PHYSICAL EXERCISE DURING PREGNANCY AND REPRODUCTIVE OUTCOMES

Mette Juhl

PhD thesis
University of Copenhagen
2009

The academic work was carried out at The National Institute of Public Health, University of Southern Denmark, Copenhagen, Denmark, and School of Public Health, University of California, Los Angeles, Los Angeles, CA, US

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This thesis is based on four papers:

Paper 1: Juhl M, Madsen M, Andersen AMN, Andersen PK, Olsen J. Predictors of regular exercise during pregnancy: A study within the Danish National Birth Cohort on pregnant women's exercise habits. Submitted.

Paper 2: Juhl M, Andersen PK, Olsen J, Madsen M, Jørgensen T, Nøhr EA, Andersen AMN. Physical exercise during pregnancy and the risk of preterm birth: A study within the Danish National Birth Cohort. Am J Epidemiol 2008;167:869-866.

Paper 3: Juhl M, Olsen J, Andersen PK, Nøhr EA, Andersen AMN. Physical exercise during pregnancy and fetal growth measures: A study within the Danish National Birth Cohort. In press. Am J Obstet Gynecol.*

Paper 4: Juhl M, Kogevinas M, Andersen PK, Andersen AMN, Olsen J. Is swimming during pregnancy a safe exercise? In press. Epidemiology.**

*A PDF proof from the American Journal of Obstetrics and Gynecology is printed here. It differs negligibly from the draft included in the version for the assessment committee.

** A revised version of the paper, which is now accepted in Epidemiology, is printed here. It differs to some extent from the draft included in the version for the assessment committee.

PREFACE

When this work was initiated, The National Institute of Public Health was an independent research institute under The Danish Ministry of Health placed in Copenhagen; therefore I was enrolled as a PhD-student at The University of Copenhagen. During the making of the thesis, the institute, however, became part of University of Southern Denmark, which explains why both universities are mentioned on the title page.

I wish to thank:

- The participating women in The Danish National Birth Cohort who took their time to contribute to this research.
- My supervisors: Anne-Marie Nybo Andersen, Per Kragh Andersen, and Jørn Olsen. I am grateful to you. All three of you have been excellent in your professional guidance and personal support and company.
- My colleagues from the hard working project group in The Danish National Birth Cohort at Statens Serum Institut.
- My present colleagues at The National Institute of Public Health, especially Marie Kruse, Louise Norman Jespersen, and colleagues in the Child Health Programme.
- My colleagues in other places, especially Mia Madsen, Katrine Strandberg-Larsen, Laust Hvas Mortensen, Ellen Aagaard Nøhr, Hanne Kjærgaard and Hanne Hegaard.
- Good friends and family for listening to complaints and excitements over the years.

The Danish National Research Foundation has established the Danish Epidemiology Science Centre, which initiated and created the Danish National Birth Cohort. The cohort is furthermore a result of a major grant from this foundation. Additional support for the Danish National Birth Cohort is obtained from the Pharmacy Foundation, the Egmont Foundation, the March of Dimes Birth Defects Foundation, and the Augustinus Foundation. This study was supported by grants from The Danish Medical Research Council, The Danish Midwifery Association, The Danish Graduate School in Public Science, The Augustinus Foundation, The National Board of Health, The Oticon Foundation, and The Julie von Müllens Foundation.

Mette Juhl
Copenhagen, Sept 2009

CONTENTS

1 INTRODUCTION

Following an international increase in obesity and lifestyle related diseases, physical activity has consolidated its place as a core topic in health promotion and preventive medicine. According to the World Health Organization, physical activity plays an essential role in the prevention of cardiovascular disease, stroke, type II diabetes, colon and breast cancer, and depression (World Health Organization 2009). Formerly, women were expected to limit physical activity when becoming pregnant, due to an assumed increased risk of spontaneous abortion and preterm birth. Even though pregnancy is a unique condition characterized by a different physiology in the mother and concern for the growing foetus, this precaution is now generally disregarded and today physical activity is also part of antenatal care. Guidelines in the US, Canada, Great Britain, Norway and Denmark recommend pregnant women to be physically active (almost) at the same level as the non-pregnant population (ACOG 2002; RCOG 2003; The Directorate for Health and Social Affairs 2005; Davies et al. 2003; National Board of Health 2009). The Danish recommendations are in line with those of The Danish Society of Obstetrics and Gynaecology (DSOG 2008). In Denmark the recommendations include a minimum of 30 minutes of moderate physical activity per day for healthy pregnant women, while women with an increased risk of pre-eclampsia or gestational diabetes should be even more active.

In addition to general health benefits, physical activity has been associated with favourable effects on maternal outcomes in pregnancy such as gestational diabetes (Dempsey et al. 2004; Dye et al. 1997; Solomon et al. 1997) and pre-eclampsia (Marcoux, Brisson, and Fabia 1989; Sorensen et al. 2003), although the assumed preventive effect on pre-eclampsia is being questioned in a Cochrane review and a recent study from The Danish National Birth Cohort (Meher and Duley 2006; Osterdal et al. 2009). When it comes to possible exercise-induced positive or negative effects on the health of the foetus, the evidence is weaker. It has been layman's belief for many years that physical activity could initiate labour activity, and imminent preterm birth has been treated with bed rest. This practice is not based on scientific evidence but emerges as a matter of precaution in the lack of well-founded treatment actions against preterm labour. Furthermore, hypotheses have been put forward that physical activity may result in reduced foetal growth due to a restricted oxygen delivery to the foetus during physical activity because of a redistribution to the working muscles instead of to the placenta and foetus (please refer to 2.2 for details on possible mechanisms). Hence, the jury is still out on concerns for the unborn child in the relation to the mother's physical activity level, and in a handful of reviews addressing maternal physical activity and reproductive outcomes it is generally agreed that literature is limited and that results are inconclusive.

A Cochrane review from 2006 examined regular aerobic exercise during pregnancy in 11 controlled trials of which seven reported on pregnancy outcomes (Kramer and McDonald 2006). From their pooled analysis there was an increased, but far from statistically significant, risk of preterm birth (relative risk 1.82, 95% confidence interval 0.35, 9.57) but no association between exercise and mean gestational age. Results on birth weight were even more inconsistent. The trials were described as ‘small and not of high methodological quality’ by the authors, who also concluded that ‘available data are insufficient to infer important risks or benefits for the mother or infant’. Other reviews point towards either no association with preterm birth or perhaps a decreased risk among exercising women (Clapp, III 2000; Dye et al. 2003; Hegaard et al. 2007; Leet and Flick 2003; Lokey et al. 1991; Riemann and Kanstrup, I 2000; Schlussel et al. 2008; Simpson 1993; Sternfeld 1997; Stevenson 1997). Likewise, either no association or a slight positive association between exercise and birth weight have been reported (Clapp, III 2000; Dye et al. 2003; Ezmerli 2000; Hegaard et al. 2007; Kramer and McDonald 2006; Riemann and Kanstrup, I 2000; Schlussel et al. 2008; Stevenson 1997). In their review evaluating 37 studies from 1980-2005, Schlüssel and colleagues stressed that future research should include intensity, duration, and frequency of physical activity to ‘contribute to the making of more detailed guidelines in antenatal care’ (Schlussel et al. 2008).

In the first study on maternal physical exercise in The Danish National Birth Cohort (DNBC) we examined the risk of miscarriage, being one of the most frequent adverse pregnancy outcomes. We found an increased risk of miscarriage among women who exercised early in pregnancy (Madsen et al. 2007). A dose-response relation was seen between the amount of exercise and the risk of miscarriage. Further, specific types of exercise, such as jogging, ball games and racket sports, were found more closely related to miscarriage than other activities. Part of the association may be explained by potential bias due to (partly) retrospectively collected exposure data. However, studies on life style factors in the very first part of pregnancy and early foetal loss using prospectively collected data are difficult to carry out and therefore rarely done.

Swimming is in general considered a safe and suitable exercise during pregnancy, and in the above study swimming was not associated with miscarriage (Madsen et al. 2007). Chemical exposures deriving from chemical disinfection processes in drinking water have, however, been associated with adverse reproductive outcomes, and since swimming pool water contains some of the same cleaning products as drinking water, this is of interest in environmental epidemiology (Bove, Shim, and Zeitz 2002; Graves, Matanoski, and Tardiff 2001; Nieuwenhuijsen et al. 2000). One study has addressed the relation between swimming in pools during pregnancy and birth weight in the off-spring, and found no association (Nieuwenhuijsen et al. 2000).

Pregnancy leads to a reduced level of physical activity for most women, the activity level is often further reduced throughout pregnancy, and the pre-pregnancy exercise level is usually not regained six months after childbirth (Fell et al. 2008; Hinton and Olson 2001; Owe, Nystad, and Bo 2008; Pereira et al. 2007; Zhang and Savitz 1996). Among women who are physically active before pregnancy, the factors associated with discontinuing sports activities during pregnancy, are similar to those for inactivity both prior to and after pregnancy (Donahue et al. 2009; Fell et al. 2008; Pereira et al. 2007). Hence, if physical activity during pregnancy is healthy - or at least harmless - for both the mother and the child, knowledge on exercise behaviour in relation to pregnancy and predictors is useful in terms of public health interventions. With the increasing focus on physical activity in general, it is essential to establish evidence based guidelines addressing physical activity during the pregnancy period.

Our findings on exercise being associated with miscarriage together with the sparse knowledge on possible effects on the foetus of maternal physical activity became the main objectives for this PhD-study at a time where physical activity is at extreme focus in public health.

1.1 AIMS AND OUTLINE OF THE THESIS

The aim is to add to scientific evidence about possible health consequences for the foetus of maternal exercise during pregnancy, based on data from the Danish National Birth Cohort. The specific aims are addressed in four papers:

Paper 1: To describe the level and character of exercise among pregnant women in the Danish National Birth Cohort and to identify lifestyle and socio-demographic factors and aspects of health and reproductive history associated with physical exercise during pregnancy.

Paper 2: To examine the association between physical exercise during pregnancy and the risk of preterm birth.

Paper 3: To examine the association between physical exercise during pregnancy and selected foetal growth measures.

Paper 4: To examine the association between swimming during pregnancy and several birth outcomes (pre- and postterm term birth; foetal growth measures, including birth weight and small-for-gestation-age; and congenital malformations).

2 BACKGROUND

2.1 Definitions and key concepts

Gestational age

The gestational age of a foetus denotes the number of days since conception, but since the precise moment of conception is rarely known, one commonly used measure of gestational age is number of days from the first day of the woman's last menstrual period. Limitations in using this measure include uncertainty regarding the date of last menstrual period (e.g. recall bias or bleeding not associated with menstrual periods) or irregular bleedings and varying timing of ovulation (Lynch and Zhang 2007). Today, almost all pregnant women in Denmark have at least one ultrasound examination during pregnancy, and hence the gestational age registered at birth is most often based on this ultrasound examination. One limitation in using ultrasound-based gestational age determination is that estimates of symmetrically large or small foetuses are often biased because normal variability is not taken into account (Lynch and Zhang 2007). Recent studies, though, on foetuses conceived through *in vitro* fertilisation, where the date of conception is known, show high accuracy in ultra-sound gestational age estimation (Chervenak et al. 1998).

The women in the DNBC were asked about gestational age twice during pregnancy and about gestational age at birth of their child when interviewed six months after delivery. Furthermore, the DNBC-database was linked to The Medical Birth Registry, which is nationwide and contains records on all births in Denmark. Such linkage is possible due to national systems of unique person identifiers, where every newborn child is assigned a unique civil registration number. In Denmark, gestational age of the offspring is usually registered by midwives within few hours after delivery. For the studies in this thesis, we have used the gestational age from the Medical Birth Registry. These data have undergone a thorough validation based on identification of records where the distance between self-reported expected date of delivery and gestational age at birth differed more than 14 days. In these cases, a gestational age was applied according to the principles used by Gardosi & Geirsson (Gardosi and Geirsson 1998).

Preterm birth

Preterm birth is defined as a delivery before 37 completed gestational weeks (less than 259 days) (Iams and Creasy 2004). Prematurity is the factor that contributes the most to perinatal and neonatal morbidity and mortality (Slattery and Morrison 2002). Also long-term consequences have been reported among children born extremely or very preterm (i.e. 22-27 and 28-31 completed weeks, respectively (Langhoff-Roos et al. 2006)), such as chronic pulmonal disease (Hentze et al. 2006), cerebral palsy (Himmelmann et al. 2005), or other neurological disorders (Marlow et al. 2005). Children born moderately preterm (i.e. 32-36 completed weeks (Langhoff-Roos et al. 2006)) seem to be at lower risk of serious long-term disorders. These children form an important group in terms of public health due to the large numbers (Kramer et al. 2000). The incidence of preterm birth seems to increase in some countries, such as the US and Denmark (Langhoff-Roos et al. 2006; Martin et al. 2008). Prediction and prevention of preterm birth is, however, still to be resolved.

Postterm birth

Postterm birth is defined as delivery after 42 completed gestational weeks, i.e. pregnancy is considered prolonged when it exceeds 294 days (Resnik and Resnik 2004). A small but consistent rise in infant mortality in deliveries after week 42 has been reported (Wilcox and Skjaerven 1992). Newborn postterm babies have a reportedly higher incidence of perinatal morbidity, such as e.g. low Apgar score, foetal distress, meconium staining (Shea, Wilcox, and Little 1998). Long-term paediatric consequences are poorly studied, but some adverse long-term outcomes may work through perinatal morbidity (Shea, Wilcox, and Little 1998). Postterm birth is preventable because of the possibility of artificial induction of labour.

Birth weight

In the attempt to find a good proxy for foetal growth, birth weight has been studied extensively, probably due to its high accessibility in both developed and developing countries. It is also monitored globally by the World Health Organization (Blanc and Wardlaw 2005). However, it has been argued that low birth weight defined as a birth weight less than 2500 g is widely misinterpreted as outcome because underlying causes like foetal growth restriction, preterm birth, and genetically small body size cannot be identified (Adams et al. 2003), and because low birth weight in itself takes no account of population specific birth weight distributions (Wilcox 2001). There seems to be a strong link between birth weight and perinatal mortality at each fixed gestational age, which could be an epiphenomenon to a common cause (Basso, Wilcox, and Weinberg 2006). As birth weight is not only a result of foetal growth but also of length of gestation, gestational age should be taken into account when studying birth weight. If possible, additional measures of body size and/or composition should also be included in studies on foetal growth.

Small- and large-for-gestational-age

Small-for-gestational-age (SGA) is usually defined as a gestation specific birth weight below the 5th or 10th percentile, according to a chosen growth curve for the foetus/newborn child, and correspondingly large-for-gestational-age (LGA) is defined as having a birth weight above the 90th or 95th percentile (Nguyen and Wilcox 2005; Sacks 2007). Growth curves based on weight at birth are assumed to underestimate foetal weight in the preterm period, because the preterm birth weights are based on abnormal deliveries and therefore on average are lower than birth weights of foetuses that stay *in utero*. Foetal growth takes place *in utero*, and therefore a measurement of the weight (and other size measures) continuously throughout pregnancy would be the ideal way to monitor foetal growth. However, ultrasound examinations are especially sensitive to measurement error and is also not feasible in many places. Intra-uterine growth restriction (IUGR) and SGA are sometimes used interchangeably, which is not appropriate since not all small babies are growth restricted, and not all growth restricted babies are in the lowest centile of size (Wilcox 1983). Using a specific cut-point for birth weight for a given gestational age does not make it possible to distinguish between normally grown babies, who just happen to be small (e.g. for genetic reasons), and pathologically small babies. E.g. a baby with an ’optimal’ birth weight of 4000 g that weighs 3500 g at birth would not be considered small for its age according to an SGA definition, even though it has obviously grown too slow according to its ’own’ growth curve.

Much attention has been given to the growth restricted infant, who is at increased risk of both short- and long-term adverse health conditions. However, also large babies seem to face increased risks of intrauterine or perinatal death, birth traumas and long-term consequences like overweight, diabetes, metabolic syndrome, asthma, and cancer (Das and Sysyn 2004). Most research on LGA, or on offspring overgrowth relates to maternal diabetes, but although diabetic mothers tend to have larger babies, they only account for less than 10% of LGA infants. Other causes of LGA comprise postterm delivery, maternal obesity, and foetal hyperinsulinemia (Das and Sysyn 2004).

In this thesis additional foetal growth indicators were included in the attempt to capture possible indicators of impaired foetal growth, also within normal limits of birth weights, and in cases where mean birth weight is not affected (Catalano et al. 1998; Stein et al. 2004). Foetal or neonate body composition is not taken into account in the SGA or LGA meausure (Sacks 2007).

2.2 Possible mechanisms between physical exercise and reproductive outcomes

Preterm birth

Few plausible mechanisms between exercise and preterm birth have been reported. Exercise increases the level of adrenaline and noradrenaline, which may trigger uterine contractions (Evenson et al. 2002; Riemann and Kanstrup, I 2000). In addition an increased risk of preterm birth with physically demanding or predominantly standing/walking work has been reported (Henriksen et al. 1995; Saurel-Cubizolles et al. 2004). In the absence of effective treatments, bed rest and relief from daily chores has been used in the prevention or treatment of preterm labour, based on the belief that rest could reduce uterine activity. A Cochrane review found only one study to meet inclusion criteria and concluded that there was no evidence to support or reject bed rest to prevent preterm birth (Sosa et al. 2004).

Foetal growth

Physical exercise may increase foetal growth due to an overall beneficial effect of exercise on the circulatory system, resulting perhaps in a larger placenta (Clapp, III and Rizk 1992; Jackson et al. 1995). Furthermore, exercise is likely to increase the intake of calories in the mother or result in a change in the composition or variation of the mother's food consumption. Exercise also has a hypoglycaemic effect (Bonen et al. 1992; Clapp, III and Capeless 1991; Lotgering et al. 1998), which may prevent the development of gestational diabetes in the mother and thereby decrease the prevalence of LGA-babies in exercising mothers (Alderman et al. 1998). However, a reduction in uterine blood flow in relation to exercise has also been reported, explained by a redistribution of blood flow away from the placenta to the working muscles (Clapp, III 1980; HART et al. 1956; Lotgering, Gilbert, and Longo 1983). In theory this might lead to foetal hypoxia, which again could result in intrauterine growth restriction if no catch up mechanisms follow the acute hypoxia. In the event of reduced uterine blood flow, not only oxygen but also the glucose provision to the foetus may be decreased, which might also lead to restricted growth.

2.3 Literature on leisure time physical activity and selected offspring health related outcomes

Preterm birth

Both preterm birth *per se* and uterine contractility as an indicator of preterm birth have been studied. A small trial (n=12) in the third trimester of pregnancy found bicycle ergometer and treadmill activities to be associated with increased uterine contractility, but found no association for rowing machine, recumbent bicycle or upper arm ergometer (Durak, Jovanovic-Peterson, and Peterson 1990). Uterine contractility was found to be correlated with type of exercise but not with level of exertion. In a cohort of 81 pregnant women climbing stairs and walking was associated with increased uterine contractility, but this was not the case for 'organized exercise' (Grisso et al. 1992). Among 30 women with elective induction of labour starting with artificial rupture of membranes, it was found that women who spent 20 minutes on cycle ergometer just after rupture of membranes had an increased uterine contractility compared with those who did not cycle (Spinnewijn et al. 1996). Other intervention studies have reported either no association between vigorous exercise during pregnancy and gestational length at time of delivery (Duncombe et al. 2006), or slightly shorter gestational length (Kardel and Kase 1998). Most cohort studies have found no association between physical exercise and preterm birth or gestational length (Grisso et al. 1992; Klebanoff, Shiono, and Carey 1990; Magann et al. 2002; Orr et al. 2006; Penttinen and Erkkola 1997; Perkins et al. 2007). Some cohort studies and a single case control study found a reduced risk of preterm birth among exercising women (Berkowitz and Papiernik 1993; Evenson et al. 2002; Hatch et al. 1998; Hegaard et al. 2008; Juhl et al. 2008; Misra et al. 1998), however, shorter gestational length has been observed after exercise during pregnancy (Clapp, III and Dickstein 1984). As mentioned, Kramer & McDonald reported an increased risk of preterm birth in a recent Cochrane review (Kramer and McDonald 2006). The findings were based, though, only on three small studies: The first study had zero events in both treatment and control group, the second study had one event in both treatment and control group, and the third study had three events in the treatment group and one in the control group. Hence risk estimates were far from statistically informative.

Birth weight/foetal growth

Cohort studies of varying size (n= 30-7101) have reported either no association between physical exercise and birth weight or SGA (Alderman et al. 1998; Hegaard et al. 2009; Klebanoff, Shiono, and Carey 1990; Magann et al. 2002; Orr et al. 2006; Penttinen and Erkkola 1997) or modest associations in opposite directions (Clapp, III and Dickstein 1984; Hatch et al. 1993; Perkins et al. 2007). Alderman and colleagues, though, found a reduced risk of LGA with maternal exercise (Alderman et al. 1998). A single case control study found exercise more prevalent among mothers of SGA-children (Campbell and Mottola 2001). The study used a rather extensive exercise measure, namely at least 5 sessions of exercise per week in late pregnancy. Most intervention studies have found no association between exercise during pregnancy and birth weight (Collings, Curet, and Mullin 1983; Duncombe et al. 2006; Kardel and Kase 1998; Lewis, Yates, and Driskell 1988; Marquez-Sterling et al. 2000). One randomized controlled trial on 46 women who did not exercise before pregnancy found that babies of mothers assigned to exercise 3-5 times per week during pregnancy to be on average 230 g heavier than babies of women who did not exercise (Clapp, III et al. 2000). On the contrary, a study on 75 regularly exercising mothers employed in the US military service and randomized to one of three intensity groups during pregnancy, showed that women with a high volume of exercise in mid/late pregnancy had lighter and thinner babies than women who were assigned to reduce their exercise volume after gestational week 20 and that a reduction in exercise from early to mid/late pregnancy was associated with increased birth weights (Clapp, III et al. 2002). Two meta-analyses (Leet and Flick 2003; Lokey et al. 1991) reported no or only minimal differences in mean birth weight in offspring of exercising mothers compared with those of non-exercisers, although vigorous exercise in late pregnancy was associated with lower birth weights (Leet and Flick 2003). The above mentioned Cochrane review concluded that findings on birth weight are inconsistent (Kramer and McDonald 2006).

Swimming and reproductive outcomes

In countries with chlorinated drinking water, it is difficult to separate exposure from swimming pools from that of drinking water. Hence, Denmark may be an ideal setting for studying swimming in pools, because chlorination is usually not used for drinking water, and swimming in indoor pools is popular. Only one study has addressed swimming in pools based on a concern that disinfection by-products deriving from the chemical cleaning processes of the water may have adverse reproductive effects. However, Niuwenhuijsen *et al* found no association between swimming during pregnancy and birth weight (Nieuwenhuijsen, Northstone, and Golding 2002). In animal toxicology literature high doses of disinfection by-products has been associated with reduced birth weight and length (Graves, Matanoski, and Tardiff 2001; Nieuwenhuijsen et al. 2000; Tardiff, Carson, and Ginevan 2006). Whether exposure to disinfection by-products in drinking water is associated with adverse birth outcomes is still inconclusive, but birth weight, SGA, preterm birth, miscarriages, stillbirths and congenital malformations have been, and are still being, studied (Graves, Matanoski, and Tardiff 2001).

2.4 Details on current guidelines

In 2004 the Danish National Board of Health published a handbook on physical exercise during pregnancy ([Physical activity - a handbook on prevention and treatment]2003). The handbook recommended that physically active women should carry on with exercise during pregnancy and that non-active women should commence exercising. These recommendations formed the basis for recent Danish guidelines published in April 2009 (National Board of Health 2009). The conclusions in the recent guidelines comply with those presented by The Danish Society of Obstetrics and Gynaecology, an association that aims at promoting the professional and scientific fields of obstetrics-gynaecology in Denmark, including formulating guidelines on clinical issues (DSOG 2008). Accordingly, healthy pregnant women should engage in moderate exercise at least 30 minutes a day, no matter their activity level before pregnancy. In the guidelines, the Borg scale of perceived exertion is shown, where moderate intensity equals 12-13, corresponding to 'some perceived exertion' (see Enclosure 1) (National Board of Health 2009). Furthermore, 'Women at increased risk of pre-eclampsia or gestational diabetes should exceed the general recommendations (amount and intensity)', and 'Women who were very physically active before pregnancy, can continue this, perhaps at a slightly reduced level, as long as they feel well' (my translation). Non-weight bearing activities such as swimming or bicycling are recommended in case of back pain or pregnancy related pelvic pain. A few precautions are taken: Women with previous miscarriages are advised not to engage in very strenuous activities. Finally, pregnant women are advised not to engage in diving, activities with heavy lifting or with a risk of 'hard bumps in the abdomen and activities with risk of uncontrolled crash or fall at high speed'. A recent review draws similar conclusions (that pregnant women should be physically active), although it is stressed in the review that the recommendations rely on sparse evidence (Hegaard et al. 2007). It seems that the physical exercise message from the handbook from 2004 have been scaled down a little and simplified in the succeeding Danish guidelines. In the handbook, it was stated that fitness training up to a hard level (Borg scale 14-15) could be commenced in pregnancy ([Physical activity - a handbook on prevention and treatment]2003). British antenatal guidelines conclude that physical activity at a moderate level is not associated with adverse outcomes, and that pregnant women should avoid contact sports, high impact sports or vigorous racquet sports due to the risk of abdominal trauma, falls or excessive joint stress (RCOG 2003). In 2002 the American College of Obstetricians and Gynecologists revised their 1994 guidelines to recommend healthy pregnant women to follow exercise guidelines for non-pregnant women, except that the non-pregnant population should do more intense exercise 20-60 minutes three to five days a week in addition to the general recommendation of 30 minutes of moderate activities at least five days per week (ACOG 2002).

3 METHODS

3.1 The Danish National Birth Cohort

The analyses in this thesis are based on data from the DNBC. The cohort was initiated in 1994, and through the years 1996-2002 100,418[1] pregnancies were enrolled. The aim of establishing the cohort was to study short- and long-term consequences of exposures early in life, including foetal life. Pregnant women were informed about the study at the first antenatal visit to the general practitioner. This is usually scheduled in gestational week 6 to 12. In Denmark, antenatal care is part of the public health system and is used by 99 percent of all pregnant women (S. Rasmussen, National Board of Health, personal communication, 2007). A woman was enrolled when a signed consent form was registered at the study secretariat. Approval to use and store data from the birth cohort for the present studies were obtained from the Steering Committee and the Danish Data Protection Agency, respectively. Furthermore, the UCLA Institutional Review Board approved the part of the studies that I worked on during my stays at University of California, Los Angeles.

When enrolled, the women were asked to complete two telephone interviews during pregnancy and two after birth, to respond to a food frequency questionnaire in mid pregnancy, and to give two blood samples during pregnancy and one cord sample from the baby at birth. Information on exposures during pregnancy, course of pregnancy, the postnatal period, the development of the child, and background information for the mother and family was included in the interviews. The interviewers were thoroughly instructed and supervised regularly by a few of the DNBC research team, including the author of this thesis. In the analyses, data from the two pregnancy interviews are used; median gestational length at the time of the interviews were 16 completed weeks (10th and 90th percentiles: 12, 23) and 31 completed weeks (10th and 90th percentiles: 28, 36), respectively. A woman was eligible to inclusion if she had a permanent address in Denmark, did not plan to have an induced abortion, and spoke Danish well enough to participate in the telephone interviews. The latter based only on considerations regarding study funding. The intention was to invite all pregnant women in Denmark during the recruitment period, which went on until 100,000 women were enrolled. In spite of a substantial effort from the study personnel, only about half of the general practitioners

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[1] In Paper 2 this number was 100,422 – a minor data cleaning procedure took place in the mean time.

