Master's Thesis

Master programme in physiotherapy

May 2021

Physical fitness in adults born small for gestational age at term:

a prospective cohort study

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Candidate number: 310
Course code: MAFYS5900

Word count, kappe: 9141
Word count, article draft: 4799

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ACKNOWLEDGEMENTS

The work on this master's thesis is coming to an end. It has been an interesting and enriching process, even though it has been challenging at times.

First and foremost, like would like to thank my supervisor Kari Anne I. Evensen for the guidance through this process. I am very grateful for all the help, patience and constructive feedback. I would also like to thank the research group of NTNU Low Birth Weight Life for the opportunity to work with your well collected data.

I could not have done this without the support of my fiancé, Sindre. Thank you for reading and commenting on my work, for supporting me through stressful times, and for taking care of the last wedding preparations while I was buried in research articles and statistical analyses.

Lastly, I would like to thank my family and friends for support and encouragement during this process, especially my sister Caroline.

Oslo, 16th of May 2021

Maria Matre

SAMMENDRAG

Å bli født «small for gestational age» (SGA) eller «liten for gestasjonsalderen» til termin, øker risikoen for helseutfordringer gjennom livet. Videre har fysisk form vist seg å være nært knyttet til helse og viktig i forebygging av sykdom og død. God fysisk form kan derfor tenkes å være særlig viktig for de som er født SGA til termin. Forskning har funnet en sammenheng mellom fødselsvekt og fysisk form i voksen alder, men det er lite forskning på fysisk form blant voksne født SGA til termin. Målet med denne masteroppgaven var derfor å undersøke om det var en forskjell mellom voksne født SGA til termin og voksne født med normal fødselsvekt til termin.

Denne prospektive kohortstudien inkluderte 107 voksne født til termin i 1986-1988; 46 ble født SGA (22 kvinner, 24 menn) og 61 ble født med normal fødselsvekt (35 kvinner, 26 menn). Muskulær form ble undersøkt med en gripestyrketest og 40-sekunders modifisert push-up test, mens kardiorespiratorisk form ble undersøkt med Åstrand-Ryming step test. To-utvalgs t-test ble brukt for å undersøke forskjell i fysisk form mellom gruppene. Resultatene ble stratifisert for kjønn, og eventuelle forskjeller ble justert for høyde, midje-hofte-ratio og sosioøkonomisk status i en generell lineær modell.

Samlet sett var det ingen forskjell i hverken muskulær eller kardiorespiratorisk form mellom voksne født SGA til termin og voksne født med normal fødselsvekt til termin. Menn i SGA-gruppen hadde imidlertid lavere gripestyrke i begge hender sammenlignet med mennene i kontrollgruppen.

Det at det var få forskjeller i fysisk form mellom gruppene, er lovende resultater. Dette antyder at voksne født SGA ikke er i dårligere fysisk form enn den generelle befolkningen. Det at mennene i SGA-gruppen hadde lavere gripestyrke sammenlignet med mennene i kontrollgruppen, kan imidlertid indikere økt risiko for helseproblemer. Økt fysisk aktivitet med fokus på aktiviteter som øker muskulær form kan derfor være gunstig for denne gruppen.

Nøkkelord: Small for gestational age, fysisk form, gripestyrke, modifisert push-up test, Åstrand-Ryhming step test

ABSTRACT

Being born small for gestational age (SGA) at term increases the risk of adverse health outcomes though life. Furthermore, physical fitness is closely linked to health and is important in the prevention of morbidity and mortality. Adequate physical fitness may therefore be particularly important for those born SGA at term. Moreover, reduced birth weight has been reported to be associated with reduced physical fitness in adulthood, but this is little investigated in adults born SGA at term. The aim of this master thesis was therefore to investigate whether physical fitness differ between term-born adults born SGA and term-born adults with normal birth weight.

This prospective cohort study included 107 adults born at term between 1986-1988; 46 were born SGA (22 women, 24 men) and 61 were born with normal birth weight (35 women, 26 men). Physical fitness was assessed by grip strength, 40-second modified push-up test and Åstrand-Ryhming step test. Differences in muscular and cardiorespiratory fitness between the groups were analysed using independent samples t-test. Differences in physical fitness were adjusted for height, waist-to-hip ratio and socioeconomic status in a general linear model.

The study showed that there overall was no difference in physical fitness between adults born SGA at term and adults born with normal birth weight at term. When stratified by sex, men in the SGA group had significantly lower grip strength in both hands compared with men in the control group.

The fact that there were few differences in physical fitness among the two groups is encouraging results. This may indicate that adults born SGA may have similar physical fitness compared with the population. However, the lower grip strength found in SGA men may indicate increased risk of negative health outcomes. Promotion of physical activities that enhances the muscular fitness may therefore be beneficial to prevent adverse health outcomes.

Keywords: Small for gestational age, physical fitness, grip strength, modified push-up test, Åstrand-Ryhming step test

ABBREVIATIONS

SGA: small for gestational age

GA: gestational age

VO_{2max}: maximal oxygen uptake

WHO: World Health Organization

CI: confidence interval

SD: standard deviation

Table of contents

PART I

1 INTRODUCTION

1.1 Background

Research addressing low birth weight has primarily concerned individuals born preterm. However, a much larger group is born small for gestational age (SGA) at term, defined as a birth weight below the 10^{th} centile (1). In Norway, approximately 5300 infants are born SGA per year (2), many of these born at term (i.e., gestational age ≥37 weeks). Being born SGA at term increases the risk of adverse health outcomes through life, including increased risk of and non-communicable diseases and reduced mental health in adulthood (3-6).

Physical fitness, particularly muscular and cardiorespiratory fitness, is closely linked with health and is important in the prevention of morbidity and mortality (7-9). Adequate physical fitness may therefore be especially important for those born SGA at term. Moreover, reduced birth weight, regardless of gestational age, has been reported to be associated with reduced physical fitness in adulthood (9-11). However, this is little investigated in adults born SGA at term. It is therefore important to gain increased knowledge on this topic, which potentially could have a big impact on public health.

