) From these results, it appears that women who

are more active during pregnancy may have elevated risks of induction and laceration, but reduced risk of episiotomy and augmentation. Again, however, absolute consensus is lacking.

The objective of this analysis was to use detailed physical activity data from a cohort of pregnant women to address associations with vaginal birth outcomes. Our study improves on previous methods by using a large sample size, extensive PA ascertainment including activity accumulated through non-recreational means, and care-giving activities, and appropriate statistical methods.

Methods

The study aim was addressed by merging two data sources. The first data source was the third Pregnancy, Infection, and Nutrition (PIN3) cohort, a large ongoing study of pregnancy in central North Carolina that provided physical activity exposure data. The PIN3 Study recruited women from January 2001 through June 2005, by study staff from prenatal clinics. Women were eligible if they presented for antenatal care before 20 weeks' gestation, intended to deliver at a University of North Carolina (UNC) hospital, were carrying a singleton fetus, were ≥ 16 years old, read and spoke English, and had access to a telephone. Complete details about the data collection protocols can be found at the PIN3 website (http://www.cpc.unc.edu/pin/design_pin3.html).

The PIN3 Study collected two detailed 7-day physical activity recalls by telephone interview, at 17-22 weeks' and 27-30 weeks' completed gestation. These recalls collected information about occupational, recreational, indoor and outdoor household, care giving, and transportation activities. In each category, women were asked about specific activities in the past 7 days that increased breathing or heart rate, the frequency and average duration for each, and to rate the intensity of the activity as "fairly light," "somewhat hard," or "hard or very hard."

Expert review of selected taped interviews ensured consistency among interviewers. The entire questionnaire, along with evidence demonstrating reliability and validity in pregnant women, can be found elsewhere.(89)

Based on the PA data, women were assigned values for total hours/week of activity, and hours per week of moderate-to-vigorous PA (MVPA—anything rated as at least “somewhat hard”). These calculations were conducted separately for each recall, and also for recreational activity only. Records for women who reported outlier values of PA were reviewed by hand. Data entry errors were corrected, and unreasonable values were set to missing.

The second data source, which provided outcomes, was the Perinatal Database maintained by the UNC Hospitals Department of Obstetrics and Gynecology. Data were collected by labor and delivery (L&D) nurses, who reviewed medical records for all admitted women to obtain complete obstetric information. Data were entered and the database administrator ran monthly validity checks to find impossible or inconsistent values.

These two data sources were merged on mother's medical record number and baby's date of birth. Following electronic merge, additional matches were made by hand. 3203 women were eligible for PIN3; of these 2006 agreed to participate (63%). Of the 2006 women who consented to be in the study, 2% became ineligible (4 multiple pregnancies, 43 pregnancy losses), 9% were lost to follow-up (126 did not complete any questionnaires or interviews; 48 asked to be dropped later in the study), and 121 (6.5%) were participating for the second or third time, leaving 1654 participants. Of these, 1488 (90%) were successfully merged with the Perinatal Database. For this analysis, we excluded all women who did not have a vaginal birth (n=542). Finally, we dropped one woman who reported 135 hours/week of physical activity because that value was implausible, leaving 945 women. Both this project and the PIN Study protocols were approved by the Institutional Review Board (IRB) at UNC; this project was also

approved by the IRB at Oregon State University. Women gave written informed consent to participate in PIN.

Outcomes

There were 7 outcomes used in this analysis: induction, labor duration (2 different definitions), augmentation, OVD, episiotomy, and severity of perineal lacerations.

Induction and augmentation were both dichotomous variables, and combined medical and surgical procedures. In this sample, the vast majority of inductions and augmentations were medical, with only 15 surgical inductions (10 of which were in conjunction with a medical induction) and 2 surgical augmentations (neither of which was performed along with a medical augmentation).

We calculated total labor duration two ways: first, as the difference between date/time of birth and date/time of admission; second as the difference between date/time of birth and maternal self-reported date/time of labor onset. Date/time of admission and date/time of birth came from the Perinatal Database. The self-reported time of labor onset came from the PIN3 Study; women were asked postpartum if they knew when their labor started. The exact question was, "We are defining the beginning of labor as the time when regular, painful uterine contractions began occurring every 3 to 5 minutes and ended in delivery. Using this definition of labor, what day and time would you say your labor began?" If they did not know the exact time, they were asked if they knew "about when" it started, and if yes, to give a date/time that was definitely before labor onset, and a date/time that was definitely after labor onset. For these women (n=29), we took the midpoint of this range as the time of labor onset. We did not have information on durations of each stage separately, nor did we have information on duration of

the third stage. For both labor duration variables, we set to missing any durations longer than 48 hours or shorter than 0 minutes.

OVD was a dichotomous variable and included all vaginal births that were not categorized as "normal spontaneous vaginal delivery." Other categories, collapsed into 'operative vaginal delivery,' included low forceps, outlet forceps, manual rotation, forceps rotation, and vacuum extractor. Non-cesarean malpresentations (n=20, includes all presentations except vertex occiput anterior) and vaginal births after cesarean (VBACs, n=28) were included and placed into either the spontaneous or the operative category, as appropriate.

Episiotomy was also a dichotomous variable, and included both midline and mediolateral surgeries. Severity of laceration was an ordinal variable with 3 categories, in order of increasing severity and likelihood of complications: no lacerations; periurethral, labial, and 1st and 2nd degree perineal lacerations; 3rd and 4th degree perineal lacerations, vaginal, and cervical lacerations. If a woman had more than one type of laceration indicated in her chart, the most severe was used.