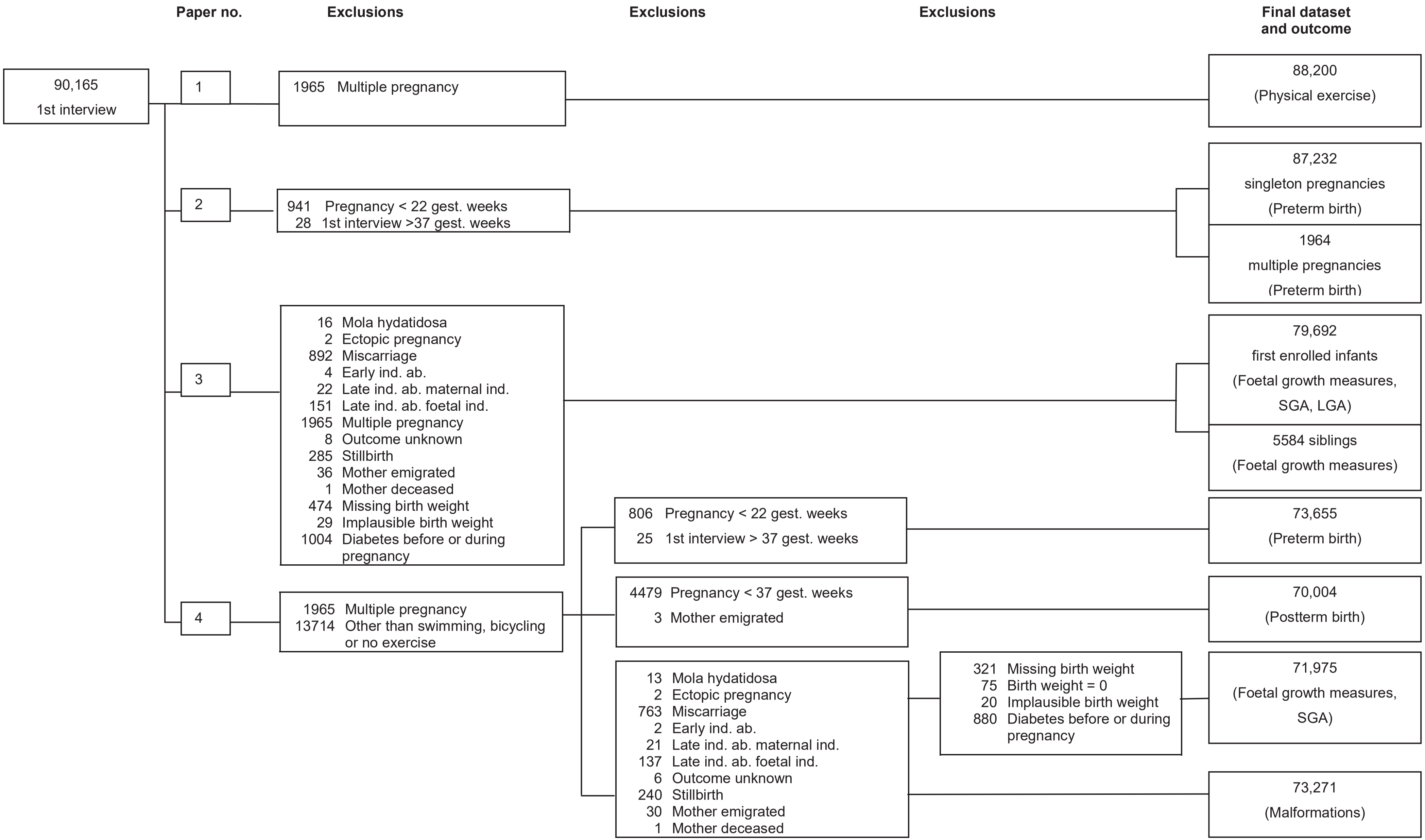
gave information about the study, and we estimate that approximately 60% of the women invited chose to participate (Olsen et al. 2001).

A number of 100,418 pregnancies were included in DNBC, however for this thesis only pregnancies where we had data from the first pregnancy interview are included (n=90,165). Reasons for not having a first interview could be an induced or spontaneous abortion before the time of the first interview or that we were not able to obtain contact for the interview. At least three attempts to get into contact for an interview were made at a convenient time chosen individually by the participants.

Data were selected differently in the four papers depending on the specific analyses. Figure 1 gives an overview of what participants were included in each of the studies. In Paper I we studied predictors of exercise; all pregnancies were included except multiple gestations, because these women are usually advised to confine physical activity due to an increased risk of preterm birth. In Paper II we used survival analysis and based exclusions on the time window for preterm birth, i.e. a pregnancy was included if not ended before gestational week 22 (the starting point for risk time) and if the first interview was carried out before 37 gestational weeks (the ending point for risk time). Sub-analysis on multiple pregnancies was also carried out. In Paper III we included live born singletons with known, plausible birth weights. Some women provided data on more than one pregnancy; these data were used in a sibling study where we studied differences in physical exercise between the pregnancies. For the main analyses, we only included the first enrolled child of each mother to avoid non-independent observations. In Paper IV we restricted data to women who reported swimming, bicycling or no exercise in the first and the second pregnancy interview, respectively, and multiple pregnancies were excluded (please note that in Figure 1 numbers from the first pregnancy interview are shown, even though we also made analyses based on the second pregnancy interview). In the analyses of preterm birth, SGA, and foetal growth in Paper IV, we included pregnancies from the same criteria as in the corresponding analyses in Papers II and III. In the malformation-analyses we only included live born singletons.

Figure 1 gives an overview of inclusions and exclusions to the four studies presented in the thesis.

Figure 1 Flow chart of Papers I-IV (next page)


Paper no.
Exclusions
Exclusions
Exclusions
Final dataset and outcome
90,165 1st interview
1
2
3
4
1965 Multiple pregnancy
941 Pregnancy < 22 gest. weeks
28 1st interview >37 gest. weeks
16 Mola hydatidosa
2 Ectopic pregnancy
892 Miscarriage
4 Early ind. ab.
22 Late ind. ab. maternal ind.
151 Late ind. ab. foetal ind.
1965 Multiple pregnancy
8 Outcome unknown
285 Stillbirth
36 Mother emigrated
1 Mother deceased
474 Missing birth weight
29 Implausible birth weight
1004 Diabetes before or during pregnancy
1965 Multiple pregnancy
13714 Other than swimming, bicycling or no exercise
806 Pregnancy < 22 gest. weeks
25 1st interview > 37 gest. weeks
4479 Pregnancy < 37 gest. weeks
3 Mother emigrated
13 Mola hydatidosa
2 Ectopic pregnancy
763 Miscarriage
2 Early ind. ab.
21 Late ind. ab. maternal ind.
137 Late ind. ab. foetal ind.
6 Outcome unknown
240 Stillbirth
30 Mother emigrated
1 Mother deceased
321 Missing birth weight
75 Birth weight = 0
20 Implausible birth weight
880 Diabetes before or during pregnancy
88,200 (Physical exercise)
87,232 singleton pregnancies (Preterm birth)
1964 multiple pregnancies (Preterm birth)
79,692 first enrolled infants (Foetal growth measures, SGA, LGA)
5584 siblings (Foetal growth measures)
73,655 (Preterm birth)
70,004 (Postterm birth)
71,975 (Foetal growth measures, SGA)
73,271 (Malformations)

3.2 Exposures

Physical exercise is the main exposure under study in this thesis; however predictors of physical exercise are being studied in Paper I, thus technically exercise is the outcome here. In the first and the second pregnancy interview in DNBC the participants were asked the questions listed in Box 1.

Box 1 Questions on physical exercise in The Danish National Birth Cohort.

1) Now that you are pregnant, do you engage in any kind of exercise?

2) What kind of exercise do you engage in?

3) How many times a week do you engage in…(answer in question 2)?

4) How many minutes a time do you engage in…(answer in question 2)?

5) Do you engage in other types of exercise?

A positive answer to the last question re-opened the above questions 2-5 until a negative response was given.

From my experience as responsible for the education and supervision of the interviewers during most of the recruitment period, a few points could be identified: Only few women expressed doubts about the timing of the questions, i.e. if the expression 'Now that you are pregnant...' have been imprecise to the women, this was not evident to us, whereas whether a certain type of activity should be included as exercise incurred more uncertainty. E.g. if a women was in doubt whether a walk with the dog or bicycling as daily commuting should be included, she would be asked: 'Do you become sweaty or short of breath?', and in case of a positive answer, the activity was coded as exercise and the following questions on frequency and duration would be posed. Hence, if a woman did not report a possible activity and did not express doubts about it, it would not be registered.

Thirteen pre-defined types of exercise were subsequently categorized into seven groups: Swimming, low impact exercise, high impact exercise, work out/fitness training, bicycling, horseback riding, and a non-classifiable category. High impact exercise is defined as activities where both feet leave the ground at the same time. Thus, jogging, ball games, and racket sports are included as high impact activities. In low impact exercise one foot is always on the ground, thus aerobic/gymnastics, and aerobic/gymnastics for pregnant women, dancing, walking/hiking, and yoga are included in this group. Swimming and bicycling are weight bearing activities and both common in Denmark, hence, treated separately. In Papers I-III we have defined preferred exercise as the type of exercise performed more than half of the total time per week spent on exercise. Women who did not perform any single activity more than 50 percent of the time were classified as ‘mixed exercisers’ and were included in the non-classifiable category mentioned above. In the attempt to isolate the DBP exposure in Paper IV, the exposed group consisted of women who reported any swimming, regardless of the amount or the proportion compared with other types of exercise.

Amount of exercise was measured in three different ways. Firstly, we calculated the total number of exercise sessions per week. In Paper I on predictors this measure was used as the primary outcome with the categories 0, 1-2, and 3+ sessions per week according to previous studies (Bouchard et al. 1994; Owe, Nystad, and Bo 2008; Zhang and Savitz 1996). Although some of the reported exercise sessions are not sessions *per se*, but rather e.g. daily bicycle commuting or a walk with the dog, the term ‘session’ is used consistently in the included papers. Secondly, we calculated the total number of minutes per week spent on exercise and categorized this into hours per week. Finally, we calculated metabolic equivalent (MET)-hours per week, a widely used measure that combines intensity and time spent on exercise into one measure (Ainsworth et al. 2000). MET-hours per week were calculated by multiplying a given MET-score for a given activity with the total number of minutes per week spent on the activity. The choice of MET-score for each activity was based on our best estimation from the updated list of MET-intensities by Ainsworth *et al* (see the Enclosure 2 for a list of all MET-scores used in this study). Total MET-hours per week were categorized into: 0, >0–5, >5–10, >10–15, and >15 (based approximately on quartiles).

In Paper II on preterm birth we studied the change in exercise pattern during pregnancy. To avoid overlapping between the first and the second pregnancy interview, we restricted data to observations with a first interview carried out before 22 completed gestational weeks and a second interview between 22 and 36 weeks, both inclusive. A change in exercise was defined as an altering between the two interviews in the response to the question of any exercise. For Paper III we constructed a measure of change in exercise level between pregnancies within the same woman; a woman could move one or two steps upwards, stay at the same level, or one or two steps downwards between no, little and much exercise, where much exercise was defined as 90 minutes per week or more.

The questions on exercise in the Danish National Birth Cohort were similar to those used in other studies on pregnant women (Dempsey et al. 2004; Misra et al. 1998; Sorensen et al. 2003) and were a modified version of the Minnesota Leisure-Time Physical Activity Questionnaire (Folsom et al. 1985; Taylor et al. 1978; Marsal et al. 1996).

3.3 Outcomes

Preterm birth was defined as delivery of a live born child after 22 and before 37 completed gestational weeks (Papers II and IV) and postterm birth as a delivery after 42 weeks. SGA and LGA were defined as having a birth weight below the 10^{th} percentile and above the 90^{th} percentile of the sex- and gestation specific birth weight within the present study population in DNBC or alternatively according to an intrauterine foetal weight standard (Marsal et al. 1996). The ponderal index, which is a measure similar to body mass index in newborns, was calculated as ((weight in g)*100/(length in cm)^3) (Nguyen and Wilcox 2005). Subgroups of congenital malformations (circulatory, respiratory, and cleft lip and cleft palate) were defined using ICD10 codes on malformations registered within the first year of life (the 10^{th} revision of International Classification of Diseases). If a child had more than one malformation, the child was counted in each applicable subgroup.

Data on gestational age at birth (days), birth weight (g), length (cm), head circumference (cm), abdominal circumference (cm), placental weight (g), and congenital malformations were derived from The Medical Birth Register, which is part of the Danish National Patient Register and comprises records on all births in Denmark.

In survival analyses of preterm birth, stillbirths were censored. The reason for not including stillbirths as events was that the time from foetal death until delivery may be dependent on gestational age. For practical reasons the overall term ‘foetal growth measures’ is used for the birth size indicators measured at birth, acknowledging that these measures are no more than proxies or indicators of foetal growth. Measures of exposures, outcomes and associations are summarized in Figure 2.

Figure 2 Measures of exposures, outcomes and associations.

Paper I	Maternal characteristics - socio-demographic - health related - behavioural	Exercise - yes/no - preferred type - frequency (sessions/week) - amount (hours/week)	Odds ratio
Paper II	Exercise - yes/no - preferred type - amount (hours/peek) - MET-hours/week - changes over the course of pregnancy	Preterm birth - yes/no - moderate, very, and extreme	Hazard ratio
Paper III	Exercise - yes/no - preferred exercise - amount (hours/peek) - changes between pregnancies (sibling study)	Offspring size at birth - weight - length - ponderal index - head circumference - abdominal circumference - placental weight Small-for-gestational-age Large-for-gestational-age	Mean difference Hazard ratio
Paper IV	Swimming - yes/no - amount (min/week)	Preterm birth Postterm birth Offspring size at birth Small-for-gestational-age Congenital malformations - overall - circulatory - respiratory - cleft lip and cleft palate	Hazard ratio Mean difference Odds ratio

3.4 Statistical methods

The four studies applied different types of statistical methods. Odds ratios of predictors of physical exercise during pregnancy (Paper I) and of congenital malformations according to exercise during pregnancy (Paper IV) were calculated using logistic regression analysis. Hazard ratios of preterm birth (Papers II and IV), SGA (Papers III and IV), and LGA (Paper IV) according to exercise were calculated using Cox regression analysis. Mean differences in foetal growth measures according to exercise (Paper III and IV) were calculated by fitting linear regression models.

The underlying time scale in the Cox proportional hazard models was gestational age in days since last menstrual period, which was calculated backwards from the gestational age at birth as registered in The Medical Birth Register. Since preterm birth is defined as a delivery between 22 and 37 completed gestational weeks, entry time into follow up was 22 gestational weeks in preterm birth analyses, and observations were censored at 37 weeks if still pregnant, whereas no time restrictions were applied to the analyses of SGA and LGA. If the first pregnancy interview had not been carried out when risk time started, entry time would be the gestational week at the time of the interview.

The Cox models were stratified by gestational age at the time of the interview in order to take different times of entry into follow-up into account. If a second pregnancy interview had been carried out, exercise data were updated at the gestational age of the second interview. In these cases the model was stratified by the time of the second interview in the record concerning the last time of pregnancy. If we only had data from the first interview, exercise data from this interview was used throughout pregnancy.

Some women participated with more than one pregnancy in the cohort. In Paper II on preterm birth we considered cluster sampling by comparing “naive” standard errors with robust standard errors, and we found no cluster effect. In Paper III on foetal growth we subdivided data into one dataset comprising only the first enrolled child of each woman and another one comprising siblings. In this study we did not evaluate a possible cluster effect, but the problem was not relevant when dividing into the two datasets.

Preterm birth is often analysed by means of logistic regression. However, we preferred to use survival analysis because 1) the women were most often not followed for the same amount of time, 2) there may be both time dependent exposure variables, such as exercise in both the first and the second pregnancy interview, and time dependent effects, such as different effects of exercise at different levels of preterm birth (i.e. different gestational lengths), and 3) gestational age as a continuum may be more informative than arbitrary cut points as in logistic regression. The basic Cox regression model is based on the assumption that an effect does not change over time, hence in the preterm birth analysis we included an interaction term between exercise and time categorised into extremely, very, and moderately preterm birth.

In the sibling study in Paper III on foetal growth measures, time unrelated factors, such as genetic and perhaps socio-economic factors, are accounted for. It should be noted though that the sibling study may oversample fecund families with larger families.

When we included quadratic spline functions for gestational age in the model, some of these were found to be statistically significant indicating a non-linear relation between gestational age and birth weight (Greenland 1995). Therefore, in the Cox analyses of foetal growth measures, gestational age was modelled as quadratic splines, and age and body mass index were modelled as restricted quadratic splines. When a quadratic function is included, extreme values will have more weight; therefore the restricted quadratic splines were used for age and body mass index to avoid too much weight on extreme values.

In all of the included studies the choice of which possible confounders to include was based on an *a priori* review of the literature, and all identified factors were included, if available in our data. Prerequisites for including all possible confounders comprise a large sample size, a small number of co-variates, and few missing values for the co-variates. All co-variates except maternal age and diet came from the first (or in a few cases the second) pregnancy interview in DNBC. Age came from the National Patient Register, and diet came from a food frequency questionnaire in DNBC. The diet variable was used in Paper I on predictors and was the only variable with a substantial number of missing values, i.e. 25,736 out of 88,200, since not all women responded to the questionnaire. Analyses were carried out both with and without the diet variable in order to assess the importance of diet and of a possible selection into response to the questionnaire.

4 RESULTS

4.1 Paper I

This paper on exercise habits and predictors of exercise during pregnancy was based on 88,200 singleton pregnancies. We found that a little more than one third of the women had been engaged in exercise when asked in early/mid pregnancy, and a little less in late pregnancy. About half of the women exercised regularly at some point during pregnancy, meaning that about half of the exercising women in early/mid pregnancy had ceased to do exercise in late pregnancy and another that another group of women had commenced exercise. Bicycling, swimming and low impact activities were the most common activities; swimming being the activity most persistently performed throughout pregnancy. Women who changed preferred exercise during pregnancy were likely to switch to activities at the same or at a lower impact level, and further, women who engaged in high impact activities in early/mid pregnancy were more likely to cease exercise completely in late pregnancy compared with women engaged in other kinds of activities.

The strongest predictors of doing any exercise during pregnancy were having a health conscious diet, high alcohol consumption, or an eating disorder. Higher parity, smoking, low self-rated health, and having a diet high in fat and low in vegetables were the strongest predictors of not doing exercise. When frequent exercise, i.e. three sessions or more per week, was studied, we found parity, alcohol consumption, and smoking to be stronger correlated with *any* exercise than with frequent exercise, and being a student and having an eating disorder were more strongly correlated with frequent exercise than with any exercise. Not being married or cohabiting was associated with frequent exercise but not with any exercise. Predictors of doing exercise throughout pregnancy were similar to those in early/mid pregnancy, and predictors for hours per week were similar to those of sessions per week. As expected, being physically active during pregnancy correlated with many background or lifestyle factors, some of which are potential causes of reproductive failures.

4.2 Paper II

In this paper on maternal exercise and preterm birth, analyses were carried out on 87,232 singleton pregnancies and 1964 multiple pregnancies, respectively. In the singleton population there were 4279 preterm deliveries (4.9%). Women who engaged in physical exercise during pregnancy had a moderately reduced risk of preterm birth, and risk estimates were of similar magnitude whether hours per week or MET-hours per week were analysed, MET-hours being a measure of metabolic expenditure where amount of exercise and intensity are combined. No dose-response relation was seen between amount of exercise and the risk of preterm birth among physically active women. When type of exercise was analysed, a slightly decreased risk of preterm birth was seen for all types of exercise compared with no exercise (except horseback riding with hazard ratio around one and with broad confidence intervals), but statistical significance was seen only for low impact activities and swimming. Exercise in second half of pregnancy seemed to account for most of the apparent decreased risk, since pregnancies where the mother had exercised in late pregnancy, no matter the level of exercise in early pregnancy, were less likely to result in a preterm delivery than cases where the mother had exercised in first part of pregnancy. Analysing moderate, very and extremely preterm birth did not indicate an interaction between exercise and the degree of preterm birth. Restricting analyses to primigravida, nullipara, or women with no symptoms of threatening preterm birth did not change the estimates substantially. Furthermore, the associations found for multiple pregnancies were similar to those of singleton pregnancies. In conclusion, among participants in The Danish National Birth Cohort, exercising mothers seem to have a slightly reduced risk of giving birth preterm. One explanation could be that women with a low generic risk of preterm birth are more likely to be physically active, a so-called healthy exerciser effect. Should the findings reflect causal links, these would have positive public health importance, since very few evidence-based strategies for preterm birth exists.

4.3 Paper III

Foetal growth measures were analysed among 79,692 singleton non-siblings and 5584 singleton siblings according to the mother's exercise during pregnancy. Our data indicated a tendency towards slightly smaller size of offspring among exercising mothers compared with non–exercisers when birth weight, birth length, ponderal index, head and abdominal circumference, and placental weight were analysed. Statistically significant trend tests were seen only for abdominal and head circumference. In addition to a number of other co-variates, gestational age at birth was also included in the linear regression model. When evaluating the included co-variates, smoking was found associated with lower birth weights and multiparity with higher birth weights. In a stratified analysis, exercise was associated with lower birth weight in babies of non-smoking mothers, whereas higher birth weights were seen among babies of exercising, smoking mothers compared with non-exercising, smoking mothers. When birth weight according to gestational age was dichotomised into SGA and LGA, respectively, logistic regression analysis showed slightly decreased risk of both SGA and LGA in the offspring of exercising women. Furthermore, women who changed exercise level between pregnancies had on average larger babies than women who exercised at the same level in the two pregnancies regardless of the direction of a change. Even though the mean differences in birth size measures may be negligibly small, our results indicating both smaller offspring birth size and a lower risk of SGA with maternal exercise are somewhat confusing. Possible explanations could be that intrauterine growth retardation can occur at a wide spectrum of birth weights for gestational age. Furthermore, exercise may have a restrictive overall effect on birth weight and at the same time may normalize glucose levels (e.g. in obese women and thus decrease the risk of LGA) and oxygen transfer (e.g. in smoking women and thus decrease the risk of SGA).

4.4 Paper IV

In this last paper of the thesis we examined the association between swimming during pregnancy and a number of birth outcomes (pre- and postterm birth; foetal growth measures, including birth weight and SGA; and congenital malformations) based on the hypothesis that bi-products from disinfectants used in swimming pool water could have unfavourable effects on the foetus or the pregnancy. Depending on the outcome, and hence the statistical method, the study populations varied from 70,004 to 73,655 pregnancies. Overall, the data did not point towards adverse birth outcomes related to swimming. When we compared swimming in early/mid pregnancy with bicycling, which we did to exclude a possible effect of exercise, measures of association were similar apart from a modest and borderline statistically significant decreased risk of preterm birth with swimming. Women who reported swimming in both the first and the second pregnancy interview tended to have heavier babies, slightly longer babies and with larger abdominal circumferences, but the differences were small. When we compared swimmers with non-exercisers, we found a modestly decreased risk of preterm birth and borderline statistically significant decreased risk of SGA and congenital malformations among swimmers. In general, there were only minor differences between measures of association for swimming in early/mid pregnancy and throughout pregnancy. In order to evaluate high exposures, swimming 1.5 hour per week or more was examined but no differences of importance were seen between high and low levels of swimming or between high levels of swimming and high levels of bicycling. In our data there were no marked differences in outcomes between swimmers and bicyclists, which could indicate that disinfection by-products at the exposure levels we studied are not causing adverse pregnancy outcomes.

5 DISCUSSION

In a little more than one third of the pregnancies the mothers engaged in exercise in the first part of pregnancy, while a little fewer did so in late pregnancy. In half of the pregnancies the woman exercised regularly at some point in pregnancy indicating that a substantial proportion of the women change their exercise habits over the course of pregnancy. Being physically active during pregnancy correlated with a number of background or lifestyle factors. Furthermore, women who engaged in physical exercise during pregnancy were less likely to give birth before term and to have an SGA or LGA baby. Slightly smaller birth size measures, such as weight and length, were also observed in exercising women, but these differences were small. The observed associations were in general not affected by amount or type of exercise. As swimming in an earlier study was found to be an activity not related to miscarriage and due to a concern that disinfection by-products in swimming pool water may be disadvantageous to the pregnancy or the foetus, we examined reproductive outcomes in women who reported swimming or other water activities during pregnancy and found that the birth outcomes under study (all of the above plus postterm birth and congenital malformations) were not related to swimming.

5.1 Comparison with existing research

5.1.1 Exercise habits and predictors (Paper I)

In DNBC, 37% of the women engaged in exercise in early/mid pregnancy and 30% in late pregnancy, and almost 50% had reported exercise in either the first or the second interview. These are two ways of reporting the exercise measure. If we compared with the corresponding measures in other studies, our statistics were lower. Previous reports varied between 42% and 67% (n=386 to n=6528). One explanation for the deviation from other studies could be definition differences in the physical activity measure; some studies used leisure time physical activity in general, including e.g. gardening (Evenson, Savitz, and Huston 2004; Ning et al. 2003; Petersen, Leet, and Brownson 2005), whereas DNBC and others asked the women about exercise and/or sports (Zhang and Savitz 1996). Another explanation could be differences in the gestational timing of reported physical activity; in one study the gestational dating of the interview was random and not registered, and the reported prevalence covered the whole pregnancy period until time of interview (Evenson, Savitz, and Huston 2004), whereas others covered only the first part of pregnancy (Ning et al. 2003). In DNBC the women were interviewed twice during pregnancy, but even with two interviews the timing was not fully distinct: We asked ‘Now that you are pregnant, do you engage in…’, and due to this wording some women may have answered according to the time around the interview and others according to the whole pregnancy until the time of the interview. Finally, when studying a behavioural factor like physical activity, substantial cultural differences must be expected.

The above possible explanations for differences in physical activity during pregnancy between studies should be interpreted with caution. The DNBC and a number of the other studies were not designed as prevalence studies with representative study populations. We know that there was a selection into the DNBC with participants being on average healthier than the background population (Nohr et al. 2006) (please see 5.2.1 on selection bias). Hence, when comparing this selected DNBC population with other studies, which may be subject to other selection mechanisms, some degree of bias is inevitable. A comparison with The Norwegian Mother and Child Cohort Study (MoBa) may be more appropriate, since the two cohorts are similar in many ways, but still the prevalence of ‘any exercise’ was substantially higher in MoBa than in DNBC (Owe, Nystad, and Bo 2008). In early/mid pregnancy it was 59% (vs. 37% in DNBC) and in late pregnancy 47% (vs. 30% in DNBC). In the MoBa study strolling was not included as exercise, whereas a differentiation between strolling and brisk walking was not possible in DNBC, so a broader range of walking intensity may have been included in the walking-category in DNBC. However, having included strolling would have made the Norwegian exercise prevalence even higher. Such differences between two in principle comparable studies speak in favour of considerable cultural differences in the engagement in physical activity.

When it comes to predictors of exercise, we observed a higher degree of consensus between studies, which is in line with the above selection bias reasoning. Except for age, the predictors identified from our data were overall in line with previous studies reporting higher education and income, younger age, not having older children, non-smoking, and pre-pregnant non-overweight (Domingues and Barros 2007; Evenson, Savitz, and Huston 2004; Ning et al. 2003; Owe, Nystad, and Bo 2008; Petersen, Leet, and Brownson 2005; Zhang and Savitz 1996). We found higher age associated with exercise engagement, especially in late pregnancy.

In two US-based studies, married women were more likely to be active than non-married women (Ning et al. 2003; Petersen, Leet, and Brownson 2005). This was supported in our data for any exercise in late pregnancy, but in early/mid pregnancy women living alone were more likely to engage in frequent exercise. Cohabiting without being formally married is frequent in Denmark, which is the reason why we did not separate the married group from the cohabiting group as they did in the US studies. From this follows at least two issues: In our data, women living alone during pregnancy form a highly selected group. Furthermore, the non-married group in the US-studies is composed differently from the Danish group because it also comprises cohabiting, although the proportion of cohabiting couples is likely to be much smaller in the US than in Denmark. Another reason for a higher degree of activity among married women in one of the US-studies may be that e.g. household activities and gardening is included (Ning et al. 2003).

Finally, we found a diet low in fat and high in vegetables associated with exercise. The only other study that included diet found a diet high in protein and low in carbohydrate associated with leisure time physical activity. One consistent finding in our study was an increased likelihood of exercising with increasing intake of alcohol (up to 5+ drinks per week, which was our highest intake category). This has not previously been reported, although Zhang *et al* found alcohol intake associated with physical activity in non-pregnant women (Zhang et al. 2006). What may be surprising in our data is that higher intakes were more strongly associated with exercise than lower intakes.

Table 1 gives an overview of studies on exercise habits and correlates of exercise during pregnancy (next page).