This master's thesis is part of the larger NTNU Low Birth Weight in a Lifetime Perspective (NTNU LBW Life) study, which is a Norwegian prospective cohort study led by Kari Anne I. Evensen. NTNU LBW Life aims to create a better understanding of how low birth weight affects physical and mental health, quality of life, cognitive and motor function, vision and brain structures throughout life. The participants in this study were initially included in 1986-88, and examinations have been carried out through this project from childhood to adolescence and into adult age. This master's thesis presents data from the latest examination of the participants at 32-34 years of age.

1.2 Aim of the master's thesis

The main objective of this master thesis was to investigate whether being born SGA at term affects physical fitness in adulthood.

The research question to be answered in this master's thesis is:

Do muscular and cardiorespiratory fitness differ between adults born SGA (birth weight <10^{th} centile) at term and adults born with normal birth weight (birth weight ≥10^{th} centile) at term?

Furthermore, we wanted to investigate whether potential confounding factors affected any differences between the two groups.

The hypothesis was that adults born SGA would have reduced physical fitness compared with term-born controls born with normal birth weight.

1.3 Clarification of concepts and delimitation of the thesis

1.3.1 Terms to describe SGA individuals

There are many reasons why individuals are born SGA. Some infants are simply genetically small. Others may be growth restricted in utero as a result of conditions in the foetus, placenta, mother or external influences, such as smoking or drug use during pregnancy (12-14). The diagnosis of intrauterine growth restriction requires several ultrasound examinations throughout the pregnancy, which is not always feasible (15). Several other terms are therefore used to capture these individuals. For instance, *low birth weight* is referred to as birth weight <2500 g, regardless of gestational age (1). Another term is *low ponderal index for gestational age*. This term refers to those born with a low ponderal index, often lower than the 10th centile, for their gestational age, measured as the infant's weight for its hight (birth weight/birth length^3) (16). However, the most commonly used term to capture individuals born growth restricted is *small for gestational age*, and birth weight below the 10th centile is the most established definition of SGA (1, 17). This definition was therefore used in this study. It is important to be aware that being born small for gestational age is not necessarily the same as being growth restricted, and that individuals with birth weight above the 10th centile also can be growth restricted (13, 15).

1.3.2 Physical fitness

Physical fitness is defined as a set of attributes that people have or achieve that relates to the ability to perform physical activity (18). Health-related physical fitness refers to the components that are important for our health, including cardiorespiratory endurance, muscular strength and endurance, body composition and flexibility (18), as seen in Figure 1.

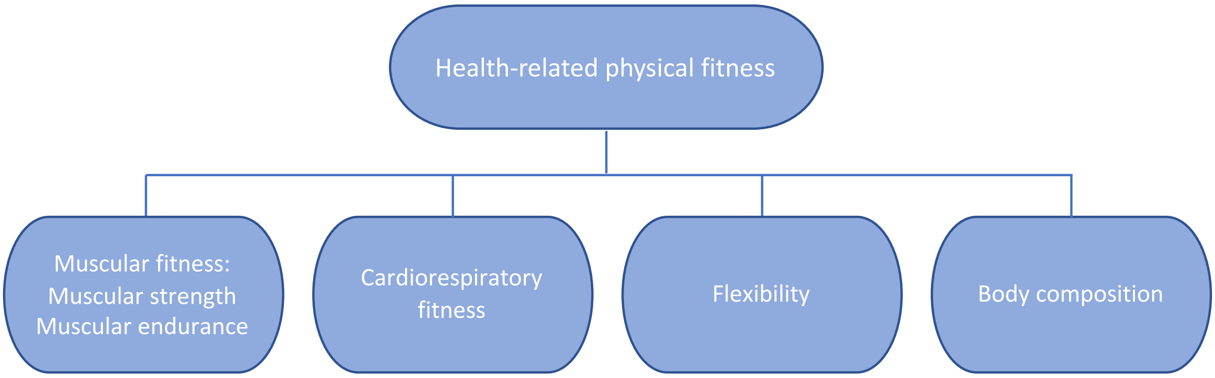

Figure 1. Health related physical fitness, adapted from American College of Sports Medicine (19).

Muscular and cardiorespiratory fitness have been reported to be particularly important when it comes to reducing the risk of developing lifestyle-related diseases and improving the overall health (19), and are therefore the two components addressed in this master's thesis.

Muscular fitness consists of two components: muscular strength and muscular endurance. Muscular strength is "the ability of a muscle group to develop maximal contractile force against a resistance in a single contraction", while muscular endurance is "the ability of a muscle group to execute repeated contractions over a period of time sufficient to cause muscular fatigue or to maintain a specific percentage of the maximum voluntary contraction for a prolonged period of time" (19). Cardiorespiratory fitness refers to "the ability of the circulatory and respiratory systems to supply oxygen during sustained physical activity" (19).

As outcome measures of muscular fitness, I have chosen maximal grip strength and number of push-ups performed in a 40-second modified push-up test. As outcome measure of cardiorespiratory fitness, heart rate after a 4-minute submaximal step test, after 2 minutes of rest and the difference between these measurement points were used. Grip strength was considered the primary outcome, as this is an established predictor of physical function, morbidity and mortality (8), and therefore a highly relevant measurement tool of health-related physical fitness.

1.3.3 ICF as a framework

The International Classification of Functioning, Disability and Health (ICF) is developed by the World health organization (20). ICF uses a biopsychosocial approach and is widely used in physiotherapy. The overall aim is to provide a unified and standard language and framework for the description of health and health-related states.

ICF organises the health information in two main domains: body functions and structures, and activities and participation. Body functions are the physiological functions of the body systems, including psychological functions, while body structures comprise the anatomical parts of the body. The activity domain involves the execution of a task or action, and the participation domain entails involvement in a life situation (20).

The model also comprises contextual factors, which includes environmental and personal factors. Environmental factors are the physical, social and attitudinal environment where people live and conduct their lives. Personal factors are described as the particular background of an individual's life and living, and comprises factors as gender, race, age, life experiences and individual characteristics, amongst others (20). The different components of the classification interact and affect each other, as illustrated in Figure 2.