Covariables

During the first telephone interview for the PIN3 Study (17-22 weeks), women self-reported their race, marital status, education, obstetric history, and household information, including income, number of adults, and number of children. From these data one can calculate the percent of the 2001 poverty level: a score of 100 indicates a household living exactly at the poverty line.(90)

Women were asked about previous pregnancies, including both live births and still births, which were combined to define parity. Parity was collapsed into primiparous vs.

multiparous, because there is a clear difference in labor pattern and outcome between these two groups, but fewer differences are observed between higher order labors.

Maternal height was measured by study staff; pre-gravid weight was self-reported. Pre-gravid body mass index (BMI) was calculated from these values. Gestational age (GA) at birth was estimated using ultrasonography if the test was performed prior to 22 weeks, and on date of last menstrual period otherwise. Birthweight was abstracted from the medical record.

Information about pregnancy complications came from the Perinatal Database. Complications considered as covariables for this analysis were contraindications to exercise during pregnancy as defined by the American College of Obstetricians and Gynecologists (ACOG, including incompetent cervix, cerclage, placenta previa/abruption, undelivered premature labor)(1) and severe hypertensive disorders of pregnancy (includes pre-eclampsia, eclampsia, and HELLP [hemolysis, elevated liver enzymes, low platelet count] syndrome). For simplicity, we refer to this combined hypertensive disorders variable as "pre-eclampsia."

Data analysis

Because 4 variables (both total PA and MVPA at the 27-30 week time point, laceration severity, and labor duration from time of labor onset) were missing more than 5% of the data, we used multiple imputation to address missing data. All effect estimates were based on the imputed sample.

In all analyses, physical activity exposure variables were left as continuous measures, and initially in a non-linear fashion using restricted cubic splines with 3 knots (percentiles 0.10, 0.50, 0.90).(85) Analysis of deviance was used to determine whether or not the non-linear term was necessary, using a criterion of $p < 0.20$ for keeping the spline. If non-linear (spline) terms were necessary, results were reported graphically only. For all figures in this paper, predicted

log odds from the models have been converted to predicted proportions, which can then loosely be interpreted as risk.

Dichotomous outcomes (induction, augmentation, episiotomy, OVD) were modeled using logistic regression, laceration severity was modeled using the proportional odds model (ordinal logistic), and continuous outcomes (labor duration from time of admission, labor duration from time of labor onset) were modeled using the ordinary least squares linear regression model. Each outcome was modeled 8 times, once with each of four exposures (total hours/week PA at 17-22 and 27-30 weeks; hours/week MVPA at 17-22 and 27-30 weeks) then each of these limited to recreational activity only. For exposures limited to recreational exposure only, all analyses controlled for activity from all other modes.

Covariables for initial models were chosen using directed acyclic graphs (DAGs)(91), which were drawn based on our understanding of the relevant physiology from the published literature. Initial models included potential confounders and effect modifiers as suggested by the DAGs; variables were eliminated in a backwards stepwise fashion using analysis of deviance X^2 $p < 0.10$ as the criterion to retain a variable. To reduce type I errors in this process, we forced all final models for a given outcome to include the same set of covariables.

For OVD, the initial model included parity as an effect modifier, and parity (main effects), maternal age, GA at birth, history of OVD, and pre-eclampsia as confounders. A nested coding scheme was used for history of operative vaginal delivery/parity to account appropriately for primiparous women. For episiotomy, the initial model included parity as an effect modifier, and parity, maternal age, and pre-eclampsia as confounders. The initial model for severity of perineal lacerations included parity as an effect modifier, and parity, maternal age, BMI, pre-eclampsia, and a history of OVD as confounders. The initial models for labor induction and augmentation included parity (effect modifier and main effects), pre-eclampsia, BMI, and

maternal age. Finally, the initial labor duration models included parity as an effect modifier, and parity and BMI as confounders.

Because PA data were very right-skewed, we then conducted a sensitivity analysis to determine the effects of women reporting large volumes of activity, whereby women in the upper 2.5 percent of PA for each exposure were dropped. All exposures were treated as continuous variables in all analyses, but for outcomes associated with PA, we did calculate risk differences for women who accumulated 2.5 hours or more per week of MVPA versus those who reported zero minutes, to allow clinicians to interpret our results in terms of patient counseling practices. Statistical significance was set at $\alpha < 0.05$. All analyses were conducted using S-Plus version 8.1 for windows (Tibco Spotfire, Palo Alto, CA).

Results

Sample demographics and exposure/outcome prevalences are shown in Table 5.1. Women in our sample were largely white, married, and well-educated. The rate of preterm birth was 12 percent; 8 percent of infants had birth weights less than 2500 g. Women decreased both volume of PA between the 17-22 week PA recall and the one conducted at 27-30 weeks. Thirty percent of women were induced; 31 percent had their labors augmented. The median labor duration calculated from time of admission was 606 minutes; from maternal self-reported time of labor onset was 495 minutes. The operative vaginal delivery and episiotomy rates were 12 percent and 4 percent, respectively. About one quarter of women had intact perineums after birth, 62% had a minor laceration (labial, periurethral, 1st or 2nd degree perineal), and the remaining 14% had more severe lacerations (vaginal, cervical, 3rd or 4th degree perineal).

To simplify the reporting of results, exposures will be referred to by number as shown in Table 5.2. In this table, the reader can see at a glance which exposures were assessed at 17-

22 weeks vs. 27-30 weeks, which include all intensities vs. only MVPA, and which are limited to recreational activity only.

Induction

In models controlling for pre-gravid BMI and pre-eclampsia, the odds of being induced were associated with exposures 2, 3, and 7 (Wald X^2 p values 0.005, 0.04, 0.05, respectively), and trended towards an association for exposures 1, 4, and 5 ($p = 0.1, 0.06, 0.1$). When women in the top 2.5 percent of each exposure category were dropped, odds of being induced were associated with exposures 2, 3, and 7 ($p = 0.008, 0.03, 0.02$), and trended towards an association for exposure 4 ($p = 0.06$).