Table 1. Studies on pregnant women's exercise habits and on correlates of physical activity/exercise during pregnancy.

First author Year	Country	Study design Study year	Material	Timing of physical activity measure and mode of data collection	Physical activity measure	Findings: Prevalence and type	Findings: Correlates of physical activity/exercise
Domingues 2007	Brazil	Survey 2004	4471 pregnant women	Questionnaire soon after delivery	Leisure time physical activity Type, frequency, duration Pre-pregnancy and three trimesters	13% any physical activity during pregnancy. 10% in first trimester, 9% in second trimester, 7% third trimester. Walking most frequent.	Schooling High income Being employed Nulliparitiy
Evenson 2004	US	Survey, not with pregnancy focus. 2000	44,657 non-pregnant 1979 pregnant	Telephone interview at any time during pregnancy as part of a survey with other focus (gest. age not collected), reported for the past month prior to interview.	Weighted prevalences Leisure time physical activity Meeting recommendations*	66% any leisure activity within the past month. 16% meeting recommendations. Most common activities: walking, swimming, weight lifting, gardening, aerobics.	Young age High education Excellent or very good health
Haakstad 2007	Norway	Survey (?)	467 pregnant women	Questionnaire in gestational week 36	General physical activity and exercise Type, frequency, duration Three trimesters	70% in first trimester, 64% in second trimester, 47% in third trimester. All activities but swimming decreased. Most common activities in first trimester: walking, bicycling, fitness training.	-
Hatch 1998	US	Cohort 1987-1989	880 pregnant women	Telephone interview week 13. Questionnaire week 28 and 36.	Leisure time physical activity. Type, frequency, duration, energy expenditure.	1., 2., 3. trimester: 60%, 57% 59% non-exercisers. Shift from weightbearing activities to gentler activities.	Nulliparity Non-smoking High income Higher educational level

Hegaard 2009	DK	Cohort 1989-1991	4558 pregnant women	Questionnaire week 16 and 30.	Sports. Type, frequency, duration.	1. 2. trimester: 73%, 79% non-exercisers.	-
Hinton 2001	US	Cohort 1994-1996	622 pregnant women	Questionnaire pre-pregnancy, 1., 2., and 3. trimester.	Regular exercise: often (daily), sometimes, rarely, never.	40% lesser active and 20% more active from pre-pregnancy to pregnancy. Pre-pregnant exercisers likely to maintain or decrease exercise level.	Correlates for change during pregnancy: exercise self-efficacy, body mass index and pre-pregnant exercise.
Mottala 2003	Canada	?	529 pregnant women. Case and controls in a study on birth weight, restricted to women delivering after week 34.	Questionnaire 2 weeks post partum	Leisure time physical activity. Type, frequency, duration. Activities classified as structured exercise programmes or recreational activities.	Pre-pregnancy, 1., 2., 3. trimester: 70%, 64%, 56%, 49% any structured exercise. Pre-pregnancy, 1., 2., 3. trimester: 81%, 76%, 73%, 66% any recreational exercise.	Predictors of quitting exercise: children at home pre-pregnant overweight high gestational weight gain
Ning 2003	US	Participants came from case-control study on pre-eclampsia. 1998-2000	386 pregnant	In-person interview during labour and delivery stay	Leisure time physical activity. Type, frequency, duration First 20 gestational weeks	61% any exercise. Most common activities: walking, swimming, gardening, jogging. In active women, frequency and duration decreased when becoming pregnant.	High education High income Married status Nulliparity No smoking High protein diet Low carbohydrate diet Ethnicity (white) Pre-pregnant physical activity

Owe 2008	Norway	Cohort 2001-2005	34,508 pregnant	Self-administered question-naires around gestational week 17 and 30.	Leisure time exercise at least three times per week	59% any exercise week 17, 47% any exercise week 30, 28% regular exercise week 17, 20% regular exercise week 30. Most common activities: Walking, bicycling. Swimming increased during pregnancy.	Pre-pregnant non-overweight Pre-pregnant exercise Low gestational weight gain Singleton pregnancy
Pereira 2007	US	Cohort	1242 pregnant women	Brief in-question interview. Questionnaire. Telephone interview.	Leisure time physical activity the year before pregnancy, first trimester, and 6 months post partum.	Activity decrease from 9.6 to 6.9 hours/week from pre-pregnancy to first trimester.	Predictors for decrease in activity level: children at home nausea/vomitting
Petersen 2005	US	Survey 1994, 1996, 1998, 2000	143,731 non-pregnant 6528 pregnant	Telephone interviews any time in pregnancy	Meeting recommendations*	64% any physical activity in pregnancy 1994 and 1996, 67% any physical activity in pregnancy 1998 and 2000 Most common activities: walking	Correlates of meeting rec-ommendations: Young age High education High income Married status (error in ab-stract) Non-smoking Ethnicity (non-hispanic white)
Zhang 1996	US	Survey 1988	9953 pregnant (livebirths)	Questionnaire postpartum (mean: 17 months after de-livery)	Pre-pregnant exercise and during pregnancy Number of 'active' months during pregnancy Type of exercise	42% any exercise during pregnancy. Most common activities: walking, swimming, aero-bics.	Young age Nulliparity Favourable reproductive history Normal- or underweight Singleton pregnancy

*Min. 5 times/week at least 30 min/time of moderate activity or min. 3 times/week at least 20 min/time of vigorous activity.

5.1.2 Exercise and preterm birth (Paper II)

The average preterm birth prevalence was 5.5% over the years 1997-2003 in DNBC, which is similar to the overall prevalence in Denmark, namely 5.2% in 1995 and 6.3% in 2004 (Langhoff-Roos et al. 2006). We found a slightly decreased risk of preterm birth among women who had exercised during pregnancy, which is supported by a few cohort studies and a single case control study (Berkowitz and Papiernik 1993; Evenson et al. 2002; Misra et al. 1998). As previously illustrated, the relation between exercise and preterm birth is inconclusive, both due to overall different results but also to a considerable extent due to different measures of physical activity. Most studies, both intervention and cohort studies report no association with gestational age or preterm birth (Duncombe et al. 2006; Grisso et al. 1992; Klebanoff, Shiono, and Carey 1990; Magann et al. 2002; Orr et al. 2006; Penttinen and Erkkola 1997; Perkins et al. 2007). Only few studies (one intervention and one cohort) have reported slightly shorter gestational lengths among exercising women (Clapp, III and Dickstein 1984; Kardel and Kase 1998). A Cochrane review suggested an increased risk of preterm birth with exercise, but this was based on only three studies with very few observations and a difference was only observed in one of the three studies, therefore I agree with the authors that these results do not add conclusive evidence (Kramer and McDonald 2006). A reduced risk of preterm birth may not be in line with the findings of a few small trials indicating an increased uterine contractility with physical activity (Durak, Jovanovic-Peterson, and Peterson 1990; Jovanovic, Kessler, and Peterson 1985; Spinnewijn et al. 1996). On the other hand, there may be substantial differences in the biological response to induced physical activity in last part of pregnancy after rupture of membranes than that of regular exercise at earlier stages of pregnancy.

5.1.3 Exercise and foetal growth measures (Paper III)

Contrary to most other studies we examined different measures of offspring size at birth and found slightly smaller babies of exercising mothers compared with those of non-exercisers. Furthermore, we found a slightly decreased risk of SGA in the offspring of exercising mothers. Two small trials (n=20 and 28) included length and/or placental weight but found no association with physical activity (Collings, Curet, and Mullin 1983; Lewis, Yates, and Driskell 1988). In two other trials (n=46 and 75), however, Clapp and colleagues found offspring of women who began exercise in early pregnancy to be heavier and longer, whereas the offspring of women who continued exercise during pregnancy were lighter and thinner (Clapp, III et al. 2000; Clapp, III et al. 2002). In studies analysing mean birth weights, existing literature is difficult to summarize because results point in different directions, and the direction of results does not seem to be correlated with study design. Apart from these two studies, most intervention studies report no association in mean birth weight (Collings, Curet, and Mullin 1983; Duncombe et al. 2006; Kardel and Kase 1998; Lewis, Yates, and Driskell 1988; Marquez-Sterling et al. 2000). For cohort studies the same non-consistent pattern is seen (Clapp, III and Dickstein 1984; Hatch et al. 1993; Klebanoff, Shiono, and Carey 1990). We found a slightly decreased risk of SGA, which is in contrast to a case-control study using an extensive case definition (5 sessions per week in last part of pregnancy) (Campbell and Mottola 2001) and a small cohort study that found an increased risk of SGA in women who continued exercising throughout pregnancy (Clapp, III and Dickstein 1984). Both studies were of modest size (n=228 and 429). A study using a highly selected group of fit pregnant women in the US Navy did not find exercise associated with SGA (Magann et al. 2002). Our data support the findings by Alderman and colleagues showing a decreased risk of LGA in the offspring of exercising (Alderman et al. 1998).

Although we observed a tendency towards smaller birth size measures (birth weight, length, ponderal index, abdominal and head circumference, and placental weight), our interpretation is that the magnitude of these associations is too small to be of clinical relevance.

Table 2 gives an overview of studies on physical activity/exercise and reproductive outcomes (next page).

Table 2. Studies on physical activity/exercise during pregnancy and reproductive outcomes.

First author Year	Country	Study design Study year	Material	Physical activity measure	Outcome	Findings
Experimental studies						
Clapp 2000	US	Randomization 1999	46 non-exercising women	1) Exercise 3-5 times/week 2) No exercise	Birth weight	Birth weight higher in exercising women (3.66 kg +/- 0.9 vs. 3.43 kg +/- 0.9
Clapp 2002	US	Randomization 2001	75 healthy, regularly exercising women	3 intensity groups: 1) Low-high 2) Mod-mod 3) High-low Treadmill, step aerobics, or stair-stepper	Foeto-placental growth	High volume of moderate-intensity, weight-bearing exercise in mid and late pregnancy reduces fetoplacental growth. A reduction in exercise enhances growth.
Collings 1983	US	15 out of 20 randomized	20 pregnant women	1) Aerobic exercise programme 2) No exercise	Foetal heart rate, labour duration, Apgar score, birth weight, length and placental weight	No ass. with foetal growth measures, labour or Apgar. A slightly increased foetal heart rate.
Duncombe 2006	Australia	Randomization?	148 women recreational exercisers	Two different definitions of vigorous exercise compared with no exercise. Amount was analysed. Questionnaire, one-week-diary, and heart rate-monitoring three times during pregnancy	Birth weight and gestational age from interview 1-2 weeks pp.	No ass. with birth weight or gestational age.
Durak 1990	US	All participants had the intervention	12 women in third trimester	207 15-minute sessions on treadmill, upper-body ergometer, rowing machine, bicycle, and recumbent bicycle	Uterine activity measured continuously by external tocometer	Bicycle (50%), treadmill (40%), and rowing machine (10%) ass. with increased uterine activity. Upper body ergometer and recumbent bicycle not ass.

Kardel 1998	Norway	No randomization 1987-1990	42 extremely fit and healthy women	Medium- / high-intensity during pregnancy	Gestational and birth weight.	No diff. in birth weight between groups. Shorter gestational age in high intensity group in women who had girls.
Lewis 1988	US	No randomization, although intended	28 healthy pregnant women (taking vitamin-mineral suppl.).	1) Walking programme (22 to 30 gest. weeks) 2) No walking programme, but participants should continue their previous exercise habits, if any	Birth weight, length, Apgar score, labour duration and maternal WG	No ass.
Marquez-Sterling 2000	US	Randomization	15 healthy, non-exercisers	1) Exercise programme 2) No exercise	Birth weight, Apgar score and fitness	No ass.
Mayberry 1992	US	All participants had the intervention	10 women on tocolytice assigned to bedrest 28-31 and again 32-36 week	20 min exercise programme lying down	Uterine activity (tocodynamometer)	No ass. with uterine activity
Spinnewijn 1996	Netherlands	All participants had the intervention	30 uncomplicated term pregnancies admitted for elective induction of labour	After artificial rupture of membranes 20 min. of cycle ergometer (until heart rate of 140 beats/min)	Foetal heart rate and intrauterine pressure.	Increased uterine contractility. No ass. with foetal heart rate.
Cohort studies						
Alderman 1998	US	1979-1988	291 pregnant women	Moderate and vigorous physical activity	Gestational age, SGA, LGA	No ass. with gestational age or SGA. Any physical activity at least 2 hours/week ass. with decreased risk of LGA (OR 0.3, CI 0.2, 0.7)
Clapp 1984	US	1981	228 pregnant women recruited from antenatal registration.	1) Sedentary before and during pregn. 2) Active before, but reduced or stopped <28. 3) Active before, maintained into third trim. Prenatal interview, twice for the active women. Self-reported heart rate.	Gestational age measured by last menstrual period, ultrasound, and neonatal exam.	Women who continued exercising during pregnancy (gr. 3. N=29) had shorter gestational age , lower birth weight, and were more likely to deliver an SGA child.

Evenson 2002	US	1995-1998	1699 women recruited from clinics	PA from prenatal interview covering 3 periods: 3 mths before, first, and second trimester. Any vigorous exercise (>=6 METs) and amount.	Preterm birth	Ass. with a reduced risk of preterm birth. Physical exercise in first trimester: OR 0.80 (0.48,1.35) Physical exercise in second trimester: OR 0.52 (0.24,1.11) No dose-response relation
Grisso 1992	US	(?)	81 low-risk from prenatal clinic	Diary on physical exercise in 3 x 72 hours	Uterine activity (3 x 72 hours with tocodynamometer)	No ass. between organized exercise and uterine activity, but climbing stairs and walking was associated with uterine activity.
Hatch 1993	US	1987-1989	876 pregnant women Population based	Questionnaire	Birth weight	Larger birth weight among exercisers: Low-moderate exercise: +124 g, p<0.10 Heavy exercise: +276 g, p<0.05 Changing pattern: +32 g
Hatch 1998	US	1987-1989	557 pregnant women	None, low-modertae, and heavy exercise in each trimester	Pre- and postterm birth	No ass. between low-moderate exercise and gestational length. Heavy exercise ass. with decreased risk of preterm birth.
Hegaard 2008	DK	1998-1991	5749 pregnant women	Sports and four categories of leisure time activity level in first trimester	Preterm birth	>1 type of sports ass. with decreased risk of preterm birth (OR=0.09, CI 0.01, 0.66). Light physical activity: OR=0.76 (0.60, 1.02) and moderate to heavy physical activity: OR=0.34 (0.14, 0.85).

Hegaard 2009	DK	1998-1991	4458 pregnant women	Sports and four categories of leisure time activity level in first trimester	Low birth weight, high birth weight, mean birth weight	No ass.
Juhl 2008	DK	1996-2002	87,232 pregnant women	Amount and type of physical exercise in early/mid pregnancy and late pregnancy	Preterm birth	Exercise ass. with reduced risk of preterm birth (HR 0.82, CI 0.76, 0.88). No dose-response relation.
Klebanoff 1990	US	1984-1987	7101 women recruited from prenatal clinics	Occupational and leisure time activity. Heavy work and heavy exercise is one group. And light work and exercise.	Preterm birth and birth weight	Heavy work/exercise not ass. with preterm birth and birth weight. Light work/exercise ass. with reduced risk of preterm birth. E.g. >=8 hr vs. 0: OR 0.59 ((0.38,0.93) Prolonged standing ass. with in-creased risk of preterm birth. Difficult to determine the effects of exercise because work and exerise were combined.
Magann 2002	US	1995-1998	750 healthy, low risk women from the navy.	1) No exercise or mandatory <3 times/week 2), 3), and 4) complicated categorisation combining type and level of exercise with duration. Questionnaires at several antanatal visits.	Preterm labour (regular contr. <36 completed weeks). SGA (<10th perc.). Questionnaire within one week pelvic pain	No ass. with SGA or PTB.
Misra 1998	US	1988-1989	1172 low income pregnant women Recruited from clinics.	Prenatal interview (week 19-27). Occupa-tional, daily life, and leisure time activity (>=60 days in first and second trimester).	Preterm birth (<37 weeks). Clinicians' best estimate.	Leisure time physical activity: preterm birth OR=0.51 (0.27,0.95). Climbing stairs, walking for a purpose, and extreme tv-watching ass. with increased risk of preterm birth.
Orr 2006	US	1993-1995	922 women from hospital based clinics. Questionnaire	Streneous / non-streneous exercise before and during pregnancy	Preterm birth and birth weight	No ass.

Penttinen 1997	Finland		30 athletes	Cases: athletes Controls: next primipara	Preterm birth, gestational age and birth weight	No ass.
Perkins 2007	US		51 healthy, non-smoking, college-educated women recruited from obst. clinics	48-hours diary, accelerometers, and heart rate monitors in week 20 and 32. Calculated into METs.	Gestational age measured by last menstrual period and ultrasound. Foetal growth ratio= Birth weight divided by median birth weight for gestational age from Zhang and Bowes curves.	No ass. with gestational age. Decreased birth weight with increased physical activity, but only in tall women. Physical activity was not ass. with maternal height.
Case-control studies						
Berkowitz 1981	US	1977-1978	175 cases (delivery <37 weeks) 313 controls (delivery >=37 weeks, random sample) from one certain hospital.	Post partum interview. Physical exercise before and during pregnancy (plus type, frequency and duration)	Gestational age	Reduced risk of preterm birth: Women with a preterm delivery were less likely to exercise.
Campbell 2001	Canada	(?)	164 SGA-cases (< 15th perc.) 365 controls (>= 15th perc.)	5+ sessions/week late in pregnancy	SGA	Increased risk of SGA: SGA-mothers more likely to exercise: OR: 4.61, $p<0.05$
Petridou 2001	Greece	1998	147 preterm infants 58 term infants Hospital-based population	Regular physical exercise	Preterm birth	Women with a preterm delivery were less likely to exercise: OR < 33 weeks: 0.45 ns OR >= 33 weeks: 0.30 sign.
Schramm 1996	US	1989-1991	450 foetal death 782 very low birth weight 802 moderately low birth weight 794 normal birth weight	3+ exercise sessions/week at three time points (3 mths prior to pregn., each trimester, and 3 mths post partum)	Very low birth weight (<1500 g)	Very low birth weight mothers less likely to regular exercise: 1. trim: 0.70 sign. 2. trim: 0.54 sign. 3. trim: 0.33 sign.

Reviews, recommendations, meta-analyses					
Artal 2003	US	Recommendations			Pregnant women should be active, if uncomplicated pregnancy. Athletes can continue, however modified. No precautions regarding preterm birth or birth weight
Clapp 2000		Review			Pregnant women should exercise. (types of exercise are described)
Davies 2003	Canada	Recommendations			Pregnant women should be active. Rec. not as specific as DK. Contraindications are highlighted.
Dye 2003		Review (narrative due to few RCTs)	Self-reported physical activity	Preterm birth and birth weight	No convincing results. Limitations in studies remain. Studies still observational
Ezmerli 2000		Review	Exercise	Many, incl. preterm labor	Exercise does not usually stimulate uterine activity
Hammer 2000		Recommendations			Detailed recomendations to clinicians. Exercise prescription should be individually based.
Hegaard 2006		Review	Leisure time PA	Preterm birth and birth weight	Poor evidence for preterm birth: No effect or reduced risk. Birth weight: No ass. or higher BW in exercising women.

Kramer 2006	Review (Cochrane)	Review 11 controlled trials (small, poor quality) 472 women	Aerobic exercise	Preterm birth and birth weight	Pooled increased preterm birth-risk with exercise: RR = 1.82 (CI: 0.35,9.57) No ass. with mean gestational age (mean diff. = +0.3, CI: -0.2,+0.9) Inconsistent results on BW. Data insufficient to infer risks or benefits.
Leet 2003	Meta-analysis	Metaanalysis 30 studies (11 experimental and 19 cohorts)	Physical exercise	Birth weight	Minimal differencies. However, continuing vigorous exercise ass. with lower birth weight.
Lokey 1991	Meta-analysis		Exercise	Many, incl. gestational age and birth weight	No ass. with gestational age or birth weight
Riemann 2000	Review and recommendations		Leisure time activities	Preterm birth and birth weight	No evidence of preterm birth. No clear results on BW, but more studies suggest smaller babies in training women than bigger babies. It seems that foetal growth is not compromised during exercise, but recommendations are difficult to draw.
Schlüssel 2008	Review		Physical activity and exercise		Some light-to-moderate physical activity is not a risk factor and may even be considered a protective factor for some outcomes. Intensity, duration and frequency should be included in future studies.

Simpson 1993	Review	Review No randomized controlled trials reported	Preterm birth and low birth weight	Ass. in both directions. Most plausible ass.: standing, long working hours,heavy lifting.
Sternfeld 1997	Review and recom-mendations	Both occupational and leisure time activities.	Foetal growth	Foetal growth: Exercise is safe. How-ever, prolonged standing is ass. with preterm birth, and limited weight gain and undernutrition is ass. with low birth weight. Women *may* exercise (not should).
Stevenson 1997 (part 1 and 2)	Review			Minimal risk for foetuses and benefi-cial for pregnant women with uncom-plicated pregnancies. No ass. with preterm birth. Most studies: Birth weight unchanged or slightly increased.

5.1.4 Swimming and reproductive outcomes (Paper IV)

Overall, we did not find swimming associated with adverse birth outcomes. Despite a substantial number of studies on drinking water and reproductive outcomes, only a single study has reported on the use of swimming pools during pregnancy using data from The Avon Longitudinal Study of Parents and Children (ALSPAC) (Nieuwenhuijsen, Northstone, and Golding 2002). The findings were very similar to ours. In the ALSPAC study they compared swimmers with never-swimmers and found increasing birth weights with increasing amount of swimming, but differences were small and not statistically significant, as in our study. The swimming measure in ALSPAC was reported in gestational week 18-20, almost equivalent to data from the first pregnancy interview in DNBC. However, the reference groups may not be directly comparable; we compared swimmers with bicyclists and non-exercisers, respectively. The reference group in the ALSPAC study comprised both non-exercisers and women doing other kinds of exercise than swimming, which corresponds to a mixture of the different reference groups, we have used. However, it is likely that a large proportion of the never-swimming group were non-exercisers. The largest differences in mean birth weight in our study were seen among women who reported swimming in late pregnancy compared with no exercise (+27 g, 95% confidence interval +3, +51). Neither of the two other studies on other pregnancy outcomes (miscarriage and neural tube defects) found associations with swimming during pregnancy (Klotz and Pyrch 1999; Waller et al. 1998). No other studies have included a variety of birth outcomes, as we have, or made comparisons with both non-exercisers and a comparable exercise category. Thus, we have studied the topic more extensively and detailed than what has been done before and conclude that swimming is not likely to be associated with adverse birth outcomes.

5.2 Methodological considerations

5.2.1 Selection bias

Selection bias is present if the association between exposure and outcome differs between study participants and those theoretically eligible for the study, including those who were invited but did not participate (Rothman, Greenland, and Lash 2008). Selection bias may occur as incomplete follow up or as non-participation at the time of enrolment (or as in DNBC at the time of an interview). Due to national registers and civil registration numbers in Denmark, less than 1% of mothers or children are lost to follow-up, and since all of the outcomes in the studies (except in Paper I) are based on register data, selection bias due to loss to follow up is considered a minor problem.

Only around 30% of the eligible women were actually enrolled in DNBC, which may constitute an important source of bias, especially for descriptive purposes. Selection into the cohort took place at (at least) two levels: At the general practitioner level, and at the individual level. The largest proportion of non-participation occurred at the level of the general practitioners, since only about 50% of the general practitioners informed the pregnant women about the study. Even though I believe this bias source to be less pronounced than that on the individual level of the women, some selection may have taken place at the general practitioner level. There might have been a selection as to what doctors chose to participate, perhaps based on the socio-economic composition of their patients, and further, we know from telephone calls to the general practitioners that some potential participants were not informed about the study due to individual considerations, such as very young age, low socio-economic status or similar, even though their doctor usually took part in the recruitment.

Selection bias into the cohort is a true concern in the first part of Paper I when assessing the prevalence of physical exercise. Prevalences were lower in DNBC than what is seen in other studies. Variations in study design and in the measure of exercise/physical activity may explain only part of this deviation. If exercise engagement is actually lower than in e.g. the US and Norway, this is somewhat surprising, because participants in DNBC were on average healthier than the general population, and thus we would have expected to see a higher exercise participation compared with all pregnant women in Denmark. If this is true, exercise engagement should be even lower for the general pregnant population in Denmark. However, acknowledging that DNBC was not designed to be representative for the pregnant population in Denmark at large, the selection into the cohort did not seem to bias risk estimates for selected associations in a study on low participation in cohort studies (Nohr et al. 2006), and hence this is not considered a major concern in the part of Paper I on predictors or in Papers II-IV.

In some analyses, data from the second pregnancy interview were necessary, which might cause further bias if participation in the second interview was associated with exercise. When we compared exercise data from the first and the second interview we found that the participation rate for the second interview was similar (92-93%) for all categories of amount and type of exercise, indicating no differential selection bias concerning accomplishment of the second interview (having a first interview was required in all analyses presented in this thesis).

A "healthy exerciser effect" and perhaps a "healthy foetus effect"

Some of our findings suggest exercise to be favourable during pregnancy, e.g. we found exercising women to be at decreased risk of preterm birth. Such findings may be explained by a "healthy exerciser effect". This is equivalent to the idea of the healthy worker effect, where non-workers may not be an appropriate comparison group for workers in the studies of occupational diseases, because severely ill or disabled person may be excluded from occupation, and thereby the working group produces better average health outcomes (Porta 2008). Women with poor health or with uncomforting symptoms in pregnancy may be less likely to exercise than healthier women, and if, at the same time, some risk factors for poor health or uncomforting symptoms are shared with risk factors for preterm birth, exercise will turn out as a preventive factor for preterm birth because of a lower generic risk among exercising women.

If participants had stopped exercising because of contractions or other symptoms of threatening preterm birth we would see 'reverse causation' leading to an underestimation of a possible beneficial exercise effect. This may partly explain our findings indicating that exercise in late pregnancy seemed to account for most of the decreased risk of preterm birth, since women who exercised in late pregnancy were less likely to give birth before term than women who exercised in first part of pregnancy. However, excluding women with symptoms of threatening preterm birth did not change the results much.

Our study on the risk on miscarrigae indicated that physical exercise was associated with an increased risk in early pregnancy up to gestational week 18 (Madsen et al. 2007). It may be speculated that some foetuses are vulnerable to their mothers being physically active in the first part of pregnancy, and that the ones who survive the first part of pregnancy are robust towards exercise and also are the ones with the least likelihood of being born preterm, in other words, a "healthy foetus effect".

5.2.2 Information bias

Information bias occurs as a consequence of measurement error, i.e. if the exposure or the outcome is subject to misclassification, this will bias the results (Rothman, Greenland, and Lash 2008). Misclassification may be differential (vary between exposure groups) or non-differential (be the same in all study groups) (Porta 2008).

5.2.2.1 Misclassification of exposure

Timing

Due to the wording of the interview questions it was not possible to analyse the precise timing of exercise during pregnancy. E.g. some of the women registered as non-exercisers or as doing only little exercise may have been exercising at higher levels earlier in pregnancy. We could have used the gestational dating of each of the interviews, but this would not have solved the problem totally, because we do not know exactly how each woman understood the wording: 'now that you are pregnant…'. Probably some have interpreted this as exercise around the time of the interview, whereas others may have reported an average over the first part of pregnancy. In survival analyses we stratified by time of interview to take into account the varying timing of the interviews.