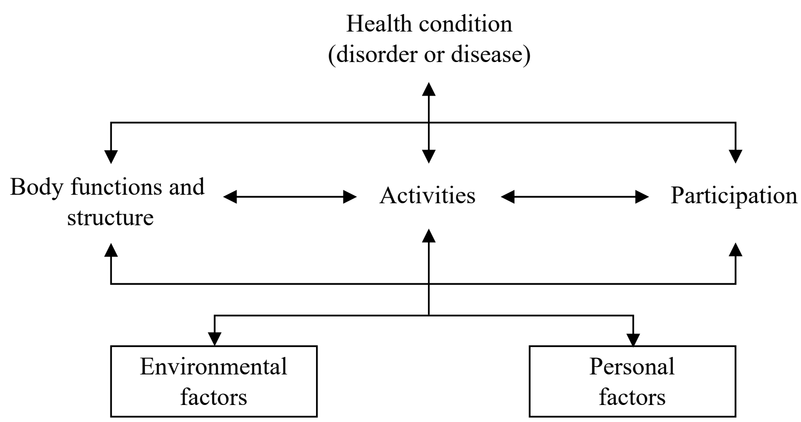

Figure 2. Interactions between the components of ICF

Within this framework, SGA can be considered as the health condition, while physical fitness can be placed in the domain body functions and structures. ICF provides a broader understanding of the topics in this master's thesis.

1.4 Description of the structure of the thesis

This master's thesis is written as a scientific article with a supplement ("kappe") that elaborates on the individual parts of the article. The supplement is part I of the thesis, while the article constitutes part II.

Part I:

The supplement contains a theory chapter, a supplementary description of the methods used and rationale for the choice of outcome measures, a summary of the results, discussion with focus on methodological aspects, and lastly, a discussion of clinical relevance and further research.

Part II:

The article is written for submission to, and according to the guidelines of, the journal Early Human Development (https://www.elsevier.com/journals/early-human-development/0378-3782/guide-for-authors). The article contains complete results with accompanying figures, tables and discussion of the results.

2 THEORY

This chapter provides a more detailed presentation the topics in the master's thesis.

2.1 Individuals born SGA

Being born SGA entails an increased risk of several adverse consequences throughout life. Within the body functions and structure domain, individuals born SGA have an increased risk of diseases such as metabolic syndrome (21) and diabetes type 2 (22). Increased risk of cardiovascular disease has also been found in some studies (23-25), but not in others (26, 27). It is thought that this elevated risk is due to reduced growth in utero that leads to permanent adaptions in structure, metabolism and endocrine functions in the foetus, formulated in the "developmental origins" hypothesis by Barker (4).

Individuals born SGA are reported to have an increased risk of shorter adult height compared with the general population (3, 28, 29). However, a recent systematic review found that >85% of children born SGA at term is likely to achieve catch-up growth, defined as a height velocity above what is common for the age (30). This often happens within the first 2 years of life. Studies also report that adults born SGA have an increased risk of obesity (31) and an altered body composition with a higher percentage of body fat compared with fat-free mass (32, 33). Rapid catch-up growth has been shown to increase this risk (34, 35).

Additionally, within the body functions and structure domain, term-born SGA individuals have a higher occurrence of psychiatric disorders (5), and are reported to have poorer cognitive function (36, 37) and reduced intelligence quotient (IQ) scores throughout development (38-40). However, these results are more subtle compared to individuals born preterm (39).

In the activity and participation domain, some studies have found motor problems to be more prevalent in children and adolescents born SGA at term (41, 42), while others have not found this increased prevalence (43, 44). The physical activity level of term-born SGA individuals has not been examined. However, the self-reported physical activity level is reported to be lower in individuals born preterm with low birth weight, than individuals born to term with normal birth weight (45, 46). Within this domain, term-born SGA individuals are also seen to have poorer school performance and lower educational attainment (6, 47-49), in addition to a lower socioeconomic functioning level (50). Furthermore, Lund et al. (6) found that adults born SGA reported of reduced mental health and well-being when they were 20 years old, and that they had fewer friends than controls. On the other hand, a British study found that term-born SGA individuals were as likely to be employed, married and satisfied with life in early adulthood as normal birth weight adults, regardless of lower academic achievement and professional attainment (49).

2.2 Physical fitness

2.2.1 Determinants and correlates of physical fitness

There are many factors that influence or are associated with physical fitness. Within the body functions and structure domain, meta-analyses have reported heritability estimates for cardiorespiratory fitness to range from 22-57% and handgrip strength to be approximately 50% (51, 52). Muscular and cardiorespiratory fitness is also determined by several physiological factors. Of particular relevance is the fibre type distribution in the muscles, comprising type I, IIa and IIx fibres (53). Type II fibres as stronger than type I fibres and have a higher shortening speed. Type IIa are considered the hybrid of type I and IIx (53). Type I fibres contain more mitochondria and myoglobin molecules and have higher capillary density, which makes them more enduring than type II fibres (53-55).

Additionally, increased waist circumference and waist-to-hip ratio and reduced fat-free mass in relation to fat mass is negatively associated with both muscular and cardiorespiratory fitness (56-59). Body mass index (BMI) shows more conflicting associations with physical fitness, most likely due to the fact that BMI does not differentiate between fat mass and fat-free mass (58, 60). Lastly, height is reported to be correlated with grip strength (57, 61).

In the activity and participation domain, it is well established that that muscular and cardiorespiratory fitness are largely determined by physical activity (62, 63). The type and intensity of the physical activity is however decisive for what effect it has. According to the overload-principle of training, the intensity needs to challenge the body sufficiently to result in increased muscular and cardiorespiratory fitness (63). Research show that physical fitness and a physically active lifestyle develops in childhood and adolescence and that it often stays stable into adulthood (64-66). Within this domain, research have also found motor skills to be related to physical fitness in adulthood (67, 68), and that the feeling of mastering physical activities is important for the motivation of being physically active (69).