Graphs of the adjusted associations for exposures 2, 3, 4, and 7 are shown in Figure 5.1, both with and without the women in the upper 2.5%. All graphs show a vertical line (in green) which marks the 90th percentile of exposure. As shown by the data density functions (in red, left-hand column, Figure 5.1), data above the 90th percentile are extremely sparse. Predicted estimates in the upper range have wide confidence intervals and therefore are unstable. Throughout this paper, we restrict firm conclusions to women *below* the 90th percentile for self-reported physical activity exposures during pregnancy—i.e. we restrict conclusions to those women one is most likely to encounter in clinical practice.

Across all exposures, women reporting no PA have an increased risk of labor induction, which drops sharply as 2-5 hours/week are accumulated. Above this level, the curve then might stay relatively flat, increase, or decrease, depending on the exposure in question. The sharp decline in risk over the first few hours/week of activity, however, remains constant.

Two MVPA exposures were associated with induction in adjusted analyses at the $p < 0.05$ level (exposures 3 and 7); these were associated with a decreased risk of induction of 6.1

percent and 7.9 percent, respectively, for women who accumulated 2.5 hours of MVPA vs. those who reported zero minutes of MVPA. When dropping women reporting the uppermost volumes of activity, again exposures 3 and 7 were significantly associated with induction—this time with reduced predicted risks of 7.3 and 8.9 percent.

Labor Duration from Time of Labor Onset

In models that controlled for primiparity, labor duration from maternal self-reported time of onset was associated with exposures 5 and 7 (F statistic p values < 0.001, 0.003, respectively), and was weakly but not significantly associated with exposures 2, 3, and 4 (p = 0.1 for each). When women in the top 2.5 percent of each exposure category were dropped, labor duration from time of labor onset was associated with exposures 2, 3, 5, and 7 (p = 0.05, 0.04, 0.007, 0.04). We did not find evidence of effect modification by primiparity.

For all exposure metrics, more activity was associated with slightly longer labor durations. For exposure 2 including all women, each additional hour/week added 3.6 (95% confidence limits -0.8, 8.0) minutes to labor duration from time of onset. Exposures 3, 4, 5, and 7 including all women were associated with an extra 3.1 (-1.1, 7.3), 4.7 (-1.6, 11.0), 19.0 (8.2, 29.7), and 19.4 (6.7, 32.0) minutes, respectively. In analyses where the upper 2.5 percent of women in each exposure were dropped, exposures 2, 3, and 7 were associated with an extra 6.1 (-0.1, 12.3), 8.7 (0.3, 17.2), and 27.1 (2.0, 52.3) minutes of labor. Exposure 5 without the topmost 2.5 percent of women, the only exposure for which a linear approximation did not suffice, was flat until 2 hours/week, after which each additional hour was associated with 50.7 additional minutes of labor. A woman who accumulated 2.5 hours of MVPA, therefore, could expect an extra 48 minutes of labor (exposure 7) compared to one who reported no MVPA. When dropping the top 2.5 percent of women in each exposure category, women who reported

2.5 hours of MVPA had predicted increased labor durations of between 22 (exposure 3) and 68 (exposure 7) minutes compared to those who reported no MVPA.

Labor Duration from Time of Admission

In models which adjusted for primiparity there were no associations with any of the eight exposures, whether or not women in the top 2.5 percent of each exposure category were included. We did not find evidence of effect modification by primiparity.

Augmentation

In models adjusting for maternal age, primiparity, and pre-eclampsia, odds of augmentation were associated with exposures 6 and 8 (Wald X^2 $p = 0.02, 0.03$); only exposure 8 remained a significant predictor after dropping the upper 2.5 percent of women in each exposure category ($p = 0.009$). As none of the exposures required non-linear terms for good model fit, odds ratios can be reported directly: the adjusted odds ratio for exposure 6 including all women is 0.92 (95% confidence limits (CI), 0.85, 0.99) for each extra hour/week of recreational PA at 27-30 weeks (indicating a protective effect for higher levels of activity), and the adjusted odds ratio for exposure 8 including all women is 0.89 (CI = 0.81, 0.99) per hour/week recreational MVPA at 27-30 weeks. The adjusted odds ratio for exposure 8 with the top 2.5 percent dropped is 0.84 (0.74, 0.97) per hour/week. Women who accumulated 2.5 hours of recreational MVPA per week (exposures 6 and 8) had reduced risk of augmentation of 5.1 percent and 6.5 percent when compared to women reporting no MVPA; this increased to 10.8 percent for exposure 8 when dropping women reporting large volumes.

Operative Vaginal Delivery

In models adjusting for primiparity, maternal age, gestational age at birth, and pre-eclampsia, OVD was associated only with exposure 3 (Wald χ^2 $p = 0.02$). When the upper 2.5 percent of women in each exposure category were dropped, OVD was associated with exposures 1, 3, and 7 ($p = 0.04, 0.03, 0.04$). There was no consistent pattern for OVD results; some significant exposures indicated an increased risk with increased activity, others a decreased risk, and others a U-shaped risk.

Episiotomy

Odds of episiotomy were not associated with any exposures.

Laceration Severity

In models adjusting for maternal age and primiparity, laceration severity was associated with exposures 1 and 3 (Wald χ^2 $p = 0.01, 0.01$), and trended towards an association for exposures 5 and 7 ($p = 0.07, 0.1$). In adjusted analyses excluding the top 2.5 percent of women in each exposure category, laceration severity trended towards an association for exposures 3 and 5 ($p = 0.08, 0.1$). There was no evidence of effect modification by primiparity.