Intensity of exercise and the use of MET-scores

A recent review concluded that most studies lack adequate information on intensity, duration, and frequency (Schlussel et al. 2008). While frequency and duration of exercise sessions may be more straightforward, we lack good data on the intensity of performed exercise. The closest we get to an intensity measure is using the type of activity as a proxy measure. In Paper II on preterm birth we made additional analyses on MET-hours per week. MET-scores were originally designed to combine intensity and time spent on exercise into one measure and were developed specifically for use in observational studies using questionnaires (Ainsworth et al. 2000). One advantage of using MET-scores is that time spent on exercise and the type of activity sometimes are so closely intercorrelated that usual confounder adjustment is not appropriate. Hence, in the analyses where we did not use MET-scores, we did not adjust activity type and amount of exercise for one another. The reason why, on the other hand, we did not use MET-scores in all the papers is that we are concerned about the validity when turning a type of exercise into a measure of intensity; there is a risk of adding random variation by applying an assumed intensity to a certain activity. By using type and amount of exercise, our core variables, we were not dependant on making the right choice of MET-scores for each activity. Even though we had two researchers independently going through all the listed MET-scores, our final choice of MET-scores for each activity is still only a 'best guess' on which intensity is the most probable in a Danish pregnant population. In the original MET-score list by Ainsworth, the range of applied MET-scores for e.g. bicycling, one of the most common activities among our participants was 4.0-16.0 with 8.0 for 'bicycling, general' (please see Enclosure 2). Furthermore, if mechanical incidents like bumps and jumps account for an association this will not necessarily show up in MET-analyses. In any case, our data did not indicate any differences of importance between using hours per week of exercise and MET-hours per week.

5.2.2.2 Misclassification of outcomes

Gestational age

No matter what method is used for calculation of gestational age, some degree of measurement error will persist. When using last menstrual period for calculation, irregular menstrual cycles, bleeding after the time of conception, insufficient recollection of last menstrual period are some common uncertain factors. When using ultrasound examination, simple measurement errors may be present, and the gestational age is often 'set back' a few days resulting in a higher reporting of preterm births (Gardosi and Geirsson 1998; Olesen et al. 2004; Tunon, Eik-Nes, and Grottum 1996; Yang et al. 2002). In this thesis we have used the gestational age as registered in the Medical Birth Registry based on the midwives' reporting just after a delivery. Since almost all women have at least one ultrasound examination during pregnancy, today this reporting is most often based on ultrasound examination. However, in principle the midwife (or physician) should make the 'best clinical estimate' when deciding the gestational age at birth, and this should be based upon all known factors: e.g. ultrasound, last menstrual period, menstrual cycle length and irregularities, and also on clinical maturity signs in the newborn. To what extent the gestational dating is actually changed after delivery based on maturity signs in the newborn is unknown. From clinical experience, however, I consider this rarely done and therefore claim that the gestational dating from the Medical Birth Registry is most often based on ultrasound examinations. When using gestational age based on ultrasound, we may introduce a systematic error if exercise had a great effect on growth in first part of pregnancy. E.g. if exercise restricts early foetal growth, foetuses of exercising mothers will on average be estimated younger than their actual age from early ultrasound examinations. The use of ultra sound examination in pregnancy has increased over the years of data collection to DNBC (Jorgensen 2003), which may bias our results if data from the last part of the data collection period to a greater extent were based on ultra sound compared with those from the first years.

Foetal growth measures

Measurement errors are unavoidable when it comes to measurement of the size of a newborn. Measures like abdominal circumference and placental weight are particularly uncertain. It seems unlikely though that these errors should differ according to exercise and result in differential misclassification.

We analysed both average mean birth size measures and SGA/LGA. Though largely used, dichotomisation as in SGA can be questioned, since intrauterine growth retardation can occur at a wide spectrum of birth weights for gestational age if the condition is defined as 'a failure of the fetus to achieve its target birth weight', where the afflicted babies not necessarily are among the smallest 5 or 10% (Basso, Wilcox, and Weinberg 2006). We believe to have covered this aspect in detail with the available data by analysing both mean birth size and SGA/LGA. It follows that the apparent contradictory results may in fact not be contradictory, i.e. smaller average birth size can be present but not necessarily show among the smallest 10%. Exercise may affect 'normal growth' but not necessarily pathological growth.

For many years, the focus has been on health risks in small babies, to a large extent based upon older observational studies and also boosted by the foetal origins hypothesis (Barker et al. 1989; Barker et al. 1990), but confounder structure regarding birth weight may be different today. Earlier, high social status was associated with better nutrition leading to better fed mothers having larger babies. Today, however, lower social classes have higher prevalence of obesity, leading to higher risk of diabetes and hence larger babies. Therefore, instead of just using birth weight, we approximated body composition analyses (acknowledging that we do not have direct measurements of organ growth etc.), and we used linear regression to analyse possible effects in both directions of growth, and finally both SGA and LGA were studied.

5.2.3 Confounding

Confounding occurs if an estimated association between exposure and outcome is affected by a common cause of the exposure and outcome (Porta 2008).

Physical exercise during pregnancy was strongly correlated with other life style factors and health conditions. Adjusting for factors like a healthy diet, no smoking, or a good self-rated health would most likely affect associations between physical exercise and health outcomes towards a protective effect of physical activity, but these 'protective' effects may be due to confounding from a cluster of other closely correlated life style factors. However, in our data we had access to a number of lifestyle factors, which we used for confounder control in the studies of reproductive outcomes (Papers II-IV).

The modestly elevated risk for preterm birth, SGA and congenital malformations seen among non-exercisers could be related to medical reasons for not doing exercise. Pregnancy complications such as bleeding in pregnancy, gestational hypertension, uterine contractions will most likely reduce the level of physical activity. If such complications also lead to restricted foetal growth, they will bias the results towards showing reduced foetal growth in women who do not exercise (reverse causation). Repeating the analyses in a population free of clinical indications for not doing exercise did not markedly alter our estimates of any importance.

Some factors may both be confounders and intermediate factors. For example, if bleeding is an early symptom of preterm birth and if bleeding reduces maternal physical activity, it works as a confounder and reverse causation is present. If, on the other hand, exercise results in contractions, which increase the risk of preterm birth, the contractions work as an intermediate between exercise and preterm birth. In the latter example, one should not adjust for contractions because a part of a possible effect would be taken out, and the measure of association would be biased toward the null. In our data it was not possible to differentiate between reverse causation and intermediate factors regarding symptoms during pregnancy. Hence in Paper II on preterm birth and Paper III on foetal growth, we repeated the analyses in a population restricted to women with no prenatally reported warning signs for preterm birth and found no important differences.

Even though previous preterm birth is a strong risk factor for preterm birth in subsequent pregnancies, we did not include this in the model in Paper II. If previous preterm birth share causes, e.g. physical exercise, with preterm birth in a subsequent pregnancy, we would take away the effect of exercise if we adjusted for previous preterm birth. In Paper II we made additional analyses restricted to primigravida and primipara, respectively, and this did not alter preterm birth risk estimates of any importance.

In Paper III we adjusted for gestational age in analyses of foetal growth measures. Gestational age is a part of birth weight and thus somewhat different from other covariates. By adjusting for gestational age in linear regression analysis, it is assumed that a given possible absolute reduction in birth weight is the same for a child born preterm, term and postterm and not relative to the mean size at birth at a given gestational age, which may be a strong assumption. In my opinion, however, birth weight does not really make sense as an indicator without taking gestational age into account one way or the other. Hence, gestational age was modelled as quadratic splines in our analyses of foetal growth measures (Greenland 1995).

Another subject of discussion in foetal growth analyses is maternal gestational weight gain, because it is not only part of the outcome but also a potential intermediate factor in the causal mechanisms between exercise and size at birth. In Paper II on foetal growth, we preferred to leave gestational weight gain out of the analyses for that reason. Our data indicated that exercisers were less likely than non-exercisers to have a high gestational weight gain, which could partly explain the apparent protective effect on LGA, and even though we adjusted for pre-pregnancy body mass index, we may see an obesity effect if body mass index was not properly adjusted for or if overweight women are likely to gain more weight during pregnancy than non-overweight women. This is supported by Haakstad *et al* who found regular exercise associated with lower gestational weight gain, however statistically significant only for data from the third trimester (Haakstad et al. 2007).

Women with any kind of diabetes were excluded in Paper II on foetal growth, because the causal directions between diabetes, exercise and birth weight are very complex, and we would not be able to tell the directions of possible effect modifications from the available data. If the women with or at increased risk of diabetes follow current advice of doing more exercise than the general pregnant population, effects in opposite directions may work: the tendency of diabetic mothers having larger babies and the possible tendency that exercise reduce birth weight. As for gestational weight gain, this should be addressed in a future study.

The presence of women who participated with more than one pregnancy made a sibling analysis possible, where time stable between-subject confounding variables are controlled for such as parental genetic factors (except that the father may not be the same), which was done in Paper III on foetal growth measures.

5.2.4 Selected statistical issues

In survival analysis of preterm birth we did not exclude pregnancies where the infant subsequently was diagnosed with a malformation. The presence of a malformation is usually not known until the baby is born, and since the selection into follow up in survival analysis should only be conditional upon factors known at that time, these pregnancies were included. Furthermore, we decided not to define infants with malformations as events, but rather made them censored at birth, because of a possible interaction between exercise and malformations on the risk of preterm birth.

The WHO definition of preterm birth includes both live- and stillbirths. Our decision of not coding stillbirths (n=285) as events in Cox regression analysis may not fully correspond to the WHO definition. However, the decision was made because the time spent *in utero* after foetal death may differ according to gestational age.

Missing values can be dealt with in different ways. One way is to limit analysis to observations with no missing in any of the included variables (complete case analysis). For descriptive purposes I prefer, however, to see the 'gross'-numbers, hence, these are shown in the descriptive tables in Papers I-III. When doing so, study populations in descriptive statistics are not identical with those of tables of measures of association, because complete case analysis is used in the regression models. For transparency reasons in the Papers, the overall numbers of observations are presented in head of the tables, and numbers of missing values for each variable are presented in footnotes. Imputation is another way of handling missing values; however we did not make use of this.

The fact that the diet variable used in Paper I on predictors had many missing values was dealt with by carrying out the analyses both with and without this variable. We found diet to be associated with exercise, but the selection into responding/non-responding the food frequency questionnaire did not seem to affect the associations between other maternal characteristics and exercise.

An alternative to adjusting for gestational age would be to analyze gestational age-specific z-scores for the foetal growth measures. We preferred, however, to present regression coefficients in grams, centimetres etc. rather than in standard deviations, since we found this approach more direct and applicable for clinical purposes.

It should be noted that studies of a size as DNCB may sometimes produce results that are statistical significant just because of the statistical power due to the large sample size, and this does not necessarily render findings of clinically relevance, as may be the case for our findings on (statistically significant) slightly smaller birth size in the offspring of exercising mothers.

5.2.5 Our findings and possible biological mechanisms

Our findings do not support the hypothesis that exercise should increase the risk of preterm birth, perhaps due to a rise in adrenaline and noradrenaline during physical activity, since we find a slightly reduced risk among exercising women (Paper I).

In Paper III on foetal growth measures we found slightly smaller babies, when examined in a linear model, but no increased risk of SGA with maternal exercise. This could be partly explained by a reduced fat mass in the offspring of exercising mothers. If we had proper measurements of body composition, such as DEXA-examinations of foetal lean and fat body mass, we might have been able to detect possible specific effects on foetal tissue growth. We did not have such detailed data, but, on the other hand, if exercise has strong specific effects on foetal growth this should be revealed with the birth size measures used in this study.

Our findings on slightly smaller babies among exercising mothers may be mediated by a reduced risk of gestational diabetes, which also corresponds with our findings on a reduced risk of LGA with exercise. Since we excluded women with previous gestational diabetes, diabetes before pregnancy, or gestational diabetes diagnosed or suspected in this pregnancy, the above speculations only apply to women with gestational diabetes diagnosed after the time of the first pregnancy interview.

An overall beneficial effect of exercise on the circulatory system of the mother might result in increased foetal growth, however our findings do not point in the direction of larger babies with exercise, perhaps apart from the decreased risk of SGA. On the other hand, if physical exercise reduces the rate of LGA infants without shifting the entire birth weight distribution downwards, exercise may be beneficial by reducing the adverse consequences of overgrowth.

5.2.6 Discussion of (future) study design

Even though The DNBC was designed as an almost ideal type of birth cohort by having recruitment in early part of pregnancy, by having prospectively collected exposure data, and by being the largest birth cohort with pregnancy recruitment in the world at the time of completed recruitment, the descriptive work from this thesis reveals a methodological challenge to observational studies when it comes to lifestyle epidemiology. Randomized controlled trials have important advantages over observational studies (e.g. they should be less susceptible to confounding), but they also have limitations since they are not always possible for ethical or practical reasons. While it may pose ethical concern to randomize women to no exercise, it seems acceptable to divert them into different activity groups or to a training programme, but for comparison this requires training not to be part of routine antenatal care. It may also be difficult to obtain a high compliance e.g. when usually non-active women are allocated to an active intervention. A randomized controlled trial may be feasible in studies of specific causal mechanisms or specific aspects of physical activity but perhaps not for physical activity in general and usually this approach is taken only for limited types of regimes of exposures (exercise). Rare outcomes such as foetal death or perhaps preterm birth may also require too large samples for controlled trials, while more frequent outcomes like pre-eclampsia, gestational diabetes, gestational weight gain, or size at birth could be studied this way. Because of the inability to study rare outcomes in controlled trials (or smaller cohorts), biomarkers could be useful. In order to examine possible effects of general exercise or overall physical activity, i.e. what ‘normal’ women do in ‘normal’ daily life, the preferred method would be observational studies with rich data on potential confounders. Hence, the analyst is faced with a choice of either observational studies that are able to accurately measure not just physical activity but also other factors strongly correlated with physical activity, e.g. dietary patterns, or randomized controlled trials.

6 CONCLUSIONS AND PERSPECTIVES

While the research findings that initiated this thesis showed an increased risk of miscarriage among exercising women, the results presented herein turned out to be reassuring. There are no convincing indications from our work that physical exercise should be harmful to the unborn child, and thus current recommendations are supported by the data available in this study. The thesis also presents new knowledge on exercise behaviour in relation to pregnancy and points out predictors of inactivity during pregnancy. Such predictors can be used to establish public health interventions aiming to increase the level of physical activity among pregnant women, which is relevant because pregnancy is associated with a reduction in physical exercise, and activity levels are not usually regained after childbirth. That is if an overall evaluation, with as many maternal and foetal outcomes as possible taken into account, is in favour of exercise during pregnancy.

The predictors of exercise during pregnancy described in the thesis can be used in the design of future studies to identify confounders or to guide sensitivity analyses on the importance of lack of data on confounders or perhaps as a reminder to read research findings with caution, because if we do not fully adjust for other healthy behaviours we may overlook side effects of exercise. For future research, both lifelong exposure up to the time of pregnancy and long-term consequences of exercise during pregnancy would be of interest.

In this work, we concentrated on ‘normal’ women, but specific studies designed to target women engaged in sports at elite level are needed. Studies on multiple pregnancies are also lacking, since these observations are most often excluded from analyses. However, exercise is interesting among women carrying more than one child, because at the same time these women are at increased risk of some of the conditions that exercise may prevent (pre-eclampsia or gestational diabetes) and at increased risk of e.g. preterm birth where the traditional treatment is sedentary behaviour. Since exercise and diet are closely correlated and both also correlated with obesity, future studies would probably benefit from combining diet and physical activity. Finally, repeated measurements of exercise, starting before pregnancy, should be recommended.

It is still unclear whether an effect of exercise on e.g. foetal growth is most pronounced in early or late pregnancy – if at all. If physical activity is believed to be overall beneficial during pregnancy, it is relevant to have knowledge of effects from both early and late pregnancy. Preventive actions may then be established in early pregnancy. In addition, exercise data from early pregnancy may be less biased because reports from later in pregnancy are dependent on the course of pregnancy. Late pregnancy measurements should also be examined because this is the gestational period with the highest foetal weight gain.

The studies included in this thesis have added reassuring findings to the increasing body of evidence on physical activity during pregnancy, but decisions on precise public health advice should take all outcomes into consideration even though these may point in different directions.

7 SUMMARY (English)

Physical activity is of crucial importance in the prevention of a number of diseases and is therefore given high priority in the treatment of illnesses and in health promotion, including antenatal care, where physical activity during pregnancy is considered to have a positive health effect on several pregnancy outcomes, e.g. pre-eclampsia and gestational diabetes. Moreover, pregnancy is often followed by a persistent weight increase, which is assumed reducible by means of physical activity during pregnancy. On the basis of these assumptions, current guidelines in Denmark and a number of other countries today recommend pregnant women to be physically active at the same level as the non-pregnant population. The Danish guidelines comprise at least 30 minutes of moderate physical activity per day. However, only limited scientific evidence exists on the influence of the mother's level of activity on the health and development of the foetus. The sparse evidence regarding foetal health, together with recent research indicating an increased risk of spontaneous abortion among exercising women, provided the rationale for this thesis. Hence, the aim of the thesis is to examine whether current guidelines are scientifically well founded when it comes to the health of the child. The thesis thus illuminates possible consequences for the foetus of maternal exercise during pregnancy. All four studies in the thesis are based on data on about 90,000 pregnancies in the Danish National Birth Cohort, where detailed information on exercise are available from two different points of time during pregnancy.

About one third of the women were engaged in exercise during pregnancy, a little more in early pregnancy and a little less in late pregnancy. Most women were engaged in swimming, bicycling, or other low impact activities. Higher age, being a student, having an eating disorder, higher alcohol intake, and a health conscious diet were predictors for regular exercise, i.e. at least three exercise sessions per week. Holding a lower professional or a skilled worker job, multiparity, lower self-rated health, fertility treatment, smoking, a lesser health conscious diet, and a body mass index outside the normal range were predictors for not being engaged in regular exercise. Exercising women were slightly less likely to give birth before term than non-exercisers. This relationship was not affected by the type of exercise and did not affect the seriousness of the preterm birth. The exercise level of the mother was not associated with the newborn's weight, length, ponderal index (corresponding to body mass index in newborns), head- and abdominal circumference, or the weight of the placenta. Yet, physically active women had a slightly lower risk of having a small- or large-for-gestational-age baby, i.e. in the lower and upper 10^{th} percentiles of the weight distribution for a given gestational age at birth. In a comparison between pregnant swimmers and bicyclists, based on the

hypothesis that exposure to chemically purified water is associated with negative reproductive outcomes, there were no substantial differences in the average size of the babies at birth or in the risk of giving birth preterm, having a prolonged pregnancy or having a baby with a congenital malformation.

Results from this thesis do not contradict the recommendations that pregnant women should be physically active, since none of our findings suggest adverse health outcomes related to exercise during pregnancy.

8 SUMMARY (Danish)

Fysisk aktivitet har vist sig at have afgørende betydning i forebyggelsen af en række sygdomme og prioriteres derfor højt i både sundhedsfremme og sygdomsbehandling. Dette gælder også i svangreomsorgen, hvor fysisk aktivitet i graviditeten menes at have en positiv effekt på en række graviditetsudfald, fx præeklampsi og gestationel diabetes. Ydermere ledsages graviditet ofte af en vedvarende vægtøgning, som må formodes at kunne reduceres ved fysisk aktivitet i graviditeten. På baggrund af disse antagelser anbefales det i aktuelle retningslinjer i Danmark og en række andre lande gravide kvinder at være fysisk aktive på niveau med den ikke-gravide befolkning. I Danmark anbefales minimum 30 minutters moderat fysisk aktivitet om dagen. Der foreligger imidlertid kun begrænset videnskabelig dokumentation vedrørende betydningen af moderens aktivitetsniveau for fosterets sundhed og udvikling. Dette forhold, sammen med nyere forskningsresultater, som finder en øget risiko for spontan abort blandt motionerende kvinder, dannede baggrund for denne ph.d.-afhandling. Formålet med afhandlingen er derfor at undersøge, om de gældende anbefalinger er videnskabeligt funderet, når det gælder barnets sundhed. Afhandlingen belyser således de mulige konsekvenser for fosteret af moderens motion under graviditeten. Alle fire studier i afhandlingen baserer sig på data fra ca. 90.000 graviditeter i den danske Bedre Sundhed for Mor og Barn kohorte, hvori der findes detaljerede oplysninger om motion fra to forskellige tidspunkter i graviditeten.

Omkring en tredjedel af kvinderne dyrkede motion; lidt flere i begyndelsen af graviditeten og lidt færre i slutningen. Flest kvinder svømmede, cyklede eller dyrkede andre 'low impact' aktiviteter. Højere alder, at være studerende, at have en spiseforstyrrelse, højere alkoholindtag og sundere kost var prædiktorer for at dyrke regelmæssig motion, defineret som motion mindst tre gange om ugen. At være i faglært job eller job, der kræver mellemlang videregående uddannelse, at have født før, lavere selvvurderet helbred, barnløshedsbehandling, rygning, mindre sund kost samt et body mass index udenfor normalområdet var tilsvarende prædiktorer for ikke at dyrke regelmæssig motion. Kvinder, der dyrkede motion i graviditeten, var lidt mindre tilbøjelige til at føde for tidligt end ikke-aktive kvinder. Denne sammenhæng var ikke påvirket af typen af motion og påvirkede ikke graden af for tidlig fødsel. Moderens aktivitetsniveau havde ikke nogen betydelig sammenhæng med det nyfødte barns fødselsvægt, længde, ponderal index (svarende til body mass index for spædbørn), hoved- og maveomfang eller vægten af moderkagen. Fysisk aktive kvinder havde dog også en let nedsat risiko for at få et 'for lille' eller 'for stort' barn, defineret som værende indenfor den nedre eller øvre 10. percentil for fødselsvægtfordelingen for en given graviditetsuge ved fødslen. I en sam-

menligning mellem gravide svømmere og cyklister (baseret på en hypotese om negative reproduktionsudfald efter eksponering for kemisk behandlet vand) sås ingen betydelige forskelle i børnenes gennemsnitlige størrelse eller i kvindernes risiko for at føde for tidligt, gå over tiden eller føde et barn med en medfødt misdannelse.

Resultaterne fra denne afhandling taler således ikke imod den generelle anbefaling om, at gravide kvinder bør være fysisk aktive, da ingen af vore resultater tyder på negative helbredsudfald relateret til motion i graviditeten.

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10 ENCLOSURE 1

The Borg Perceived Exerction Scale

6	No exertion at all
7	Extremely light
8	
9	Very light - (easy walking slowly at a comfortable pace)
10	
11	Light
12	
13	Somewhat hard (It is quite an effort; you feel tired but can continue)
14	
15	Hard (heavy)
16	
17	Very hard (very strenuous, and you are very fatigued)
18	
19	Extremely hard (You can not continue for long at this pace)
20	Maximal exertion

11 ENCLOSURE 2

Decisions about MET-scores based on our best estimation from the updated list of MET-intensities by Ainsworth *et al* (Ainsworth et al. 2000) (next page).

	MET-interval	MET-choice	Description
Pre-defined categories			
Gymnastics/aerobics for pregnant women		4	gymnastics, general
Aerobics/gymnastics	5-10	6.5	aerobic, general
Dance	3-5.5	4.5	general
Bicycling	4-16	8	general or leisure, moderate effort
Walking/hiking	3-8	3.5	walking for pleasure (walking, moderate pace, firm surface: 3.3) (walking, brisk, firm surface, walking for exercise: 3.8)
Jogging/orienteering	7-18	7	general
Ball games	3-12	3 +6 +7 +8 24 24 / 4 = 6	volleyball, non-competitive, 6-9 member team, general basketball, non-game, general soccer, casual, general handball, team
Swimming	6-11	7	swimming laps, freestyle, slow, moderate or light effort
Workout/fitness training	3-6	5.5	health club exercise, general

Badminton	4.5-8	4.5	social singles and doubles, general
Tennis	5-10	7	general
Horseback riding	2.5-6.5	4	general
Other		148.4 / 29 = 5.1	the mean of all other categories except triathlon due to the small numbers and very high MET-score
New categories (from the 'other' category)			
Yoga	2.5	2.5	stretching, hatha yoga
Roller blading	7-12.5	7	skating, roller
Rowing/kayaking	5-12	3 +3.5 +4 +5 +7 +7 29.5 29.5 / 6 = 4.9	canoing, rowing, light effort rowing, stationary, light effort paddleboat kayaking canoing, rowing, moderate effort rowing, stationary, moderate effort
Squash	12	12	squash
Martial arts	4-10	4	tai chi (n=16)

		+10 14 14 / 2 = 7	judo, jujitsu, karate, kick boxing, tae kwon do (n=14)
Swimming for pregnant women/under water exercise general or for pregnant women	4	4	water aerobics, water calisthenics
Teach physical education, exercise, sports classes or coaching	4-6.5	4	teach physical education, exercise, sports classes non-sport play or coaching: football, soccer, basketball, baseball, swimming, etc.
Golf	3.5-4.5	4.5	general
Step		5.5	health club exercise, general
Bowling	3	3	bowling
Agility	4-5	4	walk/run, playing with animals, moderate, only active periods
Mensendieck		3.5	calisthenics, home exercise, light or moderate effort, general (example: back exercises), going up & down from floor
Gymnastics for mother and child		3.5	calisthenics, home exercise, light or moderate effort, general (example: back exercises), going up & down from floor
Relaxation exercises	2.5	2.5	stretching, hatha yoga or mild stretching

Back exercises		3.5	calisthenics, home exercise, light or moderate effort, general (example: back exercises), going up & down from floor
Rehabilitation exercises		3.5	calisthenics, home exercise, light or moderate effort, general (example: back exercises), going up & down from floor
('aktivt arbejde') (skal udgå)			(n=38) mixed between physiotherapists with classes, postmen, famers, sports students etc.
Boxing	6-12	6	punching bag
Triathlon		18 +16 +11 45 / 3 = 15	running, 10.9 mph (5.5 min/mile) bicycling, >20mph, racing, not drafting swimming, crawl, fast (75 yards/min), vigorous effort (n=2)

12 PAPERS

Paper 1: Juhl M, Madsen M, Andersen AMN, Andersen PK, Olsen J. Predictors of regular exercise during pregnancy: A study within the Danish National Birth Cohort on pregnant women's exercise habits. Submitted.

Paper 2: Juhl M, Andersen PK, Olsen J, Madsen M, Jørgensen T, Nøhr EA, Andersen AMN. Physical exercise during pregnancy and the risk of preterm birth: A study within the Danish National Birth Cohort.
Am J Epidemiol 2008;167:869-866.

Paper 3: Juhl M, Olsen J, Andersen PK, Nøhr EA, Andersen AMN. Physical exercise during pregnancy and fetal growth measures: A study within the Danish National Birth Cohort. In press. Am J Obstet Gynecol.*

Paper 4: Juhl M, Kogevinas M, Andersen PK, Andersen AMN, Olsen J. Is swimming during pregnancy a safe exercise? In press. Epidemiology.**

*A PDF proof from the American Journal of Obstetrics and Gynecology is printed here. It differs negligibly from the draft included in the version for the assessment committee.

** A revised version of the paper, which is now accepted in Epidemiology, is printed here. It differs to some extent from the draft included in the version for the assessment committee.

PAPER I

EXERCISE HABITS AND PREDICTORS OF EXERCISE

PREDICTORS FOR REGULAR EXERCISE DURING PREGNANCY: A STUDY ON EXERCISE HABITS AMONG PREGNANT WOMEN IN THE DANISH NATIONAL BIRTH COHORT

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Keywords:

Exercise, physical activity, pregnancy, birth cohort, confounding

Word count: text body 3191, abstract 234.

ABSTRACT

Background: Although not based on strong evidence, physical activity is recommended for pregnant women. We present descriptive data on exercise among pregnant women, and lifestyle, socio-demographic, and health related predictors of physical exercise during pregnancy. *Methods:* Data on 88,200 singleton pregnancies from the Danish National Birth Cohort collected 1996-2002 were used in logistic regression analysis to identify predictors of exercise. *Results:* About one third of the women were engaged in exercise in early/mid pregnancy and a little less in late pregnancy. Bicycling, swimming and low impact activities were the most common activities. Regular exercise was strongly correlated with having a health conscious diet, a high alcohol consumption, or an eating disorder. Higher parity, smoking, low self-rated health, and having a diet high in fat and low in vegetables were the strongest correlates of not doing exercise. Being a student and having an eating disorder were more strongly correlated with frequent exercise (3+ sessions/week) vs. less/no exercise than with any exercise vs. no exercise. Single status was associated with frequent exercise but not with any exercise. *Conclusion:* Some of the presented predictors of regular exercise during pregnancy identify factors should be controlled for in future observational studies and may guide sensitivity analyses when data on confounders are lacking. The findings may also be useful in identifying women who could benefit from physical activity interventions, if physical activity is found to be health beneficial in pregnancy.