Personal factors, such as age and sex, also affect physical fitness. Most studies show a decline in muscular fitness approximately from midlife (57, 70-72). Cardiorespiratory fitness measured by VO_{2max} is observed to be highest in the age group of 20-29 years. From the age of 40 there is a significant decline in cardiorespiratory fitness per decade, with decreases in VO_{2max} of an average of 10% over the next decades (73, 74). Clear gender differences are found in both muscular and cardiorespiratory fitness, where males generally score better in both fitness areas (57, 73). Furthermore, decreased socioeconomic status, especially when considering the educational level, has been found to be associated with reduced physical fitness, which seems to stem from unfavourable health behaviours (70, 75, 76).

2.2.2 Consequences of reduced physical fitness

Reduced muscular and cardiorespiratory fitness can have a major impact on health. In the body functions and structure domain, both increased muscular and cardiorespiratory fitness is associated with decreased risk of multiple diseases, such as metabolic syndrome, cardiovascular disease, diabetes type 2, as well as all-cause death (7, 77-81). Muscular and cardiorespiratory fitness have also shown positive associations with mental health and health-related quality of life (82, 83). Reduced muscular fitness is also associated with increased risk of frailty and sarcopenia at older ages (84).

Within the activity and participation domain, reduced physical fitness is associated with functional limitations, especially at an older age (85-87), but this association is also reported from mid-adulthood (88). Furthermore, physical fitness has also been shown to affect the academic achievements in childhood and adolescence (89, 90), and to increase the capacity to cope with stress at work, increase work performance and decrease absenteeism rates in adulthood (91-94). Physical fitness is, consequently, important not only for the physical and mental health, but also for mastering one’s everyday life.

2.2.3 Assessment of physical fitness

Assessment of physical fitness is strongly connected to the definitions of the various components of physical fitness (19). The two muscular fitness components, strength and endurance, exists at opposite sides of a continuum (19), as shown in Figure 2. The contribution of both strength and endurance become more equal when the requirements of the task move closer to the centre (19). When measuring muscular strength, the goal is to achieve the maximal force capability, whereas when assessing the muscular endurance, the goal is to investigate the ability to perform contractions at a submaximal level for prolonged times. The two components must therefore be tested in different ways.

Figure 2 Muscular fitness continuum. Adapted from ACSM (19)

The most commonly performed static strength measurement is hand grip strength using a handgrip dynamometer, as chosen in this study. It is easy to perform for most people and only requires a hand dynamometer. Muscular endurance can either be assessed by performing a maximal number of contractions in a defined time period, by performing a maximal number of contractions of a set resistance, or by holding a static contraction for a period of time (19). Push-ups tests are commonly used to assess muscular endurance, and has also been applied in this study.

Cardiorespiratory fitness is measured by performing dynamic exercises including large muscle-groups at moderate- to high-intensities for prolonged periods (19). The gold standard measure of cardiorespiratory fitness is a maximal exercise test where expired gases are measured, commonly known as a VO_{2max} test, often performed on a treadmill or cycle ergometer in a laboratory (19). This requires special equipment and skilled personnel, which is not always feasible (95). Tests where the effort level is limited to submaximal exertion, can therefore often be more applicable. During a submaximal test, the participant performs a fixed amount of work per unit of time (19). These tests are often performed on treadmills, cycles, in the field or on bench-steps. The latter is chosen in this study.

To increase the stability of the test scores and minimise the possibility of errors, it is important that the measurement instruments are valid and reliable. Validity refers to the measurement instrument's ability to measure what it intends to measure, while reliability concerns the consistency and lack of error of the measurement (96).

More specific information about the three physical fitness tests conducted in this study will follow in the methods chapter.

2.3 Physical fitness in adults born SGA

Physical fitness in populations of term-born SGA adults has been little investigated, and only a few studies that have included adults born SGA. Evensen et al. (27), Brøns et al. (97) and Jensen et al. (98) investigated the difference in VO_{2max} between young adults (i.e., 18-24 years of age) born SGA at term and adults born with normal birth weight at term. No difference between the groups were found in these studies. Two recent Swedish registry studies found strong associations between birth weight in 18-year-old men born at term and muscular and cardiorespiratory fitness (10, 99). A one standard deviation increase in birth weight was associated with increases of approximately 1.8 kilogram-force in grip strength (10) and 7.9 Wmax, which is the maximal load (measured in watt) that the participants could manage on a cycle ergometer (99).

In the absence of further research, studies comprising similar populations may provide an indication and hypothesis of SGA adults' physical fitness, although these results cannot be transferred directly to adults born SGA.

A small study comprising young adults born at term with a ponderal index below the 10^{th} centile, which is also a proxy for intrauterine growth restriction, found no difference in VO_{2max} compared with adults born with a ponderal index above the 10^{th} centile (16, 100). The mean birth weight did not differ between the groups in this study. However, results showed that women born with low ponderal index had significantly lower grip strength and maximal voluntary strength in their quadriceps femoris compared to the women in the control group (16).

A systematic review and meta-analysis of 13 studies reported of consistent evidence of a positive association between birth weight and muscle strength, mostly measured by grip strength (11). The mean age of the participants was between 9.3 and 67.5. The meta-analysis found a 0.86 kg increase in muscular strength for every kilogram increase in birth weight, after adjustment for age, gender and height. However, this study did not take into consideration the participants' gestational age at birth, which makes it problematic to distinguish if the result is due to factors related to premature birth or low birth weight.

One of the studies included in this meta-analysis, was a study by Ridgway et al. (68) that comprised 31-years-old adults born at or above 36 weeks of gestation. The participants were about the same age as the participants included in this thesis, and are born close to term, which makes it relevant to highlight. This study found a 3 kg increase in grip strength per 1 kg increase in birth weight. The same study also found that higher birth weight predicted higher levels of cardiorespiratory fitness at age 31, measured by estimation of cardiorespiratory fitness from the heart rate after a standardized step test (68).

Te Velde et al. (101) on the other hand, found no significant associations between birth weight and muscular fitness in 36-year-old adults born after 36 weeks of gestation. Muscular fitness was measured with static arm-pull and high jump. They hypothesized that the lack of association was due to the fact that most of the participants were in the normal birth weight range, and that associations may be limited to the more extreme groups of lower birth weights.