Graphs showing the relationship between exposure 3 (with and without the upper 2.5 percent of women) and laceration severity are shown in Figure 5.2. Graphs for other exposures have the same general shape (and so are not shown): a slight increase is seen in overall risk of any laceration (gray line), which is driven by an increase in more severe lacerations (3rd or 4th degree perineal, vaginal, cervical) with increased physical activity, while risk of mild lacerations (1st or 2nd degree perineal, periurethral, labial) decreases with increased PA. For exposure 3 including all women, women who reported 2.5 hours/week of MVPA vs. those who reported none had an increased risk of severe lacerations of 1.2 percent, and a corresponding decrease

in the risk of mild lacerations of 0.5 percent; their risk of any laceration therefore increased by 0.7 percent.

Discussion

We found that PA during pregnancy was associated with decreased risk of labor induction, and that recreational PA in the early third trimester only was associated with a decreased risk of requiring labor augmentation. We also found that PA may be associated with more severe lacerations, though this increase may not be clinically significant for women who do not report large volumes of activity. Maternal PA was not associated in our sample with OVD, episiotomy, or labor duration subsequent to hospital admission. Additionally, our results suggested that increased PA may be associated with longer labor durations, but given that our measure of labor duration was quite crude, we urge caution when interpreting this result.

For labor induction we found consistent results across numerous definitions of PA. Increased PA or MVPA, all modes or recreational only, of 2-5 hours/week (among women reporting no more than a 5 hours/week) was associated with a clinically-significant decreased risk of induction. Above this level of activity the association is unclear because of the nature of the PA data, which were highly right-skewed. To address this concern, we conducted a sensitivity analysis dropping women in the upper 2.5% of activity volume for each exposure—the association with induction at low volumes of PA remained, though we are unable to comment on effects of higher levels of activity (areas of Figure 5.1 to the right of the green vertical lines).

Our induction results differ from those reported by Magann et. al. in 1996 (45); however, in that study, the only group which had an increased risk of induction were those women expending more than 2900 kilocalories per day, whereas our main induction finding is limited to

women accumulating much less physical activity. Indeed, we cannot rule out a harmful effect for women accumulating large volumes of activity—we can only report with some confidence that among women who were not overly active, a few additional hours/week of PA is associated with reduced induction risk. In a second study, Magann et. al. again reported an increased risk of induction for women who accumulated more PA.(46) However, the study population was women on active duty in the military. Generalizeability issues aside, these women reported large volumes of both occupational and leisure-time physical activity during their pregnancies, and so again our results are not comparable. Given our careful attention to appropriate statistical methods and use of a validated exposure data collection instrument, we believe that among women reporting fewer than 5 hours per week of physical activity, more physical activity is associated with lower risk of labor induction.

In Table 5.1, the median labor duration from time of admission was longer than the median labor duration from time of onset. Given that the question eliciting time of onset was phrased as "regular, painful uterine contractions began occurring every 3 to 5 minutes and ended in delivery", it seems likely that women were admitted while still in latent labor, leading to a longer admission time than labor duration from time of onset time.

Higher volumes of maternal PA were consistently associated with longer labor durations, calculated from time of labor onset. Among the statistically significant exposures, an average of 16 additional minutes of labor can be expected for each additional hour per week of PA during pregnancy. These findings were robust to dropping women reporting the uppermost volumes of activity. Previous studies on this specific topic have reported a variety of results with no consistent pattern. We do not believe that our results for this outcome are conclusive. Though we did have high-quality PA exposure data, our outcome was total labor duration (excluding the third stage), based on time of labor onset as self-reported by the mother. Ideally when

addressing labor duration, one would use labor curves, and analyze stages of labor separately. Given that our data did not allow such detailed examination of labor progress, we would not recommend changes to clinical practice based on our finding of an association between increased maternal PA and longer labor durations.

By contrast, we did not find an association between PA and labor duration calculated from time of admission. In a *post hoc* exploratory analysis, we calculated a modified Bishop's score from admission exam data reported in the Perinatal Database. The modified Bishop's score was calculated in the same way as the regular Bishop's score (93), but included only dilatation, effacement, and station information. The resulting variable ranged from 0-9. Bishop's scores are traditionally used to predict induction success; we use them here in an unusual way, as a proxy for labor progress prior to admission. PA during pregnancy was associated with the modified Bishop's score for almost all exposures, with or without the upper 2.5 percent of women—models controlling for primiparity indicated that women who were more active had higher scores when they were admitted, roughly an additional 0.05 points per additional hour of PA. This provides a possible explanation for the discrepancy in the two labor duration results—women who were more active did in fact have longer labors, but they also spent more time laboring at home before arriving at the hospital, resulting in no difference in admission durations.

Once admitted, it seems that women who engaged in more recreational PA nearer to term (27-30 weeks) had a lower risk of requiring labor augmentation. This result was robust to dropping women reporting large amounts of activity, however such associations were not observed for other exposures. It is not unreasonable that PA nearer to term would have an impact whereas activity earlier in pregnancy would not—PA has many physiologic impacts, both short- and long-term. Given the rapid physiologic changes of pregnancy, PA may well have

varying effects depending on gestational age at time of exposure. Our result is consistent with 2 others reported in the literature (31,35), but not with that reported by Magann for the women on Active Duty.(46)

We did not find an association between maternal PA and OVD. Some exposures were statistically significant predictors of OVD in adjusted analyses, but because the direction and magnitude of the association varied widely, it is unlikely that this is a true result. More probable explanations are random chance and residual or unmeasured confounding.