INTRODUCTION

According to antenatal guidelines, pregnant women are advised to be physically active [1-4], but the evidence underlying these recommendations is sparse, especially when it comes to the health of the foetus [5-7]. More evidence is needed on the subject, but as with much other research into life style matters, there exist a number of methodological issues that complicate studies within this field. Although a randomized controlled trial is often considered to be the optimal design when examining an association between exposure and outcome, we are often left with observational data when dealing physical activity in pregnancy; trials are difficult to carry out among pregnant women with good compliance over a longer period of time, and trials may also be considered unethical if physical activity is believed to involve health benefits (or hazards).

Observational studies on life style factors, including physical activity, are difficult to de-confound since many life style factors are closely interrelated. As such, a potential harm caused by physical activity may well be masked by beneficial effects of other life style factors correlated with physical activity. Full confounder adjustment is only possible if we know what to adjust for and have the necessary data. Therefore, knowledge about maternal characteristics associated with exercise during pregnancy is of key importance when evaluating confounding in observational studies on the subject.

Most population-based studies on exercise during pregnancy have been cross-sectional [8;9] or have used data collected after delivery [10;11]. The Norwegian Mother and Child Cohort is the only large study published with exercise data and data on maternal characteristics collected during pregnancy [12]. In previous studies low maternal age, multiparity, low education, not being married, poor general health, high body mass index and smoking have been found associated with little or no leisure-time physical activity during pregnancy [8-13], however, Zhang et al found older age to be related to less activity [13]. Only few studies report on type, frequency, and duration of physical activity in pregnancy.

The aim of this study was to describe the level and nature of exercise among pregnant women in the Danish National Birth Cohort and its relation to lifestyle factors, socio-demographic factors, and to the reproductive and health history.

METHODS

Study population and inclusion criteria

The study is based on data from the Danish National Birth Cohort (DNBC), a population-based cohort of pregnant women and their offspring [14]. During 1996-2002 pregnant women were approached at their first antenatal visit to the general practitioner who handed out information about the cohort together with an informed consent form. Eligibility criteria were: Being pregnant, not planning an induced abortion, and sufficient language skills to participate in computer-assisted telephone interviews in Danish. For those who gave consent, data collection included computer-assisted-telephone interviews around gestational week 12-16 and 30, questionnaires and blood samples. An English translation of the interviews is available at http://www.bsmb.dk. Approximately half of the general practitioners agreed to take part in the recruitment process, and we estimate that about 60 percent of the invited women accepted the invitation. For this study we included all the 90,165 pregnancies with available data from the first pregnancy interview, which excludes women with an early induced or spontaneous abortion and women who could not be contacted by phone when the first interview was scheduled or in three following calls. As we excluded multiple pregnancies, analyses were based on 88,200 singleton pregnancies.

Physical activity

In both pregnancy interviews, the women were asked the following questions about physical activity: *1) 'Now that you are pregnant do you engage in any kind of exercise?'* In case of a positive answer, the following questions were posed: *2) 'What kind of exercise do you engage in?', 3) 'How many times a week do you engage in…(answer in question 2)?', 4) 'How many minutes a time do you engage in…(answer in question 2)?'* and *5) 'Do you engage in other types of exercise?'* A positive answer to the last question re-opened the above questions until a negative response was given. In case of uncertainty about which activities should be included as exercise, an activity was included if the woman confirmed that the activity made her sweaty or made her short of breath.

Hours per week spent on exercise and number of exercise sessions per week were calculated, and the active women were assigned to a preferred type of exercise, defined as the type of activity performed more than 50 percent of the total activity time. Women who did not perform any single activity more than 50 percent were classified as 'mixed exercisers'. There were 13 pre-defined categories of type of exercise, which were categorized into the following seven groups: Swimming, low impact activities (aerobic/gymnastics for pregnant women, aerobic/gymnastics, dance, walking/hiking, yoga), high impact activities (jogging, ball games, and racket sports), work out/fitness training, bicycling, horseback riding, and a non-classifiable category (including the mixed category).

When evaluating possible predictors of regular exercise, physical activity was categorized into no exercise, 1-2 exercise sessions per week, and 3 sessions or more per week in line with Owe et al. and Zhang and Savitz [12;13]. Since duration can vary between exercise sessions, we made additional analyses using minutes per week with a cut point of 3½ hour per week, corresponding to current Danish Board of Health guidelines for recommended physical activity for pregnant women (as well as for the general population).

Maternal characteristics

Mother's age at conception came from the National Patient Register and information on diet came from a food frequency questionnaire in DNBC. Not all women responded to the extensive questionnaire so the diet variable had many missing values, i.e. 25,736 out of 88,200. All other co-variates came from the first pregnancy interview and had only few missing values (the numbers are shown in footnotes of Tables 2 and 3). Apart from self-rated health, the included health-related covariates describe whether the women had *ever* had the condition in question. All other covariates refer to the time of the first pregnancy interview, unless noted otherwise. The median gestational age for the interview was 114 days corresponding to 16.3 completed weeks (10^{th} and 90^{th} percentiles: 84 and 160 days).

Statistical analysis

We used logistic regression analysis to calculate odds ratios for any exercise vs. no exercise and for at least 3 sessions per week vs. less/no exercise according to maternal characteristics. Separate analyses were made using exercise data from the first pregnancy interview (early/mid pregnancy) and for the second interview (late pregnancy). Analyses were carried out adjusted within subgroups of covariates (socio-demographic, health related, and behavioural factors) and with all covariates mutually adjusted. Furthermore predictors of exercising at least 3½ hour per week were analysed. Because of the large number of missing values in the diet variable, analyses were carried out both with and without this variable in order to assess the importance of diet and of a possible selection into responding to the food frequency questionnaire.

RESULTS

[Table 1]

In a little more than one third of the pregnancies the mother had been engaged in exercise in early/mid pregnancy. In late pregnancy this proportion decreased somewhat (Table 1). In almost half of the pregnancies the mother had been engaged in exercise at some point in pregnancy, that is either at the time of the first or the second pregnancy interview (data not shown). Both in early/mid and late pregnancy most women preferred bicycling, swimming or low impact activities, and swimming was the only single activity, which was done more frequently late in pregnancy. High impact activities and horseback riding had the largest relative reductions in activity from early to late pregnancy. Most women attended only one session of exercise per week, but 4.5% of the women exercised at least 3 times per week throughout pregnancy. The majority of the active women exercised one hour or less per week, but 7.0% exercised at least 3½ hour per week in early/mid pregnancy, and 3.9% did so late in pregnancy.

Furthermore, among the women who were physically inactive around the time of the first interview, 84 % were still inactive later in pregnancy; while16 % had commenced some kind of exercise, most likely low impact activities. Among women who reported exercise in the first interview, 48 % had ceased exercising between the first and the second interview. Swimming was the activity most persistently performed during pregnancy. Almost half of the women who reported swimming in early/mid pregnancy also did so in late pregnancy, while e.g. 6% of the high impact performers still engaged in high impact activities in late pregnancy. Women who performed high impact activities in early/mid pregnancy were more likely to cease exercise completely later in pregnancy than women who joined other kind of activities. Overall, close to half of the women who reported to be physically active in early/mid pregnancy were still engaged in some kind of activity late in pregnancy. Women who changed preferred type of exercise during pregnancy in general switched to activities at the same impact level or below.

[Table 2]

Table 2 shows the distribution of exercise sessions per week in early/mid pregnancy according to socio-demographic, health related, and behavioural maternal characteristics together with adjusted odds ratios for any regular exercise and for frequent exercise, respectively. The strongest correlates of doing any exercise were having a health conscious diet, alcohol consumption, and having an eating disorder. Also women who were older than 25 years, students, or had a musculo-skeletal disorder were likely to exercise, however, associations were weak. Higher parity, smoking, low self-rated health, and a diet high in fat and low in vegetables were associated with not doing exercise. Furthermore, women who were out of work or held lower grade or unskilled jobs, who had fecundity problems or had received subfecundity treatment, and women with a low body mass index were less likely to exercise but with weaker associations.

Correlates of exercising 3 times or more per week were in general similar to those of any exercise, a few differences could be pointed out, though: Parity, alcohol consumption, smoking and subfecundity treatment were stronger correlated with any exercise than with frequent exercise. Being a student and having an eating disorder were more strongly correlated with a high frequency of exercise than with any exercise. Women out of work were less likely to do any exercise but more likely to exercise frequently. Finally, single status was associated with frequent exercise but not with any exercise. Most estimates were either stronger in the subgroup-adjusted analysis than in the fully adjusted model or similar in the two analyses.

[Table 3]

Table 3 present the exercise data from late pregnancy, in a fashion similar to Table 2 . Many estimates were equivalent to those found for exercise in early/mid pregnancy. However, higher age was more evidently correlated with both any exercise and frequent exercise in late pregnancy than in early/mid pregnancy. Single status, a high coffee intake, and a high body mass index were weakly associated with no exercise in late pregnancy. The strong relation between eating disorders and frequent exercise in early/mid pregnancy became weaker and statistically insignificant when late pregnancy data were used. It should be noted that comparisons of odds ratios from early to late pregnancy should take into consideration that the two populations, and thereby also reference groups, were not identical (Tables 2 and 3).

We analysed the likelihood of doing regular exercise throughout pregnancy and found effect measures to be very similar to those found for exercise late in pregnancy. We also analysed the likelihood of exercising 3½ hour per week or more and found older age, being out of work, living alone, and having higher alcohol consumption to be stronger related to exercise at least 3½ hour per week than 3 sessions per week, however none of the associations exceeded an odds ratio of 1.6. When we repeated the analyses without the diet variable, due to the many missing values in this variable, only minor changes were seen.

DISCUSSION

A little more than one third of the mothers had been engaged in exercise in early/mid pregnancy, and about half of them exercised regularly at some point in pregnancy. Low impact activities, swimming and bicycling were the most common types of exercise during pregnancy. Swimming was the only single activity that increased in prevalence from early to late pregnancy. Most of the active women exercised once a week and only for one hour or less. As expected, being physically active in pregnancy correlated with many factors that are potential causes of reproductive failures, and getting an estimate of any causal associations between exercise and reproductive outcomes is a challenge.

The following predicting factors are fairly consistent over previous studies: Schooling or higher education, higher income, younger age, nulliparity/not having older children, non-smoking, and pre-pregnant non-overweight (ref). Except for age, this corresponds well with our findings. In our data, the likelihood of exercise engagement increased with increasing age, and the association seemed to be stronger in late than in early/mid pregnancy. We did not study income, but our occupational status measure may work as a proxy for both education and income. In our data, married/cohabiting women were more likely to engage in any exercise in late pregnancy, but in early/mid pregnancy women living alone were more likely to engage in frequent exercise, i.e. 3 sessions or more per week, whereas it has been reported from US-based studies that married women were more likely to be physically active. Cohabiting without being formally married is frequent in Denmark, which is why we did not separate the married group from the cohabiting group, as was done in the US-studies. However, our aim was not to examine the condition of living alone while pregnant rather than marriage *per se*. Furthermore, a higher level of activity would be expected among married women when household activities are included (Ning). Finally, we found increasing alcohol intake associated with exercise, which has not previously been reported. Still, it corresponds well with existing research on alcohol indicating more favourable health outcomes with some intake compared with no intake (ref). It is surprising, though, that our data indicate higher intakes to be stronger correlated with exercise than lower intakes. This applies to an intake up to 5+ drinks per week, which was the highest intake category.

The DNBC is a cohort study with the aim of examining associations and thus not designed as a prevalence study, but even so it is interesting that the proportion of physically active women was substantially lower than in other studies showing that a prevalence of physical activity or exercise of 42%-67% among pregnant women (ref). Some studies used an overall measure of leisure time physical activity, including e.g. gardening (Evenson 2004, Ning 2003, Petersen 2005), while the women in DNBC were asked specifically about exercise, which should give a lower proportion of active women. Furthermore, the timing of physical activity may vary between studies. The wording in the DNBC questionnaire may result in a not very specific timing of the exercise measure: 'Now that you are pregnant, do you engage in…'. Hence, it might be that women who exercised in the very beginning of pregnancy did not report this.

Even though the Norwegian Mother and Child Cohort Study (MoBa) in many ways is similar to the DNBC comparable, exercise engagement is higher than in DNBC: 59% of the women exercised at some level in early/mid pregnancy and 47% in late pregnancy as opposed to 37% and 30%, respectively, in DNBC. The differences were also present for regular exercise. In MoBa strolling was not included as exercise, but this differentiation was not possible in our data, hence, a broader range of walking intensity may have been included in the walking-category in DNBC, unless the woman herself did not consider strolling to be exercise and therefore did not report this. However, having included strolling would have made prevalences in MoBa even higher. Apart from the difference in the walking measure, tendencies of preferred exercise types and changes during pregnancy in exercise habits were similar in the two cohorts.

As expected, physical exercise was strongly correlated with other life style factors and health conditions. Assumingly, most of these factors would tend to bias associations between physical exercise and health outcomes towards a protective effect of physical activity (e.g. a healthy diet, no smoking, and a good self-rated health), Hence, part of the 'protective' effects associated with life style factors like physical activity might be due to confounding from a cluster of other closely correlated life style factors. It may also be that some of the factors that we consider associated with pregnancy outcomes are based on studies, which have not taken physical activity into consideration, so that these studies are confounded by physical activity. Both explanations may well be in play. However, the picture is not entirely uniform and some correlates may work in the opposite direction leading to an underestimation of a potential protective effect (e.g. maternal age or having an eating disorder).

About 30% of all pregnant women during the recruitment period participated in the study. The DNBC was not designed to be representative for the pregnant population in Denmark at large; the participants were on average healthier than the general population, hence our exercise 'prevalence' estimates are probably higher than what is expected for the source population [15]. It is likely that the decision to participate in a cohort like the DNBC is correlated with socio-demographic and health related factors, which are further correlated with physical activity. However, we do expect that the associations we see between physical activity and maternal characteristics in this study will also be present in the population that was invited to take part in the study. Furthermore, since the largest proportion of non-participation occurred at the level of the general practitioners (only about 50% of the general practitioners informed the pregnant women about the study) this selection need not be related to the life style of the participants. In addition, carrying out the analyses both with and without the diet variable (with many missing values) indicated that the selection into responding/non-responding the food frequency questionnaire did not affect the associations between other maternal characteristics and exercise.

In the acknowledgement of the fact that most studies on lifestyle factors in pregnancy are of observational character, and this may also be so in future research, we have identified a number of predictors for regular exercise during pregnancy. This information can be used in future studies to identify confounders or to guide sensitivity analyses on the importance of lack of data on confounders. In counselling, the findings can be used to identify pregnant women with a low propensity to physical exercise while pregnant and to target activities that may fit their needs (e.g. young or less educated women or women with older children at home). These results also demonstrate why a randomised trial on reproductive effects of physical exercise would be highly valuable. If exercise in pregnancy is considered to be health beneficial, it may pose ethical concern to randomise women to no exercise, but in that case it should be possible to randomise women into groups of more or less exercise or of different types of exercise.

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Table 1. Exercise habits among participants in The Danish National Birth Cohort, 1996-2002.

	Early pregnancy (n=88200)		Late pregnancy (n=81023)		Throughout pregnancy (n=81023)	
	N	%	N	%	N	%
Preferred type of exercise*						
No exercise	55846	63.5	56384	69.7	41903	51.7
Swimming	6962	7.9	8518	10.5	2821	3.5
Low impact activities*	9947	11.3	8502	10.5	2675	3.3
High impact activities†	2498	2.8	244	0.3	149	0.2
Workout/fitness training	1488	1.7	556	0.7	238	0.3
Bicycling	8109	9.2	4299	5.3	1763	2.2
Horseback riding	992	1.1	224	0.3	186	0.2
Other	2159	2.5	2145	2.7	284	0.4
Total sessions of exercise per week						
0	55846	63.5	56384	69.7	41903	51.7
1	10904	12.4	11665	14.4	3441	4.2
2	6248	7.1	4301	5.3	1082	1.3
3	2938	3.3	1638	2.0	301	0.4
4	1863	2.1	1006	1.2	118	0.1
5	3739	4.3	1780	2.2	429	0.5
6	1451	1.7	765	1.0	75	0.0
7	1784	2.0	1106	1.4	165	0.2
8-13	1811	2.1	1058	1.3	143	0.2
14	824	1.0	796	1.0	72	0.0
>14	593	0.7	373	0.5	32	0.0
Total hours of exercise per week						
0	55846	63.5	56384	69.7	41903	51.7
(0-1]	11735	13.3	11802	14.6	3511	4.3
(1-2]	8853	10.1	6535	8.1	1523	1.9
(2-3]	4813	5.4	2705	3.3	497	0.6
(3-4]	2738	3.1	1529	1.9	180	0.2
(4-5]	1617	1.8	722	0.9	75	0.0
(5-6]	890	1.0	436	0.5	40	0.0
(6-7]	634	0.7	352	0.4	29	0.0
>7	875	1.0	407	0.5	91	0.0

Missing exercise data: in early pregnancy 199, in late pregnancy 151.

*Low impact activities = aerobic/gymnastics for pregnant women, aerobic/gymnastics, dance, walking/hiking, yoga.

†High impact activities = jogging, ball games, racket sports.

*Defined as the type of exercise performed at least 50% og the total time spent on exercise.

Table 2. Proportions and odds ratios of regular exercise in early pregnancy according to maternal charateristics among participants in The Danish National Birth Cohort, 1996-2002. N=88200.

	Number of exercise sessions per week in early pregnancy										
				Co-variates mutually adjusted within subgroups (socio-demographic, health related and behavioural)				All co-variates mutually adjusted			
	0	1-2	3+	1+ vs 0		3+ vs less		1+ vs 0		3+ vs less	
	(n=55846)	(n=17152)	(n=15003)								
Maternal characteristics	%	%	%	OR***	95% CI	OR***	95% CI	OR****	95% CI	OR****	95% CI
Socio-demographic factors											
Maternal age (years)											
<25	13	12	13	1	-	1	-	1	-	1	-
25-<35	75	79	75	1.25	1.19, 1.30	1.11	1.05, 1.18	1.08	1.02, 1.14	0.99	0.92, 1.06
35-<40	11	9	10	1.23	1.15, 1.31	1.28	1.18, 1.39	1.08	1.00, 1.17	1.13	1.03, 1.25
40+	1.1	0.8	1.2	1.32	1.14, 1.53	1.54	1.29, 1.83	1.11	0.93, 1.34	1.24	0.99, 1.54
Occupational status											
Higher grade prof.	8	11	10	1	-	1	-	1	-	1	-
Lower grade prof.	25	30	30	0.94	0.90, 1.00	1.01	0.95, 1.08	1.04	0.98, 1.11	1.09	1.01, 1.18
Skilled workers	19	19	15	0.73	0.69, 0.77	0.72	0.67, 0.77	0.87	0.81, 0.93	0.83	0.76, 0.90
Unskilled workers	28	20	21	0.61	0.58, 0.65	0.75	0.70, 0.80	0.83	0.77, 0.88	0.94	0.86, 1.02
Students	12	15	17	0.97	0.91, 1.03	1.14	1.06, 1.22	1.09	1.01, 1.17	1.26	1.15, 1.37
Out of work > 3 mths	6.4	3.7	4.8	0.64	0.60, 0.70	0.85	0.77, 0.94	0.85	0.77, 0.94	1.12	1.00, 1.27
Non-classifiable	1.0	0.9	0.9	0.77	0.66, 0.89	0.88	0.73, 1.07	0.83	0.69, 1.00	0.92	0.72, 1.17
Marital status											
Married/cohabiting	98	98	98	1	-	1	-	1	-	1	-
Not married/cohabiting	2.1	1.6	2.5	0.94	0.85, 1.04	1.18	1.05, 1.33	1.06	0.93, 1.20	1.21	1.04, 1.41
Parity											
0	41	58	57	1	-	1	-	1	-	1	-
1	40	31	31	0.54	0.52, 0.55	0.63	0.60, 0.65	0.55	0.53, 0.58	0.67	0.63, 0.70
2+	19	11	12	0.45	0.43, 0.47	0.55	0.52, 0.58	0.47	0.44, 0.49	0.58	0.54, 0.63
Health related factors											
Selfrated health											
Very good	49	58	61	1	-	1	-	1	-	1	-

Normal	47	40	36	0.68	0.66, 0.70	0.67	0.64, 0.70	0.74	0.71, 0.77	0.71	0.68, 0.75
Less good	4.4	2.5	2.5	0.47	0.43, 0.51	0.50	0.44, 0.56	0.61	0.55, 0.68	0.63	0.55, 0.72
Eating disorders											
No	99	99	99	1	-	1	-	1	-	1	-
Yes	0.7	0.6	1.2	1.31	1.12, 1.54	1.78	1.50, 2.12	1.20	0.99, 1.46	1.65	1.34, 2.04
Hypertension, ever											
No	96	96	96	1	-	1	-	1	-	1	-
Yes	4.2	3.7	4.1	0.97	0.91, 1.04	1.04	0.95, 1.14	1.03	0.95, 1.13	1.10	0.99, 1.22
Hypertension, only gestational											
No	95	96	96	1	-	1	-	1	-	1	-
Yes	5.4	4.0	4.1	0.76	0.71, 0.81	0.84	0.77, 0.91	1.06	0.98, 1.16	1.11	0.99, 1.24
Metabolic disorders											
No	98	98	98	1	-	1	-	1	-	1	-
Yes	2.1	1.6	1.8	0.84	0.76, 0.93	0.92	0.80, 1.05	0.88	0.77, 1.01	0.95	0.81, 1.13
Musculo-sceletal disorders											
No	90	91	90	1	-	1	-	1	-	1	-
Yes	9.7	9.1	10.0	1.08	1.03, 1.13	1.13	1.06, 1.20	1.15	1.09, 1.22	1.15	1.07, 1.24
Psychiatric illnesses											
No	92	94	92	1	-	1	-	1	-	1	-
Yes	8.2	6.3	8.2	0.93	0.88, 0.98	1.12	1.05, 1.19	0.97	0.90, 1.03	1.15	1.06, 1.25
Other serious illnesses											
No	95	95	95	1	-	1	-	1	-	1	-
Yes	5.1	5.0	5.1	1.08	1.02, 1.15	1.08	0.99, 1.17	1.09	1.01, 1.18	1.08	0.98, 1.19
Subfecundity											
No	87	89	88	1	-	1	-	1	-	1	-
Yes	13	11	12	0.88	0.84, 0.93	0.90	0.84, 0.96	0.85	0.80, 0.91	0.89	0.82, 0.97
Subfecundity treatment											
No	94	95	95	1	-	1	-	1	-	1	-
Yes	5.9	4.9	5.3	0.93	0.86, 1.00	1.00	0.91, 1.09	0.74	0.68, 0.81	0.86	0.77, 0.96

Behavioural factors

Coffee consumption (cups/day)

0	55	57	55	1	-	1	-	1	-	1	-
<2	16	18	19	1.04	1.00, 1.09	1.07	1.01, 1.13	1.03	0.98, 1.08	1.05	0.99, 1.11
2-<4	15	14	15	1.00	0.95, 1.05	1.07	1.01, 1.14	1.06	1.01, 1.12	1.12	1.05, 1.19
4+	15	10	11	0.90	0.84, 0.95	0.99	0.92, 1.06	0.99	0.94, 1.05	1.05	0.97, 1.13
Alcohol consumption (drinks/week)											
0	57	50	54	1	-	1	-	1	-	1	-
<1	15	17	16	1.19	1.13, 1.25	1.04	0.98, 1.10	1.19	1.13, 1.25	1.05	0.98, 1.11
1-<3	23	28	25	1.25	1.20, 1.30	1.04	0.99, 1.10	1.27	1.22, 1.32	1.07	1.01, 1.13
3-<5	3.4	3.6	3.7	1.21	1.11, 1.33	1.12	1.00, 1.26	1.24	1.13, 1.37	1.15	1.02, 1.29
5+	1.0	1.0	1.0	1.34	1.13, 1.60	1.28	1.03, 1.58	1.45	1.21, 1.73	1.32	1.06, 1.65
Smoking (g tobacco/day)											
0	82	91	89	1	-	1	-	1	-	1	-
1-<10	8.5	5.5	6.4	0.74	0.69, 0.79	0.88	0.80, 0.96	0.75	0.70, 0.80	0.88	0.80, 0.97
10+	9.5	3.5	4.7	0.51	0.47, 0.56	0.70	0.63, 0.78	0.55	0.50, 0.60	0.72	0.64, 0.80
Pre-pregnancy body mass index (kg/m2)											
<18,5	4.9	3.7	4.1	0.80	0.74, 0.87	0.83	0.75, 0.93	0.81	0.75, 0.89	0.83	0.74, 0.93
18,5-<25	66	70	72	1	-	1	-	1	-	1	-
25-<30	20	19	17	0.90	0.86, 0.94	0.88	0.83, 0.93	0.97	0.92, 1.01	0.93	0.88, 0.99
30+	8.9	7.3	7.0	0.83	0.78, 0.88	0.84	0.77, 0.91	0.94	0.89, 1.00	0.92	0.85, 1.01
Dietary pattern											
Health consciuos*	13	21	26	1.79	1.72, 1.87	1.76	1.68, 1.86	1.61	1.54, 1.69	1.60	1.52, 1.69
Intermediate	67	67	64	1	-	1	-	1	-	1	-
Western**	21	12	9.7	0.60	0.57, 0.63	0.57	0.53, 0.61	0.65	0.62, 0.69	0.61	0.57, 0.66

Missing: age 15, occupational status 0, marital status 38, parity 36, selfrated health 35, chronic diseases overall 394, eating disorders 98, hypertension 161, gestational hypertension 161, metabolic disorders 155, musculo-sceletal disorders 122, psyciatric ilnesses 71, other serious diseases 130, subfecundity 286, subfecundity treatment 33, coffee 33, alcohol 94, smoking 43, body mass index 1463, dietary pattern 25736.

*Low in fat, high in vegetables.

**High in fat, low in vegetables.

OR=odds ratio. CI=confidence interval.

Table 3. Proportions and odds ratios of regular exercise in late pregnancy according to maternal charateristics among participants in The Danish National Birth Cohort, 1996-2002. N=81023.