Thus, associations between birth weight and physical fitness in adulthood show somewhat inconsistent results. However, as there are multiple studies that have found this association, there is reason to believe that factors operating *in utero* could influence physical fitness throughout the life course. Possible explanations are not fully understood, but physiological alterations and a prioritisation of vital structures at the expense of factors important for muscular and cardiorespiratory fitness might be needed to survive in suboptimal intrauterine environment (4, 102, 103). Studies show that foetal growth restriction might lead to a reduced number of muscle fibres and a different distribution of muscle fibre composition, which may be a disadvantage in terms of muscular fitness in later life (54, 98, 103). In animal research, multiple studies have found that reduced nutrition during pregnancy can lead to increases in type I muscle fibres at the expense of type II fibres (104-106). A human study by Jensen et al. (98) found no differences in type I fibres between adults born SGA and adults born with normal birth weight, but a shift from type IIa to type IIx fibres in the SGA group.

Being born SGA at term has also been associated with reduced fat free mass in adults, which primarily refers to lower percentage of muscle mass (32-34), which could affect the physical fitness in adulthood. Additionally, SGA individuals have in some studies been reported to have an increased risk of motor problems (41, 42), and research have found motor skills to be related to physical fitness (67, 68). Increased motor problems may lead to reduced participation in sports and other physical activities and a more inactive lifestyle, and therefore also reduced physical fitness (67).

3 METHODS

In this chapter, the methods used will be summarised and the rationale for the methodological choices presented. The conduction of the physical fitness assessments, as well as the anthropometric measurements, is described in the article draft (Part II of this thesis).

3.1 Study design

This master's thesis is a prospective cohort study investigating consequences of being born SGA at term. The project has a quantitative design. Prospective cohort studies observe the participants after exposure to a certain factor and follows the participants forward in time in order to investigate the outcome (107); in this case physical fitness in adulthood following being born SGA.

In order to be able to trust the results and generalise the results to a more universal population, the methods and criteria used to include the participants and the methods used to evaluate the outcome measures are important (108). Observational studies are evaluated in terms of both internal and external validity. Internal validity refers to the ability to draw a correct conclusion of causal conditions in a study, i.e., if the observed differences can be attributed to the exposure (108). External validity is the ability to generalize the results to a target population (109). In cohort studies, common potential sources of error that can affect the validity are selections bias, information bias or influence of confounding factors (110).

3.2 Participants

The participants in this study were initially included in 1986-1988 to a multicentre study investigating the aetiology and consequences of intrauterine growth restriction (12, 111). The participants have been followed from birth into adulthood through the NTNU Low Birth Weight Life study. The control group was selected using a sealed envelope method of pregnant women living in the Trondheim area, while the SGA participants were selected from the remaining women who were at risk of giving birth to an SGA baby. At birth, the baby was defined as SGA if they had a birth weight below the 10^{th} centile at each specific gestational week, and the reference standards were sex-specific based on data from the Norwegian Medical Birth Registry (112). The control group had a birth weight $\geq 10^{th}$ centile. All participants were born at term (GA ≥ 37 weeks). Gestational age was decided from the first day of the mother's last menstruation or with ultrasound (12, 111).

Initially, 104 participants born SGA and 120 control participants were included. In the current study, 79 SGA adults and 23 control adults were invited. Ultimately, 46 adults born SGA and 61 adults from the control group were examined. A flowchart is presented in the article draft (Part II of this thesis).

3.3 Data collection

The data in this master's thesis are derived from the larger study NTNU Low Birth Weight Life. The project group of NTNU Low Birth Weight Life, led by Kari Anne I. Evensen, started the data collection in September 2019 and was supposed to complete the data collection in June 2020. Because of the COVID-19 pandemic, however, this was completed in October 2020. Testing was conducted at NTNU/St. Olavs Hospital. The participants took part in a larger ongoing data collection and underwent a selection of tests and examination throughout the testing day. The examinations were carried out in the same order for all the participants and entailed very low risk for injury or adverse events. The participants were offered a compensation of NOK 500 in addition to travel expenses.

The study is approved by the Reginal Ethical Committee (REC number 23879). Written informed consent is obtained from all participants. The data is anonymised and stored securely on a remote server at NTNU with a two-step identifier. All analyses were conducted in SPSS in Services for Sensitive Data (TSD).

3.3.1 Outcome measures

The primary outcome measure in this study was grip strength measured by a Jamar dynamometer. The secondary outcome measures were number of push-ups completed in the 40-second modified push-up test and heart rate after Åstrand-Ryhming step test, after 2 minutes of rest and the difference between these heart rate measurements. All participants were examined by three experienced and specially trained examiners who were blinded to birth weight group.

Grip strength

The grip strength assessment measures the maximal isometric strength of hand and forearm muscles. The maximal grip strength (kg) of three attempts was measured in both dominant and non-dominant hand. Grip strength has through several studies shown to be a powerful predictor of both all-cause mortality (8, 113-115) and cause-specific mortality, including mortality from cardiorespiratory disease, respiratory disease and some cancer-types (114-116). Midlife grip strength has also been shown to predict functional limitations at older ages (87). Additionally, grip strength has been reported to be associated with common mental disorders (9) and health-related quality of life (117). Thus, grip strength is a powerful marker of health. There is also some evidence for, though inconsistent, that grip strength can indicate an individual's overall strength (118-120).

The Jamar dynamometer is extensively used in research and is considered by some to be the gold standard measurement instrument (121). A recent systematic review and meta-analysis concluded that grip strength is a reliable and valid procedure among both healthy participants and across clinical populations (122). The Jamar dynamometer has shown high test-retest reliability when using position 2-5 (123), excellent concurrent validity and excellent inter-instrument reliability when compared with Dexter, Royland and Baseline-dynamometers (121, 124).

As normative values for grip strength to some extent varies in different countries, normative values from a Norwegian population should be used to compare results (125). Kjær et al. (57) found maximal grip strength in the 30-39-year-old age group to be 33.8 kg for women and 58.8 kg for men. Andersen et al. (70) reported of a maximal grip strength in the 30-39-year-old age group of 34 kg for women 59 kg for men. Leong et al. (114) studied the prognostic value of grip strength for mortality in adults aged 35-70 from 17 countries of different economic status and found an increased hazard ratio of 1.16 for all-cause mortality and 1.17 for cardiovascular mortality for every 5 kg reduction in grip strength. Kim et al. (115) reported a hazard ratio of 1.08 for all-cause mortality for every 5 kg reduction and found similar associations with cardiovascular mortality as well in a 40–69-year-old population.