Likewise, we found no association between activity and episiotomy risk. This set of analyses was statistically underpowered, because of the extremely small sample size (only 36 women had episiotomy). It seems that clinicians attending births for the women in this study were sparing in their use of episiotomy, as recommended by current best-practice guidelines.(84) Given the strong evidence against routine episiotomy, it seems unlikely that episiotomy rates will increase again. Therefore further explorations of associations with maternal PA may be unwarranted.

Women who were more active during pregnancy may be at slightly increased risk of severe lacerations. These results were stronger for exposures at the earlier timepoint (17-22 weeks), and were moderately robust to dropping women reporting volumes of activity in the uppermost 2.5 percent of each exposure category. Regardless, the effects seen among women reporting low volumes of activity (the vast majority of our sample) are quite small, on the order of 1 or 2 percent.

Our study has some limitations. First, women who participated in the PIN3 Study are not representative of childbearing women in the US as a whole. Second, we ran numerous models without explicitly correcting for multiple comparisons. We were aware of this issue throughout

the analysis, however, and restricted firm conclusions to those outcomes showing consistent associations across many exposures. Third, our PA recall questionnaire asked women to report activities which increased breathing or heart rate. Therefore light intensity activities may be under-reported. Finally, we obtained PA data during only 2 weeks during pregnancy. It is possible that PA at other times during pregnancy would have different effects, or that overall cardiovascular fitness is the “correct” exposure, and our 7-day recalls were acting as proxies.

Our study had many strengths, including a prospective design, extremely detailed physical activity data collected at two time points during pregnancy using a reliable and valid instrument, and a large sample size. Additionally, we improved on analytic methods used in previous studies by keeping PA as a continuous variable, allowing departures from linearity where warranted, assessing recreational activity separately, and utilizing appropriate multivariable techniques to address confounding.

Conclusion

We found that increased physical activity during pregnancy was associated a reduced risk of induction but a longer total labor duration based on maternal self-reported time of labor onset. Additionally, recreational PA at the start of the third trimester was associated with reduced risk of induction. PA during pregnancy was not associated with OVD, episiotomy, or labor duration subsequent to hospital admission. We cannot comment, based on our results, on associations between PA and laceration severity.

In clinical practice, one often sees pregnant women who are not physically active. We calculated risk differences for our outcomes, comparing pregnant women who reported 2.5 hours/week of MVPA to those who reported zero hours/week of MVPA. This was intended to provide clinicians with a frame of reference for counseling inactive women. For example, 2.5

hours/week MVPA vs. 0 is associated with a reduction in risk of labor induction of 7.0%. 2.5 hours/week of recreational MVPA at the beginning of the third trimester vs. 0 is associated with a reduction in risk of labor augmentation of 5.8%. Finally, our results suggest that women who reported 2.5 hours/week of MVPA vs. those who reported none experienced an average of 48 additional minutes of labor, though the pattern of our results suggests that this extra laboring time occurred prior to admission, presumably in early labor. From previously-published work of other researchers, moderate exercise 3-5 times/week vs. 0 is associated with 3.1 fewer kg of gestational weight gain (94); hours/week recreational PA above the sample median vs. 0 hours/week is associated with a 75% reduction in gestational diabetes (95); and a half-hour of walking 3-4 times/ week is associated with a 50% reduced risk of pregnancy-induced hypertension when compared with women randomized to stretching instead of walking.(96) These benefits of PA on other maternal pregnancy outcomes have been demonstrated in multiple additional studies; given the proven benefits we do not recommend that clinicians counsel women against PA during pregnancy on the basis of our increased labor duration finding.

Table 5.1. Sample characteristics, n=945 participants in the third Pregnancy, Infection, and Nutrition study who had a vaginal delivery; all data shown were calculated before imputation.

	mean	stdev ¹	median	IQR ²	missing
birthweight (grams)	3269	591	3315	3000 – 3651	4
gestational age at birth (completed weeks)	38.4	2.3	39	38 – 40	0
maternal age at conception	28.2	5.5	29	24 – 32	0
% 2001 household poverty level	383	228	379	181 – 596	43
hours/week PA ³ reported at 17-22 weeks	7.2	9.4	4.2	1.8 – 8.8	0
hours/week PA reported at 27-30 weeks	6.2	7.0	4.0	1.7 – 8.2	61
hours/week MVPA ⁴ reported at 17-22 weeks	3.4	6.9	1.0	0 – 3.8	0
hours/week MVPA reported at 27-30 weeks	2.8	5.0	1.0	0 – 3.1	61
pre-gravid BMI ⁵ (kg/m ²)	25.4	6.5	23.3	20.9 – 28.3	15
labor duration after admission (minutes) ⁶	707	489	606	350 – 952	35
self-reported labor duration (minutes) ⁷	607	454	495	267 – 791	217
	n	%			
93 married	677	72			0
Caucasian	640	68			1
maternal education: completed at least high school	865	92			0
completed at least 4 years college	547	58			
primiparous	448	47			0
preterm birth (<37 weeks)	112	12			0
low birth weight (<2500 g)	81	8			4
pre-eclampsia	35	4			4
induction	287	30			0
augmentation	294	31			0
operative vaginal delivery	116	12			0
episiotomy	36	4			0
perineal laceration severity:					143
no lacerations	190	24			
periurethral, labial, 1 st or 2 nd degree perineal	494	62			
3 rd or 4 th degree perineal, vaginal, cervical	118	14			

¹ standard deviation; ² interquartile range

³ physical activity: sum of all activities reported as at least "fairly light" during the previous week

⁴ moderate to vigorous physical activity: sum of those activities reported as at least "somewhat hard" during the previous week

⁵ body mass index; ⁶ Calculated as time of birth minus time of admission; ⁷ Calculated as time of birth minus mother's self-reported time of labor onset