	Number of exercise sessions per week in late pregnancy										
				Co-variates mutually adjusted within subgroups (socio-demographic, health related and behavioural)				All co-variates mutually adjusted			
	0	1-2	3+	1+ vs 0		3+ vs less		1+ vs 0		3+ vs less	
	(n=56384)	(n=15966)	(n=8522)								
Maternal characteristics	%	%	%	OR***	95% CI	OR***	95% CI	OR****	95% CI	OR****	95% CI
Socio-demographic factors											
Maternal age (years)											
<25	13	11	12	1	-	1	-	1	-	1	-
25-<35	75	79	76	1.41	1.34, 1.48	1.21	1.12, 1.30	1.23	1.15, 1.30	1.10	1.00, 1.20
35-<40	11	8.7	11	1.51	1.40, 1.62	1.44	1.30, 1.59	1.29	1.18, 1.41	1.26	1.11, 1.43
40+	1.1	0.8	1.2	1.61	1.37, 1.90	1.71	1.38, 2.13	1.40	1.14, 1.70	1.49	1.14, 1.94
Occupational status											
Higher grade prof.	8	12	10	1	-	1	-	1	-	1	-
Lower grade prof.	26	32	30	0.89	0.84, 0.94	0.96	0.89, 1.04	0.97	0.90, 1.03	1.09	0.99, 1.20
Skilled workers	19	18	14	0.63	0.59, 0.67	0.64	0.59, 0.71	0.75	0.69, 0.80	0.80	0.72, 0.90
Unskilled workers	28	19	21	0.55	0.51, 0.58	0.73	0.67, 0.80	0.75	0.70, 0.80	1.03	0.93, 1.14
Students	12	15	18	0.93	0.88, 1.00	1.21	1.11, 1.32	1.04	0.96, 1.12	1.42	1.28, 1.58
Out of work > 3 mths	6.1	3.2	5.1	0.62	0.57, 0.68	0.97	0.86, 1.09	0.85	0.76, 0.94	1.36	1.17, 1.57
Non-classifiable	1.0	0.9	1.0	0.70	0.60, 0.83	0.90	0.71, 1.14	0.79	0.64, 0.97	1.17	0.88, 1.55
Marital status											
Married/cohabiting	98	99	98	1	-	1	-	1	-	1	-
Not married/cohabiting	2.1	1.3	2.1	0.75	0.66, 0.84	1.06	0.90, 1.24	0.83	0.71, 0.97	1.12	0.92, 1.37
Parity											
0	40	63	58	1	-	1	-	1	-	1	-
1	41	28	30	0.44	0.43, 0.46	0.62	0.59, 0.65	0.47	0.45, 0.49	0.68	0.64, 0.72
2+	19	8.8	12	0.33	0.31, 0.34	0.53	0.49, 0.57	0.35	0.33, 0.37	0.57	0.52, 0.63
Health related factors											
Selfrated health											
Very good	50	57	63	1	-	1	-	1	-	1	-

Normal	46	40	35	0.72	0.70, 0.74	0.63	0.60, 0.67	0.80	0.76, 0.82	0.68	0.64, 0.72
Less good	4.0	2.7	2.5	0.57	0.52, 0.63	0.54	0.47, 0.62	0.71	0.64, 0.80	0.63	0.53, 0.75
Eating disorders											
No	99	99	99	1	-	1	-	1	-	1	-
Yes	0.7	0.7	1.1	1.12	0.94, 1.33	1.52	1.21, 1.90	1.00	0.81, 1.24	1.25	0.96, 1.64
Hypertension, ever											
No	96	97	96	1	-	1	-	1	-	1	-
Yes	4.3	3.5	4.1	0.89	0.82, 0.96	1.05	0.94, 1.18	0.97	0.88, 1.06	1.12	0.98, 1.28
Hypertension, only gestational											
No	94	97	96	1	-	1	-	1	-	1	-
Yes	5.6	3.3	3.9	0.63	0.59, 0.69	0.78	0.70, 0.88	0.99	0.90, 1.09	1.05	0.92, 1.21
Metabolic disorders											
No	98	98	98	1	-	1	-	1	-	1	-
Yes	2.0	1.6	1.8	0.87	0.77, 0.98	0.93	0.79, 1.11	0.97	0.84, 1.12	0.98	0.80, 1.21
Musculo-sceletal disorders											
No	90	91	91	1	-	1	-	1	-	1	-
Yes	9.7	9.5	9.3	1.04	0.98, 1.09	1.03	0.95, 1.11	1.12	1.05, 1.20	1.03	0.94, 1.14
Psychiatric illnesses											
No	92	93	92	1	-	1	-	1	-	1	-
Yes	7.9	6.8	8.2	0.97	0.91, 1.03	1.13	1.04, 1.23	1.07	1.00, 1.15	1.13	1.02, 1.25
Other serious illnesses											
No	95	95	95	1	-	1	-	1	-	1	-
Yes	5.0	4.9	5.3	1.07	1.00, 1.15	1.12	1.01, 1.24	1.04	0.96, 1.14	1.01	0.90, 1.15
Subfecundity											
No	87	87	88	1	-	1	-	1	-	1	-
Yes	13	13	12	0.92	0.87, 0.97	0.92	0.85, 1.00	0.88	0.82, 0.94	0.92	0.83, 1.02
Subfecundity treatment											
No	95	93	95	1	-	1	-	1	-	1	-
Yes	5.3	6.7	5.4	1.26	1.17, 1.37	1.01	0.90, 1.14	1.04	0.95, 1.14	0.89	0.77, 1.02
Behavioural factors											
Coffee consumption (cups/day)											

0	54	59	56	1	-	1	-	1	-	1	-
<2	16	19	19	1.06	1.01, 1.11	1.07	1.00, 1.15	1.03	0.98, 1.09	1.05	0.98, 1.13
2-<4	15	13	14	0.87	0.82, 0.92	0.99	0.91, 1.07	0.93	0.87, 0.98	1.03	0.94, 1.12
4+	15	8.4	11	0.75	0.70, 0.80	0.97	0.89, 1.07	0.85	0.80, 0.91	1.03	0.93, 1.13
Alcohol consumption (drinks/week)											
0	57	52	54	1	-	1	-	1	-	1	-
<1	15	17	16	1.10	1.05, 1.16	1.00	0.93, 1.08	1.11	1.05, 1.17	1.01	0.93, 1.09
1-<3	24	27	25	1.18	1.13, 1.24	1.01	0.94, 1.07	1.21	1.16, 1.27	1.04	0.97, 1.11
3-<5	3.5	3.4	3.7	1.17	1.06, 1.30	1.12	0.98, 1.30	1.22	1.10, 1.35	1.16	1.00, 1.34
5+	1.0	1.0	1.1	1.40	1.15, 1.70	1.33	1.02, 1.73	1.60	1.31, 1.95	1.41	1.08, 1.84
Smoking (g tobacco/day)											
0	83	92	90	1	-	1	-	1	-	1	-
1-<10	8.4	4.9	6.3	0.71	0.65, 0.76	0.91	0.81, 1.02	0.70	0.65, 0.76	0.92	0.82, 1.03
10+	9.0	2.8	4.1	0.48	0.43, 0.52	0.67	0.58, 0.77	0.52	0.47, 0.57	0.69	0.60, 0.80
Pre-pregnancy body mass index (kg/m2)											
<18,5	4.7	3.7	4.1	0.80	0.73, 0.88	0.94	0.82, 1.07	0.81	0.73, 0.89	0.93	0.81, 1.06
18,5-<25	66	72	73	1	-	1	-	1	-	1	-
25-<30	20	18	17	0.82	0.78, 0.86	0.79	0.74, 0.85	0.88	0.84, 0.92	0.85	0.79, 0.91
30+	8.9	6.6	6.9	0.77	0.72, 0.83	0.85	0.77, 0.95	0.88	0.81, 0.94	0.95	0.86, 1.06
Dietary pattern											
Health consciuos*	13	23	27	1.81	1.73, 1.89	1.80	1.69, 1.91	1.58	1.50, 1.65	1.63	1.53, 1.74
Intermediate	67	66	64	1	-	1	-	1	-	1	-
Western**	20	11	8.8	0.56	0.53, 0.59	0.54	0.49, 0.59	0.62	0.59, 0.66	0.59	0.53, 0.64

Missing: age 6, occupational status 0, marital status 30, parity 33, selfrated health 28, eating disorders 88, hypertension 143, gestational hypertension 143, metabolic disorders 142, musculo-sceletal disorders 109, psyciatric ilnesses 62, other serious diseases 116, subfecundity 255, subfecundity treatment 31, coffee 28, alcohol 83, smoking 33, body mass index 1325, dietary pattern 22148.

*Low in fat, high in vegetables.

**High in fat, low in vegetables.

OR=odds ratio. CI=confidence interval.

PAPER II

EXERCISE AND PRETERM BIRTH

American Journal of Epidemiology

Vol. 167, No. 7
DOI: 10.1093/aje/kwm364
Advance Access publication February 25, 2008

Original Contribution

Physical Exercise during Pregnancy and the Risk of Preterm Birth: A Study within the Danish National Birth Cohort

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Received for publication July 20, 2007; accepted for publication November 13, 2007.

According to many national recommendations, women should be physically active during pregnancy, but empirical evidence to support this recommendation is sparse. The authors' aim in this study was to examine the relation between physical exercise during pregnancy and the risk of preterm birth. Self-reported data on physical exercise during pregnancy were collected prospectively for 87,232 singleton pregnancies included in the Danish National Birth Cohort between 1996 and 2002. Hazard ratios for preterm birth according to hours of exercise per week, type of exercise, and metabolic equivalent-hours per week, respectively, were calculated using Cox regression analysis. Results showed a reduced risk of preterm birth among the almost 40% of women who engaged in some kind of exercise during pregnancy in comparison with nonexercisers (hazard ratio = 0.82, 95% confidence interval: 0.76, 0.88), but no dose-response relation was seen. The association was not affected by the type of exercise, and the results were not altered when the degree of preterm birth was taken into account. These findings do not indicate any adverse effects of exercise on the risk of preterm birth and therefore do not contradict current recommendations.

exercise; pregnancy; premature birth

Abbreviations: CI, confidence interval; MET, metabolic equivalent.

Health authorities in the United States, Great Britain, Norway, and Denmark recommend a level of physical activity for pregnant women similar to that of the nonpregnant population (1–4). According to the National Board of Health in Denmark, pregnant women should engage in exercise according to Borg Scale level 12–13 (5) (corresponding to moderate/somewhat hard exercise) at least 30 minutes per day (4). Furthermore, light fitness training can be commenced and hard fitness training (Borg Scale level 14–15) need not be discontinued in pregnancy. The recommendations are based on the health benefits of physical activity for the mother, including prevention of obesity (6–8), gestational diabetes (9, 10), and preeclampsia (11, 12). Whether this is good for the fetus is unclear (13).

Recent results from the Danish National Birth Cohort challenged these recommendations by indicating an increased risk of spontaneous abortion among women who engaged in physical exercise (14). The threat of preterm birth has been an indication for sick leave and confinement to bed rest.

Almost all attempts to prevent or predict preterm birth have failed, and the incidence even seems to be increasing in

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some countries, such as the United States and Denmark (15, 16). During exercise, both adrenaline and noradrenaline levels rise, and since noradrenaline affects the uterus, exercise could theoretically induce preterm birth via uterine contractions. Mechanical stimulation of the uterus during exercise has also been suggested to explain the increased uterine contractility observed in relation with physical activity (17). Intervention studies (17–20) and an observational study (21) showed conflicting results as to whether physical exercise actually increases uterine contractility.

Intervention studies have been small and carried out in selected groups (22, 23). A recent Cochrane review concluded that trials on physical exercise and preterm birth were few and too small to provide scientifically based documentation (13). From cohort studies, either no association between exercise and preterm birth (24–26) or a possible reduced risk (27–29) has been reported, and except for one cohort study that included 7,101 women (28), previous studies have been rather small.

Our aim in this study was to examine the relation between physical exercise during pregnancy and the risk of preterm birth in a large cohort of pregnant women.

MATERIALS AND METHODS

From 1996 to 2002, pregnant women were recruited into the Danish National Birth Cohort, a nationwide study of pregnant women and their offspring. The intention was to invite all eligible women in Denmark to participate in early pregnancy. Approximately 50 percent of all general practitioners in Denmark agreed to take part in the study. Recruitment was carried out mainly by the general practitioners, and approximately 60 percent of the women invited chose to participate. The national taxpayer-funded antenatal care program is used by 99 percent of all pregnant women in Denmark (S. Rasmussen, National Board of Health, personal communication, 2007). Among other things, the women agreed to participate in two computer-assisted telephone interviews during pregnancy. More details about the Danish National Birth Cohort are presented elsewhere (30).

In total, 100,422 pregnant women were enrolled in the cohort. For this study, we initially included the 90,165 pregnancies for which we had a first pregnancy interview. Subsequently, 941 pregnancies were excluded because the pregnancy ended before 22 completed weeks of gestation, and 28 pregnancies were excluded because the first pregnancy interview had been carried out later than 37 completed weeks of gestation, when the woman was no longer at risk of having a preterm birth. The final study population comprised 89,196 pregnancies, of which 1,964 were multiple pregnancies. In the main analyses, only singleton pregnancies were included ($n = 87{,}232$).

In the study population, 93 percent of women with singleton pregnancies also participated in the second interview ($n = 81{,}001$). The median gestational age for the first pregnancy interview was 114 days (10th percentile, 84 days; 90th percentile, 160 days), corresponding to 16.3 completed weeks. For the second interview, the median gestational age was 218 days (10th percentile, 195 days; 90th percentile, 249 days), corresponding to 31.1 completed weeks.

Measurement of physical exercise

Information on physical exercise was obtained from the first and second pregnancy interviews. The first question was:

1) "Now that you are pregnant, do you engage in any kind of exercise?"

   In case of a positive answer, the following questions were posed:

2) "What kind of exercise do you engage in?"
3) "How many times per week do you engage in... (answer in question 2)?"
4) "How many minutes per time do you engage in... (answer in question 2)?"
5) "Do you engage in other types of exercise?"

A positive answer to the last question released a loop with the above questions, which continued until a negative response was given. All questionnaires are available in English on the website of the Statens Serum Institut (http://www.ssi.dk/sw379.asp) (please note that this is an unauthorized translation of the interviews).

Physical exercise was subsequently categorized into total time spent in exercise, in hours per week: 0, >0–≤1, >1–≤2, >2–≤3, >3–≤5, and >5 (four women who reported more than 40 hours of exercise per week were assigned as missing). For descriptive analyses, we assigned the active women to a preferred type of exercise, defined as the type of exercise performed more than 50 percent of the time. Women who did not perform any single activity more than 50 percent of the time were classified as "mixed exercisers." There were 13 predefined categories, which were categorized into the following seven groups: 1) swimming, 2) low-impact activities (aerobics/gymnastics for pregnant women, aerobics/gymnastics, dancing, walking/hiking, yoga), 3) high-impact activities (jogging, ball games, racket sports), 4) working out/fitness training, 5) bicycling (which is a common means of commuting in Denmark), 6) horseback riding, and 7) nonclassifiable types of exercise (including the mixed category). Swimming and bicycling are non-weight-bearing activities and were therefore treated separately. Low-impact activities are activities in which at least one foot is always on the ground, whereas in high-impact activities there are moments at which both feet leave the ground simultaneously.

Furthermore, we calculated total metabolic equivalent (MET)-hours of leisure-time physical activity per week by multiplying a certain MET score by the total number of minutes per week of a given activity. The sum of total MET-hours/week for each woman was then calculated. The choice of MET score for each activity was based on our best estimation from the updated list of MET intensities by Ainsworth et al. (31) (see the Web Appendix, posted on the *Journal*'s website (www.aje.oxfordjournals.org), for a list of all MET scores used in this study). Total MET-hours per week were categorized into: 0, >0–≤5, >5–≤10, >10–≤15, and >15 (based approximately on quartiles).

For additional analyses, the pregnancies were categorized according to possible changes in exercise habits from early to late pregnancy.

TABLE 1. Distribution (%) of physical exercise according to gestational age at birth, Danish National Birth Cohort, 1996–2002

Exercise	Data from pregnancy interview 1* (n = 87,232)					Data from pregnancy interview 2† (n = 81,001)		
	No. of pregnancies	Completed weeks of gestation at birth				No. of pregnancies	Completed weeks of gestation at birth	
		22–27 (n = 333)	28–31 (n = 435)	32–36 (n = 3,511)	≥37 (n = 82,953)		22–36 (n = 2,949)	≥37 (n = 78,052)
Hours per week								
0	55,226	66	64	65	63	56,366	73	70
>0–≤1	11,616	12	12	13	13	11,801	13	15
>1–≤2	8,749	10	9	9	10	6,534	7	8
>2–≤3	4,762	5	6	6	5	2,704	3	3
>3–≤5	4,312	5	6	5	5	2,251	3	3
>5	2,373	2	2	3	3	1,194	1	1
Preferred type								
None	55,226	66	64	65	63	56,366	73	70
Swimming	6,901	9	8	7	8	8,517	10	11
Low-impact activities‡	9,857	9	11	11	11	8,501	9	11
High-impact activities§	2,459	2	2	2	3	244	0	0
Working out/fitness training	1,473	1	2	1	2	556	1	1
Bicycling	8,001	10	9	9	9	4,299	5	5
Horseback riding	988	1	1	1	1	224	0	0
Other	2,133	2	3	2	2	2,143	2	3

* There were 194 missing values for exercise variables in the first interview.

† There were 151 missing values for exercise variables in the second interview.

‡ Low-impact activities were defined as activities in which at least one foot is always on the ground (included were: aerobics/gymnastics for pregnant women, aerobics/gymnastics, dancing, walking/hiking, yoga).

§ In high-impact activities, there are moments at which both feet leave the ground simultaneously (included were: jogging, ball games, racket sports).

Measurement of other covariates

Information on potential confounders was obtained from the first pregnancy interview and was categorized as displayed in table 1. We also considered chronic diseases (yes/no), uterine fibroids or malformations or cone biopsy (yes/no), subfecundity (time to pregnancy >12 months vs. time to pregnancy ≤12 months), working hours (day, evening, night, rotating shifts without night work, rotating shifts with night work), working position (predominantly standing or walking, predominantly sitting, or a mixture), and psychosocial job strain (relaxed, active, passive, strained). Furthermore, data from the second pregnancy interview on vaginal bleeding, painful contractions, loss of amniotic fluid, and cervical incompetence were used in subanalyses.

Measurement of outcome

Gestational age was based upon information from birth record data reported to the National Patient Registry in Denmark. Preterm birth was defined as delivery (both live- and stillbirth) after 153 days and before 259 days (equivalent to 22 and 36 completed weeks of gestation, respectively). Preterm births were further categorized as extremely preterm (22–27 completed weeks of gestation), very preterm (28–31 completed weeks), or moderately preterm (32–36 completed weeks) (15).

Statistical analysis

Hazard ratios for preterm birth according to total amount of exercise per week and MET-hours per week, respectively, were estimated using a Cox regression model. Time at risk started from the day a woman completed the 22nd week of gestation or on the day of her first pregnancy interview, whatever came last. Follow-up ended at birth, emigration, or maternal death or by the time a woman completed gestational week 37, whatever came first. If a second interview was available, exercise data would be updated at the time of the second interview. In order to adjust for the different times of entry into follow-up related to the fact that some women were interviewed early in pregnancy and others later, we stratified our models by gestational age at the time of the first interview when exercise data from the first interview were used, and by gestational age at the time of the second interview when data from the second interview were used.

We conducted tests for trend over all exposure groups and for the situation in which the response of no exercise is allowed to differ from the general relation (32). To examine a possible nonlinear relation between MET score and hazard of preterm birth, we analyzed both a model with linear splines (33) and a model allowing for a quadratic relation.

The importance of type of exercise was analyzed by dividing each type into no engagement, small amounts, and large amounts, with the results for the different types of exercise being mutually adjusted for each other.

In the analysis of possible changes in exercise habits from early pregnancy to late pregnancy, we restricted the data to observations with a first pregnancy interview performed before 22 completed weeks of gestation and a second pregnancy interview performed between 22 and 36 weeks, both inclusive. Hence, entry time started by the time of the second interview.

To examine time-dependent associations, we estimated the influence on extremely, very, and moderately preterm birth, respectively, by including an interaction term between exercise and time categorized into intervals corresponding to the degree of preterm birth. This procedure corresponds to making separate analyses for each time interval, except that common estimates of the influence of each of the other covariates are obtained.

Previous preterm birth is a strong risk factor for subsequent preterm birth and is therefore likely to be a cue for reducing activity level in later pregnancies. Hence, we repeated the analyses for primigravid and nulliparous women, respectively. Likewise, we assumed that women with symptoms possibly related to preterm birth during pregnancy might decrease their physical activity. In the attempt to elucidate possible reverse causation, we carried out analyses restricted to women who reported none of these symptoms in the second interview and compared risk estimates with those for all women with a second interview. Finally, separate analyses were carried out for multiple-gestation pregnancies.

To evaluate the possible effect arising from a woman's having more than one pregnancy during follow-up, we compared all standard errors with robust standard errors taking cluster sampling into consideration (34).

The selection of potentially confounding factors was based on an a priori search of the literature, and all available factors identified were included in the model. All analyses were carried out using SAS statistical software, version 9 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

The total number of preterm births was 4,279, corresponding to 4.9 percent of all singleton pregnancies. Almost two thirds (63 percent) of the participants did not engage in any kind of physical exercise around the time of the first pregnancy interview, and at the time of the second interview this figure was 70 percent (table 1). Exercising more than 2 hours per week was infrequent, and in late pregnancy approximately half of the active women exercised for 1 hour per week or less. Among physically active women, the most common activities were swimming, low-impact activities, and bicycling. The prevalence of bicycling, however, was markedly reduced in the second interview.

Apart from parity, there were no essential differences in the occurrence of preterm birth according to the maternal characteristics considered (table 2). From the first interview to the second interview, there was a decrease in the proportion of women who exercised that was consistent over exposure groups.

Table 3 shows that women who engaged in some kind of exercise while pregnant were less likely to give birth before term than women who did not engage in physical exercise. Tests for trend indicated that the difference was seen between nonexercisers and exercisers and that the amount of time spent on exercise played less of a role; hence, there was no indication of a dose-response relation among active women. Adjustment for possible confounders did not alter the estimates substantially, either in this analysis or in the following analysis.

When the importance of type of exercise was examined, all types of exercise were associated with a reduced risk of preterm birth (except for horseback riding, which had hazard ratios around 1 and broad confidence intervals; data not shown). However, risk estimates were statistically significant only among women who engaged in low-impact activities of limited duration or in swimming.

When amount and type of exercise were combined according to MET scores, a leisure-time activity level of up to 5 MET-hours per week was associated with an almost 25 percent decreased risk of preterm birth in comparison with nonactive women, while the hazard ratio among women who exercised for more than 15 MET-hours per week was 0.88 (table 4). With regard to amount analyses in table 3, no trend was seen among exposed women in the MET analyses. Furthermore, neither a linear spline model nor a model with a quadratic relation provided a better fit than the simple linear model.

From table 5, it follows that exercise late in pregnancy was associated with a reduced risk of preterm birth, whereas for exercise in early pregnancy, no association was seen. In this analysis, adjusting for warning signs of preterm birth did not alter the estimates substantially (data not shown). When the data set was restricted to women with no prenatally recorded warning signs for preterm birth, the association among women who exercised in late pregnancy was attenuated, whereas a slightly increased risk of preterm birth was seen among women who had stopped exercising (data not shown).

The association between exercise and moderate preterm birth did not differ from what was presented in table 3 for overall preterm birth (data not shown). The hazard ratio for very preterm birth among exercisers as compared with nonexercisers was 0.86 (95 percent confidence interval (CI): 0.70, 1.07), and for extremely preterm birth the corresponding hazard ratio was 1.01 (95 percent CI: 0.74, 1.38).

When we restricted the analyses to primigravid and nulliparous women, respectively, the results were similar to those for the whole population. The hazard ratio for exercise versus no exercise for primigravidae was 0.81 (95 percent CI: 0.73, 0.89), and it was close to identical for nulliparae. Correspondingly, the estimates for women with no warning signs of preterm birth were similar to those for the total cohort (hazard ratio = 0.82, 95 percent CI: 0.73, 0.92). However, when we analyzed exercise data from the first and second pregnancy interviews separately, almost the whole association was seen in the analysis based on data from the second interview.

Finally, separate analyses were carried out for the 1,964 multiple pregnancies that had been excluded from the main

TABLE 2. Distribution of selected maternal characteristics according to gestational age at birth and physical exercise during pregnancy ($n = 87,232$), Danish National Birth Cohort, 1996–2002

Variable*	No. of pregnancies	Preterm birth† (%) ($n = 4,279$)	Term birth‡ (%) ($n = 82,953$)	Proportion (%) of exercising women§	
				Interview 1	Interview 2
Maternal age (years)					
<25	11,221	15	13	35	28
25–<35	65,920	72	76	37	31
35–<40	9,184	12	10	33	27
≥40	907	1	1	34	28
Gravidity					
1	30,260	43	34	46	40
≥2	56,938	57	66	31	25
Parity					
0	40,955	60	46	45	40
≥1	46,241	40	54	29	22
Previous spontaneous abortions					
0	70,549	79	81	38	31
1	12,560	15	14	32	28
≥2	4,052	6	5	26	24
Coffee consumption (cups/day)					
0	48,237	55	55	37	32
>0–<2	14,889	16	17	40	34
2–<4	12,625	13	15	36	28
≥4	11,449	16	13	30	22
Alcohol consumption (drinks/week)					
0	48,247	59	55	34	29
>0–<1	13,722	15	16	39	32
1–<3	21,256	22	25	40	33
3–<5	3,054	3	4	38	31
≥5	859	1	1	37	32
Smoking in early pregnancy (tobacco g/day)					
0	64,504	69	74	39	33
1–<10	12,434	15	14	33	26
≥10	10,062	15	11	24	19
Body mass index¶					
<18.5	3,878	5	4	31	26
18.5–<25	58,253	66	68	38	32
25–<30	16,596	19	19	34	27
≥30	7,066	10	8	32	25
Occupational status					
Higher-grade professional	7,944	8	9	42	37
Lower-grade professional	23,744	25	27	41	35
Skilled worker	16,151	19	18	34	27
Unskilled worker	22,030	28	25	30	23
Student	11,670	13	13	43	37
Out of work for >3 months	4,857	6	6	28	22
Nonclassifiable	836	1	1	35	29

* Missing values: for gravidity, $n = 34$; for parity, $n = 36$; for previous spontaneous abortion, $n = 71$; for coffee consumption, $n = 32$; for alcohol consumption, $n = 94$; for smoking, $n = 232$; for body mass index, $n = 1,439$.

† Delivery between 22 and 36 completed weeks of gestation, inclusive.

‡ Delivery at 37 completed weeks of gestation or later, including postterm births.

§ Missing values for exercise variables: first interview, $n = 194$; second interview, $n = 151$.

¶ Weight (kg)/height (m)^2.

TABLE 3. Crude and adjusted hazard ratios for preterm birth according to amount of physical exercise during pregnancy ($n = 87,232$), Danish National Birth Cohort, 1996–2002

Exercise	Crude HR*	Adjusted HR†	95% CI*	*p* for trend	*p* for trend‡
None	1	1			
Any	0.86	0.82	0.76, 0.88		
Hours/week					
0	1	1		0.0002	0.2461
>0–≤1	0.82	0.80	0.72, 0.87		
>1–≤2	0.86	0.81	0.72, 0.92		
>2–≤3	0.93	0.89	0.76, 1.05		
>3–≤5	0.94	0.89	0.75, 1.06		
>5	0.87	0.81	0.64, 1.04		

* HR, hazard ratio; CI, confidence interval.

† Adjusted for age, gravidity, parity, previous spontaneous abortions, uterine fibroids/malformations/cone biopsy, subfecundity, coffee consumption, alcohol consumption, smoking, body mass index, job status, working hours, working position, and job strain.

‡ When zero exposure was separated from the dose-response.

analyses (1,933 twin births and 31 triplet births). In multiple pregnancies, the hazard ratio for preterm birth was 0.87 (95 percent CI: 0.74, 1.03) among women who engaged in any kind of exercise in comparison with nonactive women (data not shown). When amount or type of exercise was subcategorized, hazard ratios were just below or around 1, with broad confidence intervals.

The cluster effect due to the fact that some participants had more than one pregnancy in the cohort was found to be negligible (data not shown).

DISCUSSION

In almost 90,000 pregnancies, a little more than one third of the women engaged in physical exercise in early pregnancy, and this proportion decreased somewhat in late pregnancy. These women had a moderately reduced risk of preterm birth, but no dose-response relation was seen. The findings indicate either that physical exercise is associated with a reduced risk of preterm birth or that women with a low generic risk of preterm birth are more likely to be physically active (a ‘‘healthy exerciser effect’’). Restricting analyses to primigravidae, nulliparae, or women with no symptoms of threatening preterm birth did not change the estimates substantially, nor did detailed analyses of the types of exercise performed.

These results corroborate previous findings, which mostly have been based on small cohorts (24–27, 29) or intervention studies of highly selected samples (22, 23). It may be expected that participants in the Danish National Birth Cohort are healthier, on average, than the general pregnant population, but the overall rates of preterm birth were rather similar among participants (5.5 percent over the years 1997–2003) and the general population (5.2 in 1995 and 6.3 percent in 2004) (15).

The specific time of reported exercise was not very precise in this study, and it is possible that some women registered as nonexercisers or with low levels of exercise had been exercising at higher levels earlier in pregnancy. If participants had stopped because of contractions or other symptoms of threatening preterm birth, we could see ‘‘reverse causation’’ leading to overestimation of a possible beneficial effect. On the other hand, excluding women with symptoms of threatening preterm birth did not change the results much.

In this study, we analyzed amount of exercise, type of exercise, and MET scores. One limitation in using MET scores is the risk of adding random variation by applying an assumed intensity to the included activities. Furthermore, if mechanical incidents like bumps and jumps account for an association, this will not necessarily show up in MET analyses.