40-second modified push-up test

The push-up test measures the muscular strength and endurance capacity of the upper body (126). The test is modified to improve standardisation, as small variations of the position or execution of the push-up can lead to different biomechanical requirements (127). Sufficient upper body muscle strength is necessary for functional independence as the upper body controls the ability to perform everyday activities such as reaching, pulling, pushing and lifting (128).

The 40-second modified push-up test is one of the tests included in the ALPHA-FIT test battery, which is funded by the European Commission and developed for assessing levels of physical activity and fitness in adults aged 18-69 (128). Content and predictive validity of the ALPHA-FIT test was evaluated by studying the associations between health-related fitness and self-rated health in adults of 35-80 years of age (129). They found that lower fitness in modified push-ups was associated with more back pain and poorer perceived back function. They also found that mid- and high fitness in modified push-ups was associated with good perceived health in comparison with the low-fitness category (129). Thus, the modified push-up test has been reported to be a valid test of health-related physical fitness. The 40-second modified push-up test has also shown acceptable inter-rater reliability (ICC 0.88, SEM 2.6) and small test-retest variation, although some learning effect was reported, with a mean of 3 more push-ups on the second measurement day (126, 130).

Normative values of the 40-second modified push-up test has been developed in Norwegian populations (57, 70). Anderssen et al. (70) found that men in the age group 30-39 years completed a mean of 14 push-ups in 40 seconds. Women in this study conducted modified push-ups on their knees, which makes it unsuitable for comparison with this study. In the study by Kjær et al. (57), the average number of push-up were 9.5 (SD+/- 4.4) repetitions for women and 14.3 (SD +/-5.0) repetitions for men in the 30-39-year-old age group.

Åstrand-Ryhming step-test

The Åstrand-Ryhming step test is a four-minute submaximal step-test, which measurers cardiorespiratory fitness (131). Åstrand and Ryhming (131) evaluated the validity of their step test and nomogram and concluded that the step test is an appropriate method of predicting VO_{2max}. They reported a standard error of measurement of 0.28 L min $^{-1}$ (6.8%) when comparing directly measured maximal oxygen uptake from a maximal treadmill test with the estimation of the VO_{2max} from the step test. This study included a small group of healthy men and women of 18-30 years-of-age, which may not provide an accurate representation in the general adult population (131). A systematic review investigating the validity of multiple step-test protocols also concluded that submaximal step tests can be a valid method of assessing cardiorespiratory fitness, but that the participant's ability to maintain a steady stepping tempo and technique is essential to getting an accurate measure (132). Reliability of the step test has not been assessed.

Heart rate increases with work intensity from a baseline at rest and up to the maximal heart rate at very high work intensities (133). Submaximal testing is based on the supposition that there is a linearity between heart rate and oxygen consumption as exercise intensities increases (134, 135). Heart rate can therefore, to some extent, reflect the aerobic capacity of the individual when measured at given external work intensities, where a lower heart rate at the specific external work intensity indicates better aerobic capacity (134, 135). Additionally, the rate at which the heart rate slows down after exercise has been shown to indicate the aerobic fitness level (136), as well as being a predictor of mortality (137). In individuals with lower levels of cardiorespiratory fitness, heart rate recovery has been found to be slower compared to more well-trained individuals (136).

Normative values using heart rate after 4-minute step test has not, to our knowledge, been developed in Norway.

3.4 Choice of potential confounding factors

Confounding factors are variables that are associated with both the dependent and independent variable that could lead to over- or underestimation of the result, or change the result (107). The potential confounding factors, height, waist-to-hip ratio and socioeconomic status were therefore chosen because they have been reported to be associated with both being born SGA (29, 31, 50) and physical fitness (56, 61, 76).

3.5 Statistical analysis

The analyses were conducted in SPSS, version 27 (IBM Statistics). Demographic data are described using descriptive statistics. Categorical variables are described by number and percentage, and continuous variables are described with central tendency and variation. Averages and standard deviations were used to describe normally distributed data, and median and interquartile range for data that were not normally distributed (138). Differences between groups concerning descriptive data were analysed using independent samples t-test for continuous variables with a normal distribution, and Mann Whitney U-test for continuous variables with a non-normal distribution. Normal distribution was checked by observing histograms, Q-Q-plot and boxplot. Differences in categorical variables in the two groups were described using Chi square test. A p-value of less than 0.05 was considered statistically significant.

Based on the research question, the difference in physical fitness between the two groups was compared using independent samples t-test, as the dependent variables were normally distributed.

If a significant group difference in physical fitness was found, the result was adjusted for possible confounding factors. A univariate general linear model (GLM) was used with the outcome measure as dependent variable. Group was entered as a fixed factor, and the covariates height, waist-to-hip ratio and socioeconomic status were entered one at a time. We evaluated the effect of the covariates on the group difference in the dependent variable. The assumption of normal distribution was checked by visual inspection of Q-Q-plots of the standardised residuals.

4 SUMMARY OF RESULTS

This chapter contains a summary of the main findings in the study. For more detailed results, see the result chapter in the article draft in Part II of this thesis.

Mean birth weight in the SGA group was 2918 (SD 216) g and 3686 (SD 467) g in the control group ($p<0.001$). There were 22 (47.8%) women in the SGA group compared with 35 (57.4%) in the control group ($p=0.433$). At follow-up, the SGA group had significantly lower height than the participants in the control group ($p=0.045$). Men born SGA also had significantly higher waist-to-hip ratio than the men in the control group ($p=0.034$), while women in the SGA group were slightly younger than women in the control group ($p=0.016$). Weight, BMI and socioeconomic status, did not differ between the two groups.