Table 5.2. Physical Activity exposure definitions applied to the Pregnancy, Infection, and Nutrition study.

exposure	definition	all intensities	MVPA only	recreational activity only	17-22 weeks	27-30 weeks
1	total hours/week physical activity (all intensities), assessed by 7-day recall between 17 and 22 weeks completed gestation	x			x	
2	total hours/week physical activity (all intensities), assessed by 7-day recall between 27 and 30 weeks completed gestation	x				x
3	hours/week moderate-to-vigorous physical activity, assessed by 7-day recall, 17-22 weeks		x		x	
4	hours/week moderate-to-vigorous physical activity, assessed by 7-day recall, 27-30 weeks		x			x
5	total hours/week recreational physical activity (all intensities), 7-day recall, 17-22 weeks	x		x	x	
6	total hours/week recreational physical activity (all intensities), 7-day recall, 27-30 weeks	x		x		x
7	hours/week recreational moderate-to-vigorous physical activity, 7-day recall, 17-22 weeks		x	x	x	
8	hours/week recreational moderate-to-vigorous physical activity, 7-day recall, 27-30 weeks		x	x		x

Figure 5.1 (shown on next page). Predicted proportion of inductions (and point-wise 95% confidence intervals) at different levels of self-reported physical activity for 945 women in the third Pregnancy, Infection, and Nutrition cohort who had a vaginal birth. Curves shown are for women without pre-eclampsia and with pre-gravid BMI set at the sample median (23.3 kg/m^2). The green vertical lines indicate the 90th percentile for each exposure, above which results are not stable. The red curves in the left-hand column show data density functions for each exposure.