Information about physical activity was self-reported. Although objective measures would have been preferred, this was not feasible in a study of this size. Because of the prospective nature of the data collection, misclassification of physical activity is most likely to have been nondifferential and would most likely have biased the association towards the null. The questions on exercise posed to participants in the Danish National Birth Cohort were similar to those used in other studies of pregnant women (12, 29, 35) and were

TABLE 4. Crude and adjusted hazard ratios for preterm birth according to metabolic equivalent-hours of physical exercise per week during pregnancy ($n = 87,232$), Danish National Birth Cohort, 1996–2002

Exercise (MET*-hours/week)	No. of pregnancies	Crude HR*	Adjusted HR†	95% CI*	*p* for trend	*p* for trend‡
0	55,412	1	1		<0.0001	0.1104
>0–≤5	6,393	0.80	0.77	0.68, 0.87		
>5–≤10	10,009	0.85	0.82	0.74, 0.91		
>10–≤15	5,668	0.88	0.83	0.71, 0.96		
>15	9,750	0.92	0.88	0.78, 1.00		

* MET, metabolic equivalent; HR, hazard ratio; CI, confidence interval.

† Adjusted for age, gravidity, parity, previous spontaneous abortions, uterine fibroids/malformations/cone biopsy, subfecundity, coffee consumption, alcohol consumption, smoking, body mass index, job status, working hours, working position, and job strain.

‡ When zero exposure was separated from the dose-response.

TABLE 5. Crude and adjusted hazard ratios for preterm birth according to possible changes in physical activity level during pregnancy ($n = 67{,}861$), Danish National Birth Cohort, 1996–2002

Exercise (yes/no) (+/−)		No. of pregnancies	Crude HR*	Adjusted HR†	95% CI*
<22 weeks‡	≥22 weeks§				
−	−	34,767	1	1	
+	−	12,233	1.08	1.06	0.96, 1.18
−	+	8,128	0.89	0.83	0.73, 0.95
+	+	12,733	0.86	0.81	0.72, 0.91

* HR, hazard ratio; CI, confidence interval.

† Adjusted for age, gravidity, parity, previous spontaneous abortions, uterine fibroids/malformations/cone biopsy, subfecundity, coffee consumption, alcohol consumption, smoking, body mass index, job status, working hours, working position, and job strain.

‡ Data from the first pregnancy interview, carried out before 22 completed weeks of gestation.

§ Data from the second pregnancy interview, carried out between 22 and 36 completed weeks of gestation, inclusive.

modified from the Minnesota Leisure-Time Physical Activity Questionnaire (36, 37).

This study concentrated on leisure-time activities. Hence, it was not our intention to cover physical activity as a whole in an attempt to explain the physiologic mechanisms behind a possible association with preterm birth. Our aim was to contribute to the discussion regarding whether it is safe to continue or commence leisure-time physical exercise during pregnancy. To account for a possible work-related effect, different measures of strain at work were included as covariates. Unfortunately, information on prepregnancy physical activity was not part of the collected data.

Since preterm birth is a strong predictor of subsequent preterm birth, a previous preterm birth may lead to behavioral modifications, which cannot be well controlled. However, in analyses including only primigravidae or primiparae, the estimates found for the whole cohort were not altered.

We did not separate preterm births into spontaneous births and medically induced births. Savitz et al. (38) concluded that the overall risk profiles of pregnancies resulting in the different types of preterm birth are often similar, which justifies aggregation of the two types of preterm birth. When the preterm births were subclassified according to severity, the protective association in the overall analyses disappeared among very preterm and extremely preterm births, but because of limited power, we cannot conclude that there is a different association with physical exercise across gestational ages at birth.

The observed associations need not reflect causal effects but could be results of uncontrolled confounding or reverse causation, even though subanalyses did not indicate the latter. The results suggest a protective effect of exercise or perhaps that pregnancies ending in preterm delivery follow an early onset of symptoms that may interfere with the capacity to be physically active. A possible mechanism behind the findings is that increased insulin sensitivity caused by exercise may decrease the inflammatory response that is a suggested risk factor for preterm birth (39).

The results of this study do not suggest any negative effects of physical exercise on the risk of preterm birth; rather, they suggest a minor protective association. Should our findings reflect causal links, they would be of positive public health importance, since very few evidence-based strategies for prevention of preterm birth exist, and prescribing long-term rest to pregnant women may carry unwanted risks.

ACKNOWLEDGMENTS

The Danish National Research Foundation established the Danish Epidemiology Science Centre, which initiated and created the Danish National Birth Cohort. Furthermore, the cohort was established with the support of a major grant from this foundation. Additional support for the Danish National Birth Cohort is obtained from the Pharmacy Foundation, the Egmont Foundation, the March of Dimes Birth Defects Foundation, and the Augustinus Foundation. This specific study was supported by grants from the Danish Medical Research Council, the Augustinus Foundation, the Danish Midwifery Association, and the Danish Graduate School in Public Health Science.

The authors are grateful to Katrine Strandberg Larsen for insightful advice regarding use of data from the Danish National Birth Cohort.

The Scientific Ethical Committee in Denmark approved the data collection in the Danish National Birth Cohort research database. Approval to use data from the birth cohort for the present study on preterm birth was obtained. The Danish Data Protection Agency approved the storage, handling, and linkage of the data.

Conflict of interest: none declared.

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PAPER III

EXERCISE AND FOETAL GROWTH

BASIC SCIENCE: OBSTETRICS

Physical exercise during pregnancy and fetal growth measures: a study withinthe Danish National Birth Cohort

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OBJECTIVE: The objective of the study was to examine the association between physical exercise during pregnancy and fetal growth measures.

STUDY DESIGN: Data on 79,692 liveborn singletons from the Danish National Birth Cohort were collected between 1996 and 2002. Mean differences in birth weight, length, ponderal index, head and abdominal circumference, and placental weight and hazard ratios of small- and large-for-gestational-age babies were calculated.

RESULTS: Our data indicated smaller babies in exercising women compared with nonexercisers, but the differences were small, and only a few were statistically significant. Exercising women had a slightly decreased risk of having a child small for gestational age (hazard ratio, 0.87; 95% confidence interval 0.83–0.92) and large for gestational age (hazard ratio, 0.93; 95% confidence interval 0.89–0.98).

CONCLUSION: The findings do not indicate sizable effects on fetal growth measures related to exercise apart from a modest decreased risk of small- and large-for-gestational-age. These findings do not speak against advising pregnant women to be physically active during pregnancy.

Key words: birth cohort, birthweight, fetal growth, physical activity

Cite this article as: Juhl M, Olsen J, Andersen PK, et al. Physical exercise during pregnancy and fetal growth measures: a study within the Danish National Birth Cohort. Am J Obstet Gynecol 2009;201:xx-xx.

In line with an increasing focus on physical activity as a preventive action against obesity and obesity-related diseases, national guidelines in many countries now recommend a substantial level of physical activity during pregnancy.[1-4] Hence, in Denmark, a minimum of 30 minutes of moderate physical activity per day is recommended for healthy pregnant women.[2] Exercise in pregnancy causes an acute reduction in oxygen and nutrient delivery to the placental site.[5-7] On the other hand, maternal blood volume, cardiac output, and placental function has been found to be increased in exercising women,[8-13] and the question remains whether these mechanisms adequately provide what the fetus needs of oxygen and nutrients.[8,11,12,14,16]

Size at birth is a function of time spent in utero and the fetal growth rate. We already studied the association between physical exercise and preterm birth using data from the Danish National Birth Cohort and found a slightly decreased risk among exercising women compared with nonexercisers.[17] The present study addresses fetal growth, which is an indicator of both fetal health and health later in life.[18-23]

With a few exceptions existing studies on exercise and fetal growth have been small and carried out on highly selected groups of women.[10,11,24-34] Two meta-analyses reported either no or only minimal differences in mean birthweight in offspring of exercising mothers compared with those of nonexercisers, and so did 3 observational studies of varying size (n = 148-7101),[35,36] although lower birthweights were observed with vigorous exercise in late pregnancy.[35] A Cochrane review on 11 randomized trials reported that existing data were not sufficient to "infer important risks or benefits for the mother or infant."[37]

Most studies have addressed birthweight or small for gestational age (SGA), and a few have included birth

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Presented at the 18th World Congress of Epidemiology, Porto Alegre, Brazil, Sept. 20-24, 2008, and the National Day of Midwifery Research, Copenhagen, Denmark, Oct. 3, 2008.

Received Jan. 28, 2009; revised May 18, 2009; accepted July 14, 2009.

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The Danish National Research Foundation established the Danish Epidemiology Science Centre, which initiated and created the Danish National Birth Cohort. The cohort is a result of a major Grant from this foundation. Additional support for the Danish National Birth Cohort is obtained from the Pharmacy Foundation, the Egmont Foundation, the March of Dimes Birth Defects Foundation, and the Augustinus Foundation. This specific study was supported by Grants from the Danish Medical Research Council, the Augustinus Foundation, the Danish Midwifery Association, the Danish Graduate School in Public Health Sciences, and the Danish National Board of Health. None of the funders were involved in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the article.

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length or placental weight. It is recognized that fetal growth may be impaired, even if birthweight is within normal limits, and more sensitive markers of growth may therefore be needed.[38,39] Small abdominal circumference is associated with liver size and possibly high serum cholesterol later in life,[40] and small head circumference correlates with brain size[41] and has been associated with lower IQ,[42] high blood pressure,[40] and higher risk of cardiovascular disease[22,43] as well as impaired glucose tolerance.[44]

The aim of this study was to examine the association between physical exercise during pregnancy and fetal growth measures: birthweight, length, ponderal index, abdominal and head circumference, and placental weight.

Materials and Methods

The Danish National Birth Cohort Study (DNBC) is a cohort of a little more than 100,000 pregnancies with written informed consents from the mothers. The initial data collection included telephone interviews, questionnaires, and blood samples and took place between 1996 and 2002.

For this study, we used data from 2 pregnancy interviews carried out at approximately 16 and 31 completed weeks of gestation. More details about the cohort are presented elsewhere.[45] Some of the women provided data on more than 1 pregnancy, and these data were used to do a study among siblings using differences in physical exercise between the pregnancies as the exposure.

The Scientific Ethical Committee has approved the data collection in the Danish National Birth Cohort research database. Approval to use data from the birth cohort for the present study on preterm birth has been obtained. The Danish Data Protection Agency has approved storage, handling, and linkage of data. All of the participants signed an informed consent form before being included in the study.

Study population

A total of 100,418 pregnancies were recruited to the DNBC, and only pregnancies in which we had data from the first pregnancy interview were included (n = 90,165). Reasons for not having a first interview would be having an induced or spontaneous abortion before the interview was done or that we did not obtain contact with the woman for the first interview.

The following exclusions were made: molar or ectopic pregnancies (n = 18), miscarriages (n = 892), early induced abortions (n = 4), late induced abortions (n = 173), stillborn singletons (n = 285), multiple pregnancies (n = 1965), mother emigrated (n = 36), deceased in pregnancy (n = 1), and unknown outcome (n = 8), which resulted in 86,783 pregnancies live born singletons. Furthermore, 503 were excluded because of missing or implausible birthweight according to a method described by Alexander et al.[46]

A number of 1004 pregnancies were excluded because of self-reported diabetes in or before pregnancy. Finally, only the first enrolled child of each mother was included to avoid nonindependent observations (5584 pregnancies excluded), except in the sibling study. Thus, the final data set comprised 79,692 liveborn infants.

Exposure measures

In the first and second pregnancy interview, the women were asked the following questions: (1) "Now that you are pregnant, do you engage in any kind of exercise?" In the case of a positive answer, the following questions were posed: (2) "What kind of exercise do you engage in?"; (3) "How many times a week do you engage in . . . (answer in question 2)?"; (4) "How many minutes a time do you engage in . . . (answer in question 2)?"; and (5) "Do you engage in other types of exercise?" A positive answer to the last question released a loop with the aforementioned questions until a negative response was given. All questionnaires are available in English at www.bsmb.dk.

For each of the 2 pregnancy interviews, the total number of minutes spent on exercise per week was categorized into hours per week. For additional analyses, the active women were assigned to 1 of the following types of activities defined as the type of activity performed more than 50% of the total activity time: swimming, low-impact activities (aerobic/gymnastics for pregnant women, aerobic/gymnastics, dance, walking/hiking, yoga), high-impact activities (jogging, ball games, racket sports), workout/fitness training, bicycling, horseback riding, and a nonclassifiable category.

Data on gestational age at birth (days), mother's age at conception (years), and sex of the offspring were taken from the hospital birth record obtained from the National Discharge Registry. The other covariates came from the first pregnancy interview and were prepregnant body mass index (kilograms per square meter), occupational status, parity, and smoking, coded as presented in Table 1.

Outcome measures

From the National Discharge Registry, we had data on birthweight (grams) length (centimeters), ponderal index ([weight in grams*100]/[length in cubic centimeters]),[47] abdominal and head circumference (centimeters), and placental weight (grams). For practical reasons we use the overall term fetal growth measures for the endpoints in the study, acknowledging that these measures are no more than proxies or indicators of fetal growth.

SGA and large for gestational age (LGA) were calculated as the 10th percentile or below and as the 90th percentile or above of the sex- and gestation-specific birthweight within the present study population. Analyses were repeated using an intrauterine fetal weight standard.[48]

Statistical analysis

We examined the association between amount of exercise in pregnancy and birthweight, length, ponderal index, abdominal and head circumference, and placental weight, respectively, by fitting linear regression models. Both exercise data from the first and the second pregnancy interview were analyzed, but only data from the first interview are presented in the tables. Likelihood ratio tests for interaction between exercise and parity, gender of the offspring, and smoking were made.

TABLE 1

Maternal characteristics according to leisure time physical activity in early/mid pregnancy, The Danish National Birth Cohort, 1996-2002, n = 79,692

Variable	%	Amount of exercise (h/wk) 0	> 0 –≤ 1	> 1 –≤ 2	> 2 –≤ 3	> 3 –≤ 4	> 4 –≤ 5	>5	Mean birthweight, g	SGA	LGA
n	–	49929	10704	8156	4447	2551	1494	2236	–	7797	8268
Age at conception, y											
<25	13	14	13	12	13	14	13	16	3508	16	11
25 to <35	75	74	78	78	76	76	76	73	3586	72	76
35 to <40	10	11	8.8	9.3	9.9	9.3	9.5	9.4	3585	9.9	12
40+	1	1.1	0.7	0.8	1.1	1.1	1.4	1.5	3552	1.3	1.3
Parity											
Nulliparous	50	44	58	61	61	65	62	67	3485	65	25
Pluriparous	50	56	42	39	39	35	38	33	3668	35	65
Sociooccupational status											
Higher grade professionals	8.9	8.1	10	10	10	10	10	9.1	3609	7.8	9.2
Lower grade professionals	27	25	30	30	32	32	32	27	3609	24	29
Skilled workers	19	19	20	18	17	15	15	13	3569	19	18
Unskilled workers	26	28	22	20	19	18	20	25	3543	29	25
Students	14	12	14	16	18	19	18	19	3567	14	13
Out of work[a]	5.1	5.8	3.5	3.8	3.8	4.2	4.1	5.5	3557	5.3	5.6
Nonclassifiable	1	1	0.9	0.9	0.8	1.2	0.7	0.8	3519	1.1	0.8
Prepregnancy body mass index											
<18.5	4.5	4.9	4	3.4	3.7	4.2	3.7	5.2	3350	8.4	1.6
18.5 to <25	68	67	70	71	72	74	75	73	3556	70	60
25 to <30	19	20	19	18	18	16	16	16	3651	16	25
30+	8	8.7	7.6	7	6.5	6	4.8	5.8	3678	6.5	14
Smoking in early/midpregnancy, cig/d											
0	74	70	80	79	78	78	81	76	3617	60	81
1 to <10	15	15	13	13	14	13	13	15	3490	20	11
10+	12	14	7.7	7.6	8	8.6	6.6	8.8	3421	20	8

Missing values for amount of exercise: 175, for parity: 36, for pre-pregnancy body mass index: 1342, and for smoking: 212.
CI, confidence interval; *LGA*, large for gestational age; *SGA*, small for gestational age.

[a] More than 3 months prior to interview.

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In addition, a sibling analysis was made to examine whether changes in exercise between 2 pregnancies correlated with birthweight measures. In the case of more than 2 liveborn children in the cohort (n = 63), only the first 2 pregnancies were included. Hence, 5521 pairs of siblings were studied.

Five categories of change in exercise between pregnancies were generated: from much to nothing (–2), from much to little or from little to nothing (–1), no change (0), from nothing to little or from little to much (+1), and from nothing to much (+2). Little exercise was defined as less than 90 min/wk and much exercise as 90 minutes or more. Adjustment for time-varying variables was made. Those were the same as in the main analyses except for occupational status. Covariates were modeled as in main analyses except that each covariate was included in the model with values from both the first and the second pregnancy.

Finally, we estimated the hazard rate of SGA and LGA in the offspring as a function of gestational days by means of a Cox regression model. Using a model for the hazard rate (rather than, in general, logistic regression) has a number of advantages. First, gestational age is directly incorporated in the model; second, it enables us to take the different times of entry into follow-up into account; and lastly, it makes it possible to update exposure data in cases in which a second interview is available. Follow-up ended at birth, emigration, or maternal death. An event was defined as delivery of a liveborn SGA or LGA baby, respectively. If a second interview was available, exercise data were updated by the time of the second interview.

Analyses on fetal growth measures and SGA/LGA were further carried out on a population without possible clinical contraindications for exercise. In these analyses the following exclusions were made: not having a second pregnancy interview (because a number of pregnancy complications were reported here), metabolic disorders, hypertensive disorders (including gestational hypertension and preeclampsia) or other serious illnesses, vaginal bleeding, painful contractions, loss of amniotic fluid, and cervical incompetence or dilatation.

Gestational age at birth in days was modeled as quadratic splines in all linear regression models. To avoid too much weight on extreme values, maternal age and prepregnant body mass index were modeled as restricted quadratic splines.

An alternative to this way of adjustment for gestational age would be to analyze gestational age–specific z-scores for the fetal growth measures. However, we believe that the interpretation of regression coefficients is more direct when they are expressed in grams, centimeters, etc rather than in SDs. The remaining adjustment variables were included as categorical variables and categorized as displayed in Table 1. The decision on which factors to adjust for was made a priori. All analyses were carried out using SAS statistical software (version 9; SAS Institute, Cary, NC).

RESULTS

Table 1 shows some characteristics of the women according to exercise, mean birthweight, SGA, and LGA. In 37% of 79,692 pregnancies, the mother engaged in leisure time physical activity at the time of the first pregnancy interview. This proportion decreased to 31% at the time of the second pregnancy interview. Compared with active women, nonexercisers had lower sociooccupational status; were more often parous, overweight, or obese; and were more likely to smoke 10 cigarettes per day or more. Compared with other physically active women, heavy exercisers (>5 h/wk) were more likely to be in the outer age groups, nullipara, unskilled workers, students or out of work, and underweight. Women who had given birth before, women with higher sociooccupational status or higher body mass index, and nonsmoking women tended to have offspring with larger birthweights. SGA in the offspring was more common among mothers who were young, nulliparous, or smokers or with low body mass.

Table 2 presents mean differences in fetal growth measures among women engaged in exercise during early/midpregnancy compared with nonexercisers. In the analysis only adjusted for gestational age, birthweight seemed to decrease with increasing amount of exercise, but this association almost disappeared after controlling for potential confounding factors.

Most estimates in the analyses of the 6 different fetal growth measures showed a tendency toward decreasing size in offspring of women who exercised, but the differences were small. There were statistically significant trend tests for abdominal and head circumference. In the birthweight analysis, smoking and parity were the 2 covariates that confounded the association the most: smoking in a negative and parity in a positive direction, whereas inclusion of prepregnant body mass index, age, occupational status, or sex of offspring had only minor influence on the estimates.

We also fitted the linear regression model to exercise data from the second pregnancy interview to the linear regression model and estimated mean differences according to amount of exercise. We found statistically significant trend tests for birthweight, abdominal circumference, and head circumference, indicating smaller size with increasing amount of exercise, but as seen for data from the first interview, the differences were small and with no consistent differences over exercise categories (data not shown).

When we tested for interaction sex of the offspring and parity did not significantly modify the association between exercise and fetal growth measures. However, including an interaction term with smoking led to statistically significant *P* values between physical exercise and birthweight ($P < .001$), birth length ($P = .0005$), abdominal circumference ($P = .0007$), and head circumference ($P < .0001$).

Differences in birthweight according to smoking status are presented in Table 3. Among nonsmokers, exercise was associated with smaller babies compared with no exercise, whereas smokers who exercised had on average larger babies than smokers who did not exercise. Among moderately exercising women, the association was stronger among women who smoked 10 cigarettes per day or more than among those smoking less. For more extensive amount of exercise, this tendency was not evident and estimates not statistically significant.

Table 4 shows mean birthweight differences in siblings according to changes in exercise between the pregnancies in a sample of women with at least 2 liveborn children in the cohort. Women who changed exercise level between pregnancies had on average larger babies than women who exercised at the same level

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TABLE 2

Mean differences in fetal growth measures according to leisure time physical activity during pregnancy, The Danish National Birth Cohort, 1996-2002, n = 79,692

	Birthweight, g (mean = 3575)				Birth length, cm (mean = 52.2)				Ponderal index, g*100/cm³ (mean = 2.53)				Abdominal circumference, cm (mean = 33.5)				Head circumference (cm) (mean = 35.3)				Placental weight (g) (mean = 661)			
Exercise (h/wk)	Crude[a]	Adjusted[b]	95% CI	P value for trend	Crude[a]	Adjusted[b]	95% CI	P value for trend	Crude[a]	Adjusted[b]	95% CI	P value for trend	Crude[a]	Adjusted[b]	95% CI	P value for trend	Crude[a]	Adjusted[b]	95% CI	P value for trend	Crude[a]	Adjusted[b]	95% CI	P value for trend
0	0	0	–	0.1276	0	0	–	0.1968	0	0	–		0	0	–		0	0	–	< .0001	0	0	–	0.0604
>0–≤1	−6	1	−8 to 10		0.03	0.01	−0.03 to 0.06		−0.01	−0.009	−0.007 to 0.06	0.7429	−0.02	0.02	−0.02 to 0.07	0.0460	−0.02	−0.004	−0.04 to 0.03		−7	−3	−6 to 0	
>1–≤2	−6	5	−6 to 15		0.03	0.02	−0.03 to 0.07		−0.04	−0.04	−0.1 to 0.04		−0.04	0.02	−0.03 to 0.07		−0.04	−0.02	−0.06 to 0.02		−4	1	−3 to 4	
>2–≤3	−14	0	−14 to 13		−0.007	−0.009	−0.07 to 0.06		−0.04	−0.03	−0.1 to 0.06		−0.11	−0.03	−0.09 to 0.04		−0.08	−0.05	−0.1 to −0.003		−7	0	−5 to 4	
>3–≤4	−30	−8	−26 to 9		−0.04	−0.01	−0.09 to 0.07		−0.05	−0.04	−0.2 to 0.08		−0.18	−0.07	−0.2 to 0.02		−0.11	−0.06	−0.1 to 0.0005		−14	−6	−12 to 0	
>4–≤5	−24	−6	−27 to 16		−0.01	−0.01	−0.1 to 0.1		−0.05	−0.05	−0.2 to 0.1		−0.19	−0.1	−0.2 to 0.01		−0.12	−0.08	−0.2 to −0.002		−13	−6	−13 to 2	
>5	−46	−11	−30 to 7		−0.14	−0.07	−0.2 to 0.02		−0.05	−0.03	−0.2 to 0.1		−0.21	−0.1	−0.1 to 0.04		−0.21	−0.1	−0.2 to −0.06		−13	−4	−10 to 2	

Missing values for length: 591, for ponderal index: 591, for abdominal circumeference: 3619, for head circumference: 1871, and for placental weight: 2707. Missing values for amount of exercise: 175, for parity: 36, for prepregnancy body mass index: 1342, and for smoking: 212.

CI, confidence interval.

[a] Adjusted for gestational age; [b] Adjusted for gestational age, sex, maternal age, pre-pregnant body mass index, occupational status, parity, and smoking.

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in the 2 pregnancies, regardless of the direction of a change. No dose-response relation was seen.

Table 5 shows adjusted hazard ratios for SGA and LGA according to exercise when a 10% cut point within the DNBC was used. Exercise was associated with a slightly decreased risk of both SGA and LGA compared with no exercise. There was a dose-response relation with LGA, indicating a decreasing risk with increasing amount of exercise. When using another standard for SGA based on estimated fetal weights,[48] as opposed to weight at birth, we saw the same pattern; only the overall odds ratio of exercise compared with no exercise was slightly lower (0.80; 95% confidence interval, 0.72–0.88).

In a subanalysis we examined the association between the specific type of exercise and birthweight to take the intensity of performed exercise into account. The largest decrease in birthweight was seen among women engaged in high-impact activities and horseback riding in late pregnancy, but no statistically significant estimates were found.

COMMENT

Overall, this study did not indicate a strong negative effect of leisure-time physical exercise during pregnancy on fetal growth measures recorded at birth. There was a tendency toward smaller size of offspring with exercise and some of the trend tests performed were statistically significant, but the differences are probably too small to cause concern. The results may indicate that the offspring of smoking mothers benefit more from exercise than nonsmokers, although this finding need to be supported by other data. Finally, a slightly decreased risk of both SGA and LGA was seen in offspring of exercising women compared with nonexercisers.

Strengths of the study included the use of more measures for fetal growth than most previous studies, which enabled us to examine possible effects on organ growth in the offspring. We used a large population-based pregnancy cohort with prospectively collected exposure data. The presence of women who par-

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TABLE 3
Adjusted mean differences in birthweight (g) according to leisure time physical activity and smoking during pregnancy, The Danish National Birth Cohort, 1996-2002, n = 79,692

	Smoking in early/midpregnancy, cig/d					
	0 (n = 58,435)		1 −< 10 (n = 11,627)		10+ (n = 9418)	
Exercise (h/wk)	Adjusted[a]	95% CI	Adjusted[a]	95% CI	Adjusted[a]	95% CI
0	0	–	0	–	0	–
>0−≤1	−11	−22 to −1	34	9–59	51	19–82
>1−≤2	−9	−21 to 2	33	5–60	79	43–115
>2−≤3	−14	−30 to 1	15	−21 to 51	92	45–139
>3−≤4	−23	−43 to −3	45	−3 to 94	25	−34 to 84
>4−≤5	−18	−43 to 7	36	−27 to 99	25	−62 to 111
>5	−23	−44 to −1	6	−41 to 54	45	−17 to 107

Missing values for amount of exercise: 175, for parity: 36, for pre-pregnancy body mass index: 1342, and for smoking: 212.
CI, confidence interval.
[a] Adjusted for gestational age, sex, maternal age, prepregnant body mass index, occupational status, parity, and smoking.
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ticipated with more than 1 pregnancy made a sibling analysis possible, in which time-stable between-subject confounding variables are partly controlled for such as parental genetic factors (except when the father is not the same). The sibling-pair analysis showed that both women who exercised more and women who exercised less in a subsequent pregnancy tended to have babies with higher birthweights than those who did not change exercise level.

In this study we neither adjusted for gestational weight gain nor tested for interaction between exercise and gestational weight gain because of 2 methodological issues. First, gestational weight gain is a function of some of the outcomes under study (birthweight and placental weight), and gestational weight gain may be an intermediate factor between exercise and size at birth. Our data indicated that exercisers were less likely than nonexercisers to have a high gestational weight gain, which could partly explain the apparent protective effect on LGA.

Confounding by indication, other types of confounding and reverse causation may partly explain the modest associations found. Pregnancy complications such as bleeding in pregnancy, gestational hypertension, uterine contractions, or other indications of impaired intrauterine growth may affect the level and intensity of physical activity. To the extent that these complications lead to restricted fetal growth, they will bias the results toward showing low fetal growth in women who do not exercise. Randomized controlled trials should be immune to confounding by indication, but most trials so far have been too small to detect modest deficits in fetal growth. Repeating the analyses in a population free of clinical indications for not doing exercise did not alter the estimates of any importance.

TABLE 4
Mean differences in birthweight difference among siblings according to exercise level in the 2 pregnancies, The Danish National Birth Cohort, 1996-2002, n = 5521

		Change in birthweight, g (mean 130)			
Change in exercise between the 2 pregnancies	N	Crude[a]	Adjusted[b]	95% CI	*P* value
From much exercise[c] to nothing	806	42	30	−4 to 64	0.0752
From much to little exercise or from little to nothing	859	57	44	11–77	
No change[d]	3180	0	0	–	
From nothing to little or from little to much	392	31	17	−29 to 63	
From nothing to much	255	17	26	−29 to 82	

Missing values in change in exercise: 29.
CI, confidence interval.
[a] Adjusted for gestational age; [b] Adjusted for gestational age, sex, maternal age, prepregnant body mass index, parity, and smoking; [c] ≥90 m/wk; [d] This category included both exercisers and nonexercisers.
Juhl. Physical exercise during pregnancy and fetal growth measures. Am J Obstet Gynecol 2009.