Mean grip strength in the dominant hand was 37.0 (SD 8.2) kg in the SGA group and 38.7 (SD 10.2) kg in the control group ($p=348$). Men in the SGA group had a mean grip strength of 42.5 (SD 6.4) kg in the dominant hand and 39.7 (SD 7.0) kg in the non-dominant hand, while the men in the control group had a mean grip strength of 47.4 (SD 8.1) kg in the dominant hand and 44.5 (SD 8.4) kg in the non-dominant hand. This was a mean difference of 4.8 kg in both dominant (95% CI, -9.0, -6.0, $p=0.025$) and non-dominant (95% CI, -9.2, -0.4, $p=0.035$) hand, which was statistically significant difference. However, when adjusting for the men's height, the difference decreased to 2.8 kg in both dominant (95% CI, -7.3, 1.7, $p=0.214$) and non-dominant (95% CI, -7.6, 2.0, $p=0.248$) hand, and were no longer significant. Adjusting for waist-to-hip ratio or socioeconomic status did not affect the difference in grip strength.

There were no significant group differences in the 40-second modified push-up test or Åstrand-Ryhming step test in the total material or stratified by sex.

Sensitivity analysis

The results were essentially the same when excluding pregnant participants, outliers or participants that were not able to do any push-ups or were not able to finish the push-up test or step test. The results were mostly the same when excluding participants that had any pain, musculoskeletal diagnosis or recent injuries that could affect the physical fitness tests. There was a small increase in number of push-ups in favour of the SGA-group, that lead to a mean difference of 1.8 push-ups (95% CI: 0.05, 3.5, $p=0.044$), but the difference was not significant when stratified by sex (data not shown).

5 DISCUSSION

The discussion in the article draft (part II of this thesis) addresses some of the methodological considerations in this study concerning selection and information bias and discussion of the main results. The following chapter contains an extended discussion of the methods used in this study, where strengths and limitations will be further addressed. Additionally, clinical importance and implications will be discussed.

5.1 Discussion of method

5.1.1 Design

The aim of this master's thesis was to investigate whether being born SGA at term affects physical fitness in adulthood. The design of this project is a prospective cohort study. Prospective cohort studies are reported to have the ability to find evidence for associations between exposure and outcome (107, 108). A definite causality cannot be established through a cohort study, as there is always a possibility that the result may be explained by other variables that differ between the groups. However, these studies may contribute to provide evidence in the search for a causal connection (107, 139). The exposure in this study is being born SGA, while the outcome is physical fitness in adulthood. Thus, a difference found between the groups in physical fitness, could therefore support the hypothesis of a causal relationship between being born SGA and physical fitness in adulthood.

5.1.2 Participants

Cohort studies are designed to be representative for particular populations (109); in this study, adults born SGA to term in Norway. As there are many factors that can lead to an SGA birth (12-14), the SGA populations is a very heterogeneous population. Having many exclusion criteria may therefore limit the representativeness as the exclusion criteria will restrict who is eligible and the study population will be a more specific group (107). In this study, there were few exclusion criteria, which therefore could be argued to contribute to make the study population representative for similar populations.

The characteristics of the control group is also important for the external validity of the study. Inclusion criteria was birth weight at or above the 10th centile, and they were selected using a sealed envelope method, ensuring a random control sample. Both the SGA group and the control group were from the Trondheim area and born in the same period of time. On the one hand, this is a strength, as the two groups are comparable with regards to socio-demographic and cultural conditions. On the other hand, this could lead to a homogeneous study sample that limits the generalisability of the study. However, with the wide exclusion criteria and the sealed envelope method used to select the control group, there is reason to believe that the control group is representative for the population.

There is a chance that the results from this study will be less relevant to individuals born SGA today. The participants were included in 1986-1988. Due to advances in medicine, more infants survive suboptimal pregnancies and receive better neonatal care (140). Better care may lead to SGA individuals born today not having exactly the same characteristics as the participants in this study. The decline in infant mortality has continued since the late 1980s (140). With higher rate of survival, it is possible that this could lead to those surviving having more complications than before, and an increased risk of adverse health outcomes in the future. This would require further research. For the present, there is reason to believe that this study will be of relevance for current individuals born SGA.

5.1.3 Outcome measures

In order to prevent information bias, it is important that all tests are conducted in a standardized manner and that all participants were assessed equally (141). This was ensured through trained and experienced examiners who were blinded to birth weight group. Additionally, in order to trust the results of the study it is also important that the assessment tools are reliable and valid.

Grip strength

The Jamar hand dynamometer is a widely used instrument for measuring hand grip strength. It has proven to be a valid and reliable measurement instrument (121). It is important to ensure that the grip strength assessment is conducted in the same way for all participants, as grip strength varies depending on hand position, angle of the elbow and standing or seated position during the test (142-144). Thus, it is a strength of this study that the positioning was standardised and carried out equally for all participants. A possible weakness of the study could be that the hand position on the dynamometer did not suit all the participants. Adapting the hand position to each individual could have been beneficial. While this may be the case, the Jamar hand dynamometer has shown good reliability when using hand position 3 and 4 (123), as in this study, and is therefore considered to suit most participants.

Push-up test

The push-up test has been reported to be valid for testing health-related physical fitness (129). Additionally, the test has shown good inter-rater reliability (126, 130). However, as small variations in the push-up position or execution can affect the result (127), it is important that the examiners instruct the participants and assess the performance of each participant equally. The modification of the test and the fact that the examiners were specially trained in advance contribute to the standardisation of the test, and hence a more reliable result. Additionally, another positive aspect of the modification, is that it contributes to ensure that the participants complete the entire path of motion. Suni (126) reported a learning effect when assessing test-retest reliability of the test, probably due to the complexity of the push-up, and suggested that the participants should practice the test before being tested. The participants in this study did one sequence of the push-up before being timed. This is not necessarily sufficient practice, but to avoid fatigue before testing, only one attempt was chosen.

Step test

Even though Åstrand and Ryhming (131) found their step test to be valid for assessing cardiorespiratory fitness in young adults, and Bennett et al. (132) concluded that step tests can be a valid method of measuring cardiorespiratory fitness, there are several limitations important to be aware of. A step too high for the individual participant could challenge the muscular endurance to a greater extent than the cardiorespiratory fitness (132). In this study the step hight was adapted to gender to minimize this risk. Whether this was sufficient for all participants, is not known, as there was a variation in height among participants.