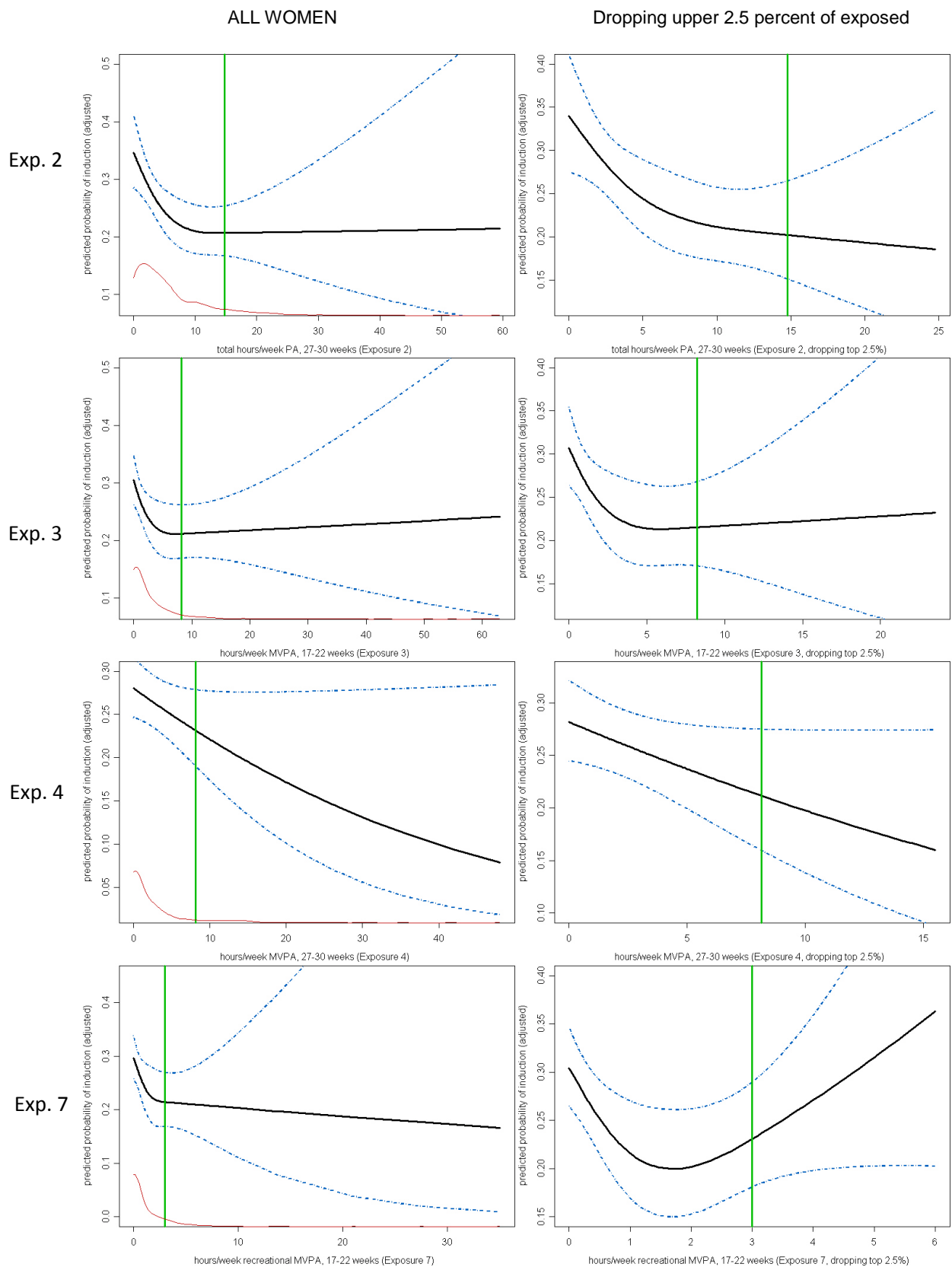
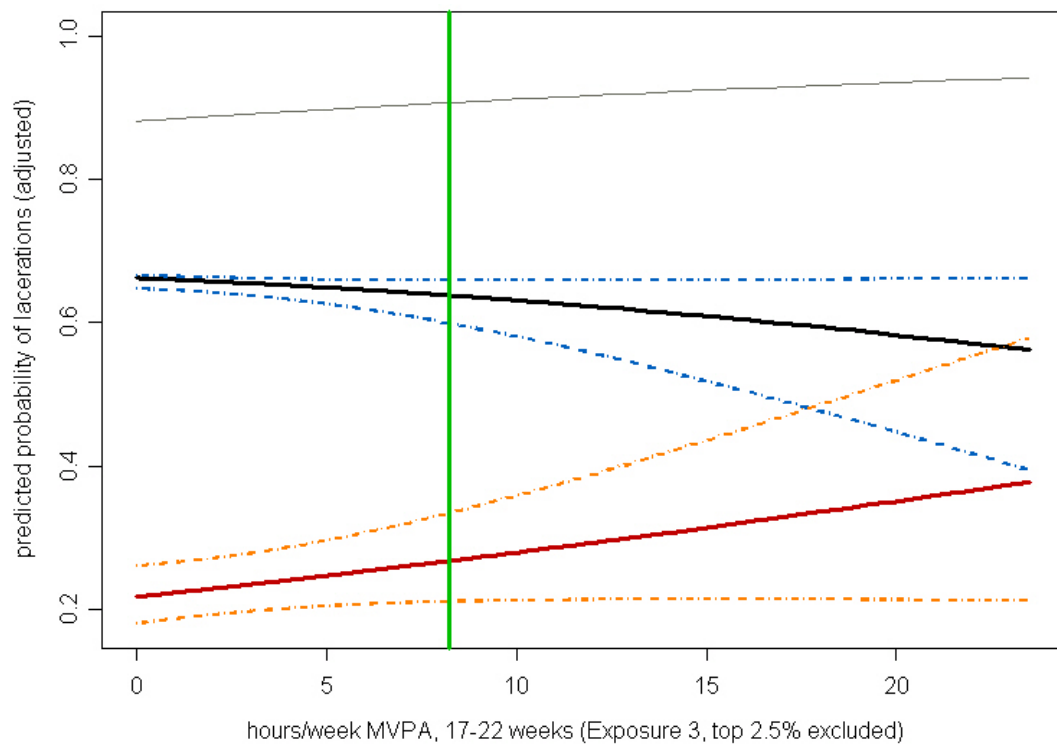
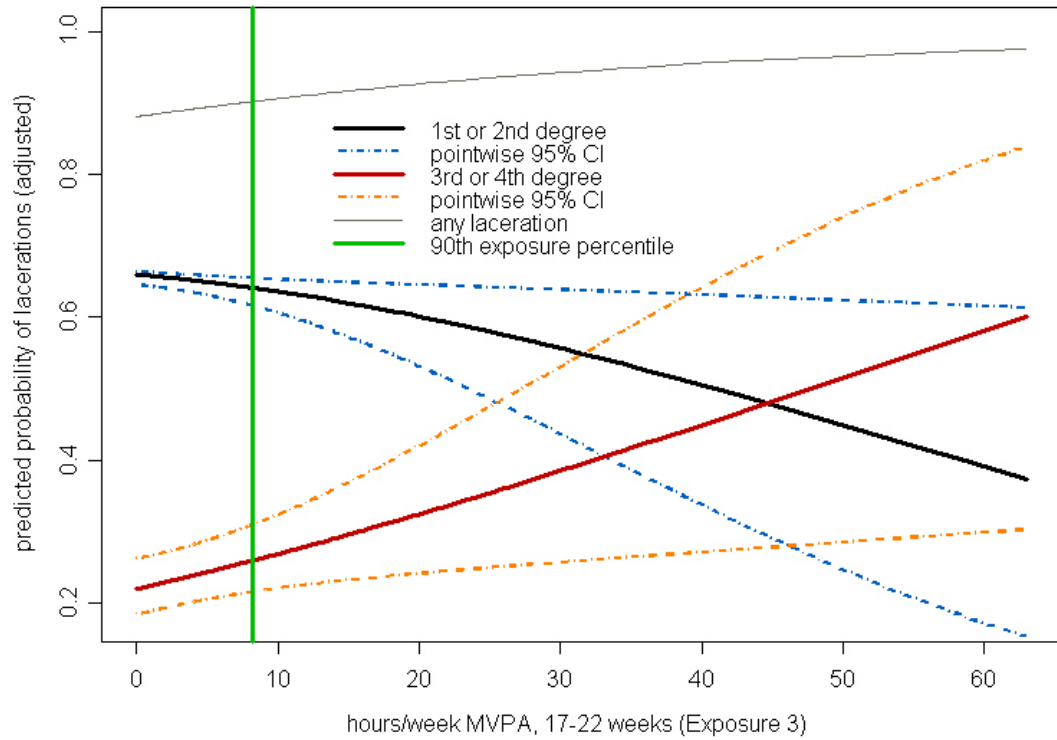


Figure 5.2. Predicted risk of laceration severity for Exposure 3 (hours/week moderate-to-vigorous physical activity, 17-22 weeks). Curves shown are for primiparous women with maternal age set to the sample median (29 years). The green vertical lines indicate the 90th exposure percentile, above which predicted estimates are unstable.