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TABLE 5

HRs of SGA and LGA according to leisure time physical activity, The Danish National Birth Cohort, 1996-2002, n = 79,692

	SGA[a]			LGA[b]		
Exercise	HR[c]	95% CI	*P* value for trend	HR[c]	95% CI	*P* value for trend
No exercise	1	–		1	–	
Exercise	0.88	0.83–0.93		0.93	0.88–0.98	
H/wk						
0	1	–	0.1168	1	–	0.0037
>0–≤1	0.87	0.81–0.93		0.98	0.92–1.05	
>1–≤2	0.83	0.76–0.91		0.90	0.82–0.98	
>2–≤3	1.00	0.89–1.14		0.85	0.74–0.98	
>3–≤5	0.83	0.72–0.95		0.89	0.77–1.04	
>5	1.04	0.87–1.23		0.72	0.57–0.91	

CI, confidence interval; *HR*, hazard ratio; *LGA*, large for gestational age; *SGA*, small for gestational age.

[a] With a 10% cut point of an internal reference in the Danish National Birth Cohort; [b] With a 90% cut point of an internal reference in the Danish National Birth Cohort; [c] Adjusted for maternal age, pre-pregnant body mass index, occupational status, parity, and smoking.

Juhl. Physical exercise during pregnancy and fetal growth measures. Am J Obstet Gynecol 2009.

We estimated both the hazard of being born SGA given exercise and the difference in mean birthweight and other size measures among exercising and nonexercising women. The use of dichotomized outcome measures such as SGA and LGA can be questioned because intrauterine growth retardation can occur at a wide spectrum of birthweights for gestational age.[49] This may partly explain why we at the same time found a slightly reduced risk of SGA and a tendency toward smaller birth size measures when analyzing in a linear regression model.

Self-reported physical exercise may be overreported because physical activity today is considered healthy. However, we believe this kind of information bias to be nondifferential because exposure data were prospectively collected. We do not have adequate data on physical activity at work, and it is possible that this source of exposure reduces our exposure contrast, which may lead to an underestimation of effect size.

Random measurement errors are unavoidable for some of the endpoints used, especially abdominal circumference and placental weight. It seems unlikely, however, that these errors should differ according to exercise and thereby bias the results away from the null.

Our data indicated that women who exercise have fewer risk factors for fetal growth impairment than women who do not exercise. Confounding is therefore expected to produce an underestimation of fetal growth impairment among those who exercise unless the confounders are adjusted for. The results may also indicate that the energy used to perform exercise is probably readily compensated by increase in energy intake, which is expected in countries with no shortage on access to food. Our results need not apply to countries in which this may not be the case or for women with health problems that have an impact on appetite.

These results are in line with most previous research, although it is difficult to compare results because exposure data differ greatly. The largest observational study so far, which included 7101 pregnant women, found no association between heavy work and/or heavy exercise and birthweight, but possible effects related to leisure-time physical activity could not be isolated because exercise and work exposures were combined.[28]

This study does not suggest negative effects of physical exercise in pregnancy on birthweight and other indicators of fetal growth. A modest decreased risk of SGA was observed for physically active women.[15] ■

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PAPER IV

SWIMMING AND REPRODUCTIVE OUTCOMES

Original article

IS SWIMMING DURING PREGNANCY A SAFE EXERCISE?

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Running head:
Swimming in pregnancy and birth outcomes

Acknowledgements and funding:
The Danish National Research Foundation has established the Danish Epidemiology Science Centre that initiated and created the Danish National Birth Cohort. The cohort is furthermore a result of a major grant from this foundation. Additional support for the Danish National Birth Cohort is obtained from the Pharmacy Foundation, the Egmont Foundation, the March of Dimes Birth Defects Foundation, and the Augustinus Foundation. This specific study was supported by grants from the Danish Medical Research Council, the Augustinus Foundation, The Danish Midwifery Association, the Danish Graduate School in Public Health Sciences, and The Danish National Board of Health. None of the funders were involved in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. The authors have no potential conflicts of interest to disclose.

Background Exercise in pregnancy is recommended in many countries, and swimming is by many considered an ideal activity for pregnant women. Disinfection by-products in swimming pool water may, however, be associated with adverse effects on different reproductive outcomes. We examined the association between swimming in pregnancy and pre- and postterm birth, fetal growth measures, small-for-gestational-age, and congenital malformations.

Methods We used self-reported exercise data that were prospectively collected twice during pregnancy on 74,486 singleton pregnancies where the mother had reported swimming, bicycling or no exercise. Recruitment to The Danish National Birth Cohort took place 1996-2002. Using Cox, linear and logistic regression analysis, depending on the outcome, we compared swimmers with physically inactive pregnant women and, in order to separate a possible swimming effect from an effect of exercise, bicyclists were included as an additional comparison group.

Results Risk estimates were similar for swimmers and bicyclists including those who practiced swimming throughout pregnancy and those who practiced swimming more than 1.5 hours per week. Compared with non-exercisers, women who swam in early/mid pregnancy had a slightly reduced risk of giving birth preterm (hazard ratio 0.80, 95% confidence interval 0.72-0.88), or giving birth to a child with congenital malformations (odds ratio= 0.89, 95% confidence interval 0.80-0.98).

Conclusions These data do not indicate that swimming in pool water is associated with adverse reproductive outcomes, such as preterm birth, postterm birth, fetal growth measures, small-for-gestational age, and congenital malformations.

Some disinfection by-products (DBPs) in drinking water may be fetotoxic and thus increase the risk of adverse reproductive outcomes among highly exposed pregnant women. End points such as time to pregnancy,[1] preterm birth,[2] low birth weight or small-for-gestational-age (SGA),[3-14] spontaneous abortions[15-22] or birth defects[3;15;23-30] have been studied, but the empirical evidence for any of these potential hazards is inconclusive and potential biological mechanisms are poorly understood.[10] Chemical disinfection processes in swimming pools result in the formation of DBPs through the reaction of chlorine with organic matter.[31] Swimming pool water contains natural organic matter from the tap water itself but also from bathers' sweat, urine, skin particles, hair, microorganisms, cosmetics, and other personal care products.[32] The specific types and levels of DBPs formed depend on numerous factors, including the type and amount of disinfectant used, characteristics of the swimming pool and pool water, and swimmer hygiene.[31] Exposure to DBPs from swimming pools may occur through ingestion, inhalation, or dermal absorption when swimming.[33-40] For several DBPs, including the most common trihalomethanes, inhalation and dermal absorption contribute more to the total uptake than exposure through ingestion.[41] Only one study has investigated swimming in pools and birth weight and did not find any association.[42] Using data from Denmark, where chlorination of drinking water is rarely used, enhances the possibility of isolating possible effects of swimming pool water as opposed to studies in settings with chlorinated drinking water . Hence, data from The Danish National Birth Cohort (DNBC) provides a favourable opportunity to study potential side effects of swimming during pregnancy. Further, swimming in indoor pools is a recommended, and common, activity during pregnancy.[43;44]

We examined the association between swimming in pregnancy and several birth outcomes (pre- and postterm term birth; fetal growth measures, including birth weight and SGA; and congenital malformations) in a large cohort of pregnant women in Denmark. We compared swimmers and bicyclists, respectively, with physically inactive pregnant women. Bicyclists were included as an additional comparison group in the attempt to separate a possible swimming effect from that of exercise *per se*. The latter was evaluated in previous publications.[43;45;46]

METHODS

Subjects

The DNBC is a nationwide population-based cohort with prospectively collected data from pregnant women and their offspring. The intention was to invite as many eligible women in Denmark as possible in a given time period, and inclusion criteria were 1) living in Denmark 2) not planning an induced abortion, and 3) speaking Danish well enough to participate in four telephone interviews during pregnancy and early motherhood. Recruitment took place between 1996 and 2002 using general practitioners to present the consent form together with written information at the first antenatal visit in early pregnancy. The initial data collection included telephone interviews, questionnaires, and blood samples. Timing of the two pregnancy interviews used in this study scheduled to take place in pregnancy week 12-16 and 30. The median gestational age for the first pregnancy interview was 114 days (10th percentile, 84 days; 90th percentile, 160 days), corresponding to 16.3 completed weeks. For the second interview, the median gestational age was 218 days (10th percentile, 195 days; 90th percentile, 249 days), corresponding to 31.1 completed weeks. About half of the general practitioners agreed to take part in the recruitment process, and we estimate that about 60 percent of the invited women accepted the invitation. More details about the cohort are presented elsewhere.[47]

Study Population(s)

To this study we included all pregnancies with available data from the first pregnancy interview (n=90,165), and that excludes women who had an early induced or spontaneous abortion before the time of the first interview or who could not be contacted by phone for this interview. We excluded 1965 multiple pregnancies, and we only included pregnancies where the mother had reported swimming, bicycling or no exercise. Main analyses were based on swimming data from the first pregnancy interview, and Figure 1 describes the selection of women to this study. Specific exclusions were made for each of the four endpoints studied, and this resulted in minor variations in sample size (Figure 1). In order to be included in analyses of swimming throughout pregnancy, the women should report swimming, bicycling, or no exercise in both interviews. Since many women changed their exercise habits from the first to the second interview, there is a difference of about 25,000 between the two analyses. Altogether 48,781 pregnancies were included in this study..

Data on Swimming

From the first and the second pregnancy interview we used self-reported data on engagement in physical exercise (yes/no), type of exercise, and duration of each exercise session. We generated three exposure categories: 1) any reported swimming, 2) any reported bicycling but no swimming, and 3) no exercise. We present data from early/mid pregnancy and throughout pregnancy. The questionnaires are available at www.bsmb.dk.

All water activities were included in the swimming group, including antenatal water-exercises or baby-swimming with older children, and since our data did not include information on exercise intensity, we expect both the bicycling and the swimming group to include all levels from mild to vigorous training.

Other Variables

From the National Discharge Registry we had mother's age at conception and sex of the offspring. From the first pregnancy interview we used data on pre-pregnancy body mass index, occupational status, gravidity, parity, previous spontaneous abortions, bleeding in early pregnancy, chronic diseases, uterine fibroids/malformations/cone biopsy, subfecundity, smoking, coffee and alcohol consumption, working hours, working position, physically strenuous work and psychosocial jobstrain. The adjustment variables varied between the analyses depending on the endpoint studied and are displayed in footnotes to the tables 2-4. The decision on which factors to adjust for was made *a priori*, based upon existing knowledge on risk factors for a given end point.

Reproductive Endpoints

Data on gestational age at birth (days), birth weight (g), length (cm), ponderal index (calculated as (weight in g*100)/(length in cm^3),[48] head circumference (cm), abdominal circumference (cm), placental weight (g), and congenital malformations were abstracted from the National Discharge Registry. We defined preterm birth as a delivery after 153 gestational days (22 completed weeks) but before 259 days (37 completed weeks) and postterm birth as a delivery at or after 294 gestational days (42 completed weeks). For SGA we used a 10 percent cut point of the sex- and gestation specific birth weight within the DNBC. Subgroups of congenital malformations, as displayed in Table 2 and 3, were defined using ICD10 codes on malformations registered within the first year of life (the 10th revision of International Classification of Diseases). If a child had more than one malformation, the child was included in each subgroup.

Statistical Analysis

We examined reproductive endpoints between swimmers, bicyclists, and non-exercisers. To evaluate the importance of time spent in swimming pools, we also calculated measures of association for two levels of time spent on swimming and bicycling (<90 and 90+ min/week) relative to no exercise. We considered bicyclists a reasonable comparison group to swimmers, because, similar to swimming, bicycling is a non-weight bearing sport, which can be performed at all different levels. Further we compared swimmers with non-exercisers in the attempt to exclude that a possible association between swimming and birth outcomes was explained by physical activity and not swimming.

We estimated hazard ratios for preterm birth and SGA using Cox regression analysis. If a second pregnancy interview was available, exercise data was updated by the time of the second interview. In order to adjust for the different entry times into follow-up, we stratified our models by gestational age at the time of the first and the second interview, respectively. For preterm birth, time at risk started from the day a woman completed the 22nd gestational week or on the day of her first pregnancy interview, whatever came last. Follow up ended at birth or by the time a woman completed gestational week 37, whatever came first. For SGA analyses, the Cox model was set up in the same way, except that time at risk was not restricted as described above. Hence, no time restrictions were applied to the analyses of SGA, whereas entry time into follow up in the preterm birth analyses was 22 gestational weeks, since preterm birth is defined as a delivery between 22 and 37 completed gestational weeks. We calculated mean differences in birth weight, length, ponderal index, head and abdominal circumference, and placental weight by fitting linear regression models. Logistic regression analysis was used to estimate odds ratios for postterm birth, any congenital malformation, and subgroups of malformations.

RESULTS

Table 1 shows the distribution of each examined outcome according to swimming, bicycling and no exercise. In this population, consisting only of women who reported swimming, bicycling or no exercise, 75% did not engage in exercise, 14% had reported swimming, and 11% had reported bicycling (and no swimming). There were fewer preterm births among swimming mothers compared with the other groups. Apart from this, there were only minor differences between swimmers and bicyclists. There were fewer postterm deliveries, more SGA-babies, and a slightly higher occurrence of malformations in the offspring among non-exercising mothers compared with swimmers and bicyclists.

Table 2 shows the association between swimming and bicycling in early/mid pregnancy and pre- and postterm birth, SGA, congenital malformations, and fetal growth measures compared with no exercise. There was a slightly decreased risk of preterm birth and an even minor decreased prevalence of overall congenital malformations among swimmers compared with non-exercisers. No major differences were observed between swimming and bicycling. Risk estimates for respiratory and cleft lip/palate malformations indicated a decreased risk among swimmers compared with non-exercisers, but estimates are based on small numbers with substantial uncertainty. Except for cleft lip/palate malformations, malfomation estimates were similar among swimmers and bicyclists.

In table 3 we used a measure of swimming, bicycling, and no exercise, respectively, reported at both the first and the second pregnancy interview. The results were very similar to those from early/mid pregnancy.

In table 4 the amount of swimming is evaluated. The table shows only minor differences between high and low levels of swimming, and, further, the relation between high levels of swimming and high levels of bicycling reflects the results presented in Table 2.

DISCUSSION

This study does not indicate any adverse effects of swimming, or other water activities, in early/mid pregnancy on pre- and postterm birth, SGA, birth weight and other fetal growth measures, or congenital malformations. Similar reassuring results were found for those who practiced swimming throughout pregnancy and those who reported higher amounts of swimming, i.e. at least 1.5 hour per week. These findings do not rule out that chemicals used in indoor pools are fetotoxic at other exposure levels. Furthermore, although this is a large mother-child cohort, the study has limited power to detect an increased risk for rare outcomes such as specific congenital malformations. Our findings are in line with those of the only previously published study with a specific focus on swimming during pregnancy by Niewenhuijsen et al. indicating no association between swimming and birth weight.[42] We did not observe marked differences in outcomes between swimmers and bicyclists, and the use of a secondary exercise group for comparison (bicyclists) should strengthen our results and further support previous findings. . Our data, however, suggest that physical exercise may be beneficial, or alternatively that the modestly elevated risk for preterm birth and perhaps congenital malformations seen among non-exercisers compared with swimmers could be related to medical reasons for not doing exercise (confounding by the indication for not being physically active). Reverse causation may also explain these differences if an affected fetus impairs maternal health during pregnancy, although this seems unlikely particularly in the early phase of pregnancy. Even though both swimming and bicycling have been found to increase the uteroplacental resistance, and thereby reduce blood flow to the uterus, the flow in the umbilical artery has been found to remain unchanged,[49] which supports the fact that we did not identify substantial birth weight differences in the offspring between the two exercise groups.

Bicycling is a common means of commuting in Denmark, and many of the bicyclists in the study most likely used their bike for commuting as part of a daily routine. Since data on physical activity were both self-reported and did not include information on intensity, we expect the bicycling group to include all levels of intensity. Information on swimming faces a similar problem, since both swimming and all other water activities were included. Subdividing the swimming- and bicycling groups into two levels of weekly time spent on the activity, did not bring about new conclusions. Even though we have considered bicycling a fair comparison with swimming in this paper, there may be arguments against this assumption: Bicycling is being done in a sitting position, which might increase abdominal pressure on the pelvis, bicycling is perhaps more aerobic, since breathing is not as limited as it is during swimming, bicycling uses the lower body which has larger musculature while swimming may use more of the upper body, and swimming may allow for better heat dissipation from the mother's body. We have, however, not been able to identify another exercise group that could more adequately act as a comparison group.

Our study addresses population based experience, and most of the participating women are not expected to be heavily exposed to swimming pool chemicals. There is practically no publicly available information on levels of DBPs in swimming pools in Denmark. Studies on swimming pools in other countries, such as Spain, indicate that levels of trihalomethanes in swimming pools are not higher than those found in drinking water [50].

These findings suggest that the current practice of swimming in pools for pregnant women is safe for the endpoints we studied.

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Figure 1. Flow chart with exclusions and final number of participants for each sub-dataset. The Danish National Birth Cohort. 1996-2002.

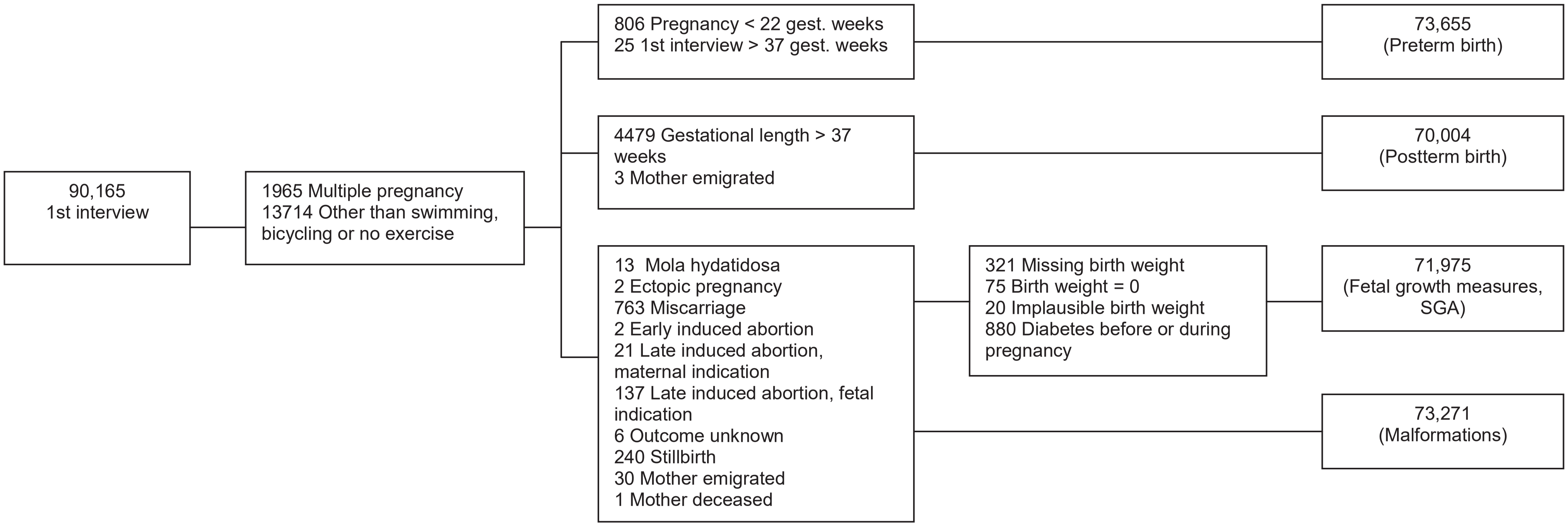

Table 1. The distribution of selected reproductive outcomes according to swimming, bicycling and no exercise in early/mid pregnancy among participants in the Danish National Birth Cohort. 1996-2002. Percentages in brackets.

	Swimming	Bicycling (no swimming)	No exercise	Total
Preterm birth				
All pregnancies	10270	8159	55226	73655
Preterm birth	485 (4.7)	409 (5.0)	2779 (5.0)	
Postterm birth				
All pregnancies	9783	7752	52469	70004
Postterm birth*	946 (9.7)	746 (9.6)	4795 (9.1)	
Small-for-gestational-age				
All pregnancies	10088	7977	53910	71975
Small-for-gestational-age	914 (9.1)	737 (9.2)	5110 (9.5)	
Birth weight				
All pregnancies	10088	7977	53910	71975
Birth weight (means in gram)	3581	3594	3585	
Congenital malformations				
All pregnancies	10215	8115	54941	73271
Malformations, overall	505 (4.9)	403 (5.0)	2832 (5.2)	
Circulatory malformations	108 (1.1)	77 (1.0)	549 (1.0)	
Respiratory malformations	9 (0.1)	9 (0.1)	95 (0.2)	
Cleft lip and cleft palate	13 (0.1)	19 (0.2)	109 (0.2)	

*Percentages calculated among term and postterm births. Preterm births excluded.

Table 2. Adjusted relative and absolute measures of association for selected reproductive outcomes for swimming and bicycling vs. no exercise in early/mid pregnancy. The Danish National Birth Cohort. 1996-2002.

	Swimming		Bicycling		No exercise	
	Measure of association[a]	95% CI	Measure of association[a]	95% CI	(ref)	
Preterm birth (HR)[b]	0.80	0.72, 0.88	0.95	0.83, 1.08	1	
Postterm birth (OR)	0.97	0.90, 1.04	1.02	0.94, 1.11	1	
SGA (HR)[b]	0.97	0.90, 1.04	0.97	0.87, 1.08	1	
Birth weight (g)[c]	7	-3, 16	-1	-12, 9	0	
Length (cm)[c]	0.02	-0.03, 0.06	0	-0.05, 0.04	0	
Ponderal index ((g*100)/cm^3)[c]	0.002	-0.004, 0.008	-0.002	-0.009, 0.004	0	
Head circumference (cm)[c]	-0.03	-0.06, 0.007	-0.04	-0.08, -0.0008	0	
Abdominal circumference (cm)[c]	0.02	-0.02, 0.07	-0.03	-0.08, 0.01	0	
Placental weight (g)[c]	-1	-4, 2	-1	-5, 2	0	
Congenital malformations, any (OR)	0.89	0.80, 0.98	0.94	0.84, 1.04	1	1
Circulatory system (OR)	1.01	0.82, 1.25	0.93	0.73, 1.19	1	
Respiratory system (OR)	0.59	0.29, 1.17	0.61	0.30, 1.27	1	
Cleft lip/palate (OR)	0.63	0.35, 1.13	1.17	0.72, 1.92	1	

[a]Adjustment variables for each outcome:

All outcomes: maternal age, parity, occupational status, and smoking during pregnancy.

Preterm birth: gravidity, previous spontaneous abortions, illnesses overall, abdominal diseases, subfecundity, bleeding early in pregnancy, coffee and alcohol consumption, pre-pregnancy body mass index, working hours, working position, physically strenuous work, psycho-social jobstrain.

Postterm birth: previous spontaneous abortions, bleeding in early pregnancy, sex of the offspring.

SGA: pre-pregnancy body mass index.

Fetal growth: gestational age, pre-pregnancy body mass index, sex of the offspring.

Congenital malformations: alcohol consumption, sex of the offspring.

[b]In the calculation of hazard ratios, exercise data were updated with data from late in pregnancy, if a second pregnancy interview was available.

[c]Mean differences.

CI: confidence interval. HR: hazard ratio. OR: odds ratio. SGA: small-for-gestational-age.

Table 3. Adjusted relative and absolute measures of association for selected reproductive outcomes for swimming and bicycling vs. no exercise throughout pregnancy. The Danish National Birth Cohort. 1996-2002.

	Swimming		Bicycling		No exercise
	Measure of association[a]	95% CI	Measure of association[a]	95% CI	(ref)
Preterm birth (HR)[b]	0.82	0.70, 0.96	0.83	0.63, 1.09	1
Postterm birth (OR)	1.06	0.96, 1.17	1.16	0.99, 1.36	1
SGA (HR)[b]	0.94	0.85, 1.04	1.06	0.91, 1.23	1
Birth weight (g)[c]	5	-8, 19	-21	-42, 0	0
Length (cm)[c]	0.03	-0.03, 0.1	-0.09	-0.2, 0.01	0
Ponderal index ((g*100)/cm^3)[c]	0	-0.009, 0.009	-0.006	-0.02, 0.008	0
Head circumference (cm)[c]	-0.04	-0.09, 0.005	-0.1	-0.2, -0.04	0
Abdominal circumference (cm)[c]	0.02	-0.05, 0.08	-0.2	-0.3, -0.07	0
Placental weight (g)[c]	0	-5, 4	-5	-12, 2	0
Congenital malformations, any (OR)	0.87	0.75, 1.00	0.87	0.69, 1.10	1
Circulatory system (OR)	1.06	0.78, 1.43	1.09	0.68, 1.76	1
Respiratory system (OR)	0.49	0.15, 1.58	1.16	0.36, 3.71	1
Cleft lip/palate (OR)	0.94	0.46, 1.91	0.62	0.15, 2.52	1

[a]Adjustment variables for each outcome:

All outcomes: maternal age, parity, occupational status, and smoking during pregnancy.

Preterm birth: gravidity, previous spontaneous abortions, illnesses overall, abdominal diseases, subfecundity, bleeding early in pregnancy, coffee and alcohol consumption, pre-pregnancy body mass index, working hours, working position, physically strenuous work, psycho-social jobstrain.

Postterm birth: previous spontaneous abortions, bleeding in early pregnancy, sex of the offspring.

SGA: pre-pregnancy body mass index.

Fetal growth: gestational age, pre-pregnancy body mass index, sex of the offspring.

Congenital malformations: alcohol consumption, sex of the offspring.

[b]In the calculation of hazard ratios, exercise data were updated with data from late in pregnancy, if a second pregnancy interview was available.

[c]Mean differences.

CI: confidence interval. HR: hazard ratio. OR: odds ratio. SGA: small-for-gestational-age.

Table 4. Adjusted relative and absolute measures of association for selected reproductive outcomes for different levels of swimming and bicycling vs. no exercise in early/mid pregnancy. The Danish National Birth Cohort. 1996-2002.

	Swimming 90+ min		Swimming <90 min		Bicycling <90 min		Bicycling 90+ min		No exercise
	Measure of association[a]	95% CI	Measure of association[a]	95% CI	Measure of association[a]	95% CI	Measure of association[a]	95% CI	(ref)
Preterm birth (HR)[b]	0.78	0.61, 1.00	0.80	0.72, 0.89	0.99	0.85, 1.15	0.86	0.69, 1.08	1
Postterm birth (OR)	1.02	0.86, 1.22	0.96	0.88, 1.04	1.04	0.95, 1.15	0.99	0.86, 1.14	1
SGA (HR)[b]	0.95	0.80, 1.13	0.92	0.85, 0.99	0.99	0.86, 1.14	1.03	0.86, 1.24	1
Birth weight (g)[c]	20	-3, 42	5	-6, 15	2	-10, 14	-9	-26, 9	0
Congenital malformations, any (OR)	1.02	0.81, 1.27	0.87	0.78, 0.96	0.94	0.83, 1.07	0.93	0.78, 1.12	1

[a]Adjustment variables for each outcome:

All outcomes: maternal age, parity, occupational status, and smoking during pregnancy.

Preterm birth: gravidity, previous spontaneous abortions, illnesses overall, abdominal diseases, subfecundity, bleeding early in pregnancy,

coffee and alcohol consumption, pre-pregnancy body mass index, working hours, working position, physically strenuous work, psycho-social jobstrain.

Postterm birth: previous spontaneous abortions, bleeding in early pregnancy, sex of the offspring.

SGA: pre-pregnancy body mass index.

Fetal growth: gestational age, pre-pregnancy body mass index, sex of the offspring.

Congenital malformations: alcohol consumption, sex of the offspring.

[b]In the calculation of hazard ratios, exercise data were updated with data from late in pregnancy, if a second pregnancy interview was available.

[c]Mean differences.

CI: confidence interval. HR: hazard ratio. OR: odds ratio. SGA: small-for-gestational-age.