Heart rate was used as an outcome measure to investigate the cardiorespiratory fitness in this study, which has been shown to increase linearly with VO_{2max}, to some extent (134, 135). However, there are a number of factors that can affect the heart rate to deviate from this linear assumption (132, 145), including height and body composition. For example, smaller or heavier individuals that have the same VO_{2max} as taller and leaner individuals, is likely to have a higher heart rate during the test, and thus have a lower VO_{2max} estimation. This will also affect the heart rate recovery. Higher exercise intensities will result in higher heart rates, which is likely to create a larger decrease in heart rate after the step test is completed (136). Thus, a maximal test with measurement of VO_{2max} would have been a more accurate assessment of the participants' cardiorespiratory fitness. However, this is more time consuming and requires that the participants are motivated to push themselves to the maximum to get a valid result. A submaximal test was therefore considered more feasible. Even if it is not an optimal outcome measure to assess the participants' cardiorespiratory fitness, the test might still give an indication of their fitness level.

5.1.4 Statistical analysis

The objective of this study was to investigate whether there was any difference in physical fitness between the SGA and the control group. An independent samples t-test was used to assess group differences. A grip strength difference of 5 kg was found in both dominant and non-dominant hand between SGA and control men, and the p-value indicated that this difference was significant. However, the 95% CI was rather wide, and the result should therefore be interpreted with caution.

The difference in grip strength found in men was adjusted for three potential confounders: height, waist-to-hip ratio and socioeconomic status. Other possible factors that could affect the results, that we were not able to adjust for, are the physical activity level of the participants, proportion of fat-free mass to fat mass, and hereditary factors. Physical activity is strongly associated with physical fitness (62, 63), and the possibility that differences in physical activity level have affected the fitness of the participants cannot be ruled out. Additionally, as the proportion of fat-free mass relative to fat mass has been reported to be decreased in individuals born SGA (31-33), this may also be of relevance to their physical fitness. Furthermore, there is a strong hereditary contribution to both muscular and cardiorespiratory fitness that could not be estimated in this study. However, genetic contribution on grip strength is reported to be approximately 50% (52), which means that environmental factors remain essential. Nevertheless, we cannot rule out the possibility of other potential confounding factors affecting the result.

5.2 Clinical importance and implications

5.2.1 Similar muscular and cardiorespiratory fitness in SGA and control individuals

The results in this study showed that there overall was no difference in muscular and cardiorespiratory fitness between adults born SGA at term and adults born with normal birth weight at term. This is encouraging results, as it indicates that the physical fitness in adults born SGA might not be that different to the rest of the population. This may suggest that physical fitness might not be an area that requires an explicit focus, and that it may not affect the public health as much as it potentially could have.

While this may be the case, there are known potential negative consequences of being born SGA that can affect several parts of life, including both the body function and structure domain and the activity and participation domain. Possible consequences include an increased risk of non-communicable diseases, psychiatric diseases and reduced mental health and well-being (5, 6, 21-23). Research show that increasing physical fitness and having an active lifestyle is associated with decreased risk of non-communicable diseases, as well as improved mental health and increased health-related quality of life (7, 77, 82, 83, 146). Consequently, even though the physical fitness of SGA individuals may not be that different to the rest of the population, the promotion of physical fitness may be particularly important in this group, as it might contribute to prevent adverse consequences of being born SGA.

5.2.2 Lower grip strength in men born SGA

When the unadjusted analysis was stratified by sex, men in the SGA group had approximately 5 kg lower grip strength in both the dominant and non-dominant hand compared with men in the control group. This difference decreased and was no longer significant when adjusted for height. However, as many individuals born SGA are reported to have lower height in adulthood, and as persistent short stature is associated with poorer health (147-149), it can be argued that the results should not be adjusted for height.

The reduced grip strength in SGA men found in the unadjusted analysis is consistent with multiple other studies that has found associations between birth weight and grip strength in adulthood (10, 11), even though these studies have not explicitly studied SGA individuals born at term. Furthermore, there is research reporting that foetal growth restriction, which SGA is an indicator of, may affect muscle morphology (103). Some studies have also found that SGA individuals are more likely to have motor problems (41, 42), and motor problems are associated with reduced grip strength (67, 68). Consequently, the results of this thesis might contribute to point to the direction that being born SGA affects grip strength in men.

Grip strength has been reported to be a biomarker of current and future health (87, 113, 150). In the body functions and structure domain, reduced grip strength is associated with increased risk of all-cause death and cause-specific death, including death from cardiorespiratory disease (114, 115). Every 5 kg reduction in grip strength has been reported to be associated with this increased risk, which corresponds to the unadjusted difference between the SGA and control men in the current study. In the activity and participation domain, reduced grip strength is associated with reduced mobility and function at older ages (87). As grip strength is reported to track through life (87), a reduced grip strength when entering mid-adulthood could indicate increased risk of functional problems later in life. Preventative measures in order to increase the muscular fitness should therefore be a focus.

Physical activity has a great influence on physical fitness (62, 63). To increase the muscular strength, the focus should be on activities that specifically challenges the strength (63). Research show that physically active lifestyles develop in childhood and stays relatively stable into adulthood (65, 66). Promoting physical activities in childhood that helps increase the muscular fitness may therefore have long-term beneficial effects on adult muscle strength, and furthermore, contribute to prevent reduced function, mortality and morbidity later in life. It is especially important to find activities that are enjoyable to the individual, as those who enjoy participation are more likely to be more physically active (69).

6 CONCLUSION

This master's thesis shows encouraging results concerning physical fitness in individuals born SGA, entering mid-adulthood. Contrary to the hypothesis of the study, there were no other differences in either muscular or cardiorespiratory fitness between the groups, neither in the total groups nor stratified by sex, which are promising results. Men born SGA did, however, have reduced grip strength compared with men in the control group, which may indicate an increased risk of negative health outcomes. Increasing muscular fitness may therefore be beneficial to prevent adverse health outcomes in men born SGA.

7 IMPLICATIONS FOR FUTURE RESEARCH

A decline in muscular strength is expected with aging (57) and grip strength is