DISCUSSION

This dissertation project explored associations between maternal physical activity (PA) during pregnancy and birth outcomes. Our results showed that associations often have a dose-response curve, this curve is sometimes non-linear, and it can vary depending on gestational age (GA) at time of exposure. Furthermore, PA was associated with induction risk (among women accumulating fewer than 5 hours/week, more activity is associated with reduced induction risk), augmentation risk (more moderate-to-vigorous PA [MVPA] at 27-30 weeks reduces the need for augmentation), and labor duration from time of onset (increased PA is associated with longer labor durations). PA during pregnancy might be associated with increased laceration severity, but this is not a clinically-significant increase among women who do not report large amounts of activity (the only group about whom comments can be made, given the skewness of the data). PA during pregnancy does not appear to be associated with cesarean, operative vaginal delivery (OVD), labor duration from time of admission, or episiotomy risk.

Limitations

This project had several limitations. First, all PA exposure data relied on self-report. Though the recall instrument has proven reasonably reliable and valid in pregnant women (89), the data are still self-reported, and thus subject to recall and social-desirability biases. Additionally, half of the exposures rely on total PA, including light intensity activities. However, since the questionnaire asked women specifically to recall only those activities which increased breathing or heart rate, it is likely that light

intensity activities were underreported. It is unclear how this would affect the results and how much under-reporting took place.

Along those same lines, the exposures used in this dissertation were 7-day windows of activity during pregnancy. For many of the outcomes, a plausible biologic pathway includes lifetime PA accumulation. This concern cannot be addressed directly using the PIN3 data, but it seems likely that women who are physically active during pregnancy are also the ones who are physically active when not pregnant, so perhaps the exposures in PIN3 are adequate proxies of lifetime exposure. Additionally, the PIN3 study asked only about two 7-day windows during pregnancy. It is entirely possible that these two windows were not representative of women's PA during other weeks of their pregnancy.

Third, as detailed in Paper 1, indication for some procedures may be important. However, outcomes data come from medical records and were not of sufficient quality to entertain such an analysis. Fourth, the ideal way to study labor duration is through the use of labor curves. This study did not achieve this ideal, nor were we able to discern anything beyond total duration of the first and second stages of labor.

Fifth, as detailed in the Methods section, Paper 2 predicted log odds for all outcomes to simplify reporting of results. For many of the dichotomous outcomes, the prevalence of the outcome was more common than is usually recommended for logistic regression. This causes the odds ratio not to be a perfect estimate of the risk ratio, but it is unclear how strong this bias would be. Given the consistency of results for the two strongest associations (induction and labor duration), however, it is unlikely that the results would change drastically.

Lastly, the PIN3 study enrolled women living in central North Carolina who were seeking early prenatal care at a clinic affiliated with UNC Hospitals, and who intended to deliver at a UNC Hospital. Women who enrolled are not representative of all women delivering at UNC Hospitals; the study sample was largely white, well-educated, married, and from a reasonable wealthy household. In turn, women planning to deliver at UNC hospitals are probably not representative of all childbearing women in central North Carolina; nor are they representative of all childbearing women in the US or globally.

Study Strengths

This project was an improvement over previous efforts in several areas. First, though self-reported exposure data has known measurement issues, exposure ascertainment in the PIN3 Study occurred prospectively, so all exposures were determined before any birth outcomes had occurred. Additionally, birth outcome data come from a separate, clinical source—nurses maintaining the perinatal database likely were not aware of a woman's participation in the PIN3 study, and certainly were unaware of her physical activity exposure status. Thus differential measurement bias is not a concern.

This study had a larger sample size than most others examining PA and maternal birth outcomes. Women were recruited to be in the PIN3 study without knowledge of their physical activity exposure status, and were recruited from antenatal care clinics. Many previous studies enrolled only athletes, who are probably different than most pregnant women.

This study was the first study to control for confounding in a systematic and somewhat-complete manner, as well as the first to treat PA as a continuous measure. Both of these improve the internal validity.

The PIN3 Study collected more detailed exposure data than any previous study on this topic. Two complete 7-day recalls during pregnancy, including activity from all modes, yield a more complete picture of pregnant women's physical activity patterns than any previous study.

Finally, this was a secondary data analysis. While this admittedly has some drawbacks, the benefits should not be underestimated. This analysis cost a fraction of the budget for the PIN3 study, and also cost much less than the cost of maintaining the perinatal database. It was completed in under 2 years. Secondary data analyses such as this one are a wise use of limited research resources.

Mechanisms

In this project, PA was associated with longer labor durations when measured from time of onset, but not with labor duration when measured from time of admission; this is likely explained by the corresponding increase in modified Bishop's score seen in women who are more active (see Paper 2). This finding could also explain the lack of association seen for other outcomes. Cesarean and OVD are both dependent at least partly on *admission* duration. Laboring in the hospital without sufficient progress leads to various interventions, which in turn can lead to operative delivery of one type or another. If PA is not associated with admission duration, this could explain why associations with cesarean and OVD were not present in these data. It could also explain why stronger associations were not seen with augmentation.

This study found a reasonably strong association between PA and reduced induction risk. Walking is a commonly-cited method for self-inducing one's labor (97-99)—perhaps there is some truth to this old wives' tale, though evidence in favor is muted somewhat by lack of a substantially stronger effect at the 27-30 week time point.

Public Health Implications

Women participating in the PIN3 study generally did not accumulate sufficient physical activity to meet current guidelines.(Borodulin) This is of concern because there are many known benefits of physical activity, both generally and during pregnancy. These include reduced risk of gestational diabetes, reduced gestational weight gain, reduced risk of pregnancy-induced hypertension (though not necessarily of pre-eclampsia) and faster postpartum return to pregravid weight.(94-96) This project adds to this body of knowledge by suggesting that PA during pregnancy may reduce a woman's risk of being induced or of requiring pharmacologic labor augmentation, but on the other hand it may increase her labor duration. These results require confirmation in other research settings before clinical or public health interventions can be considered.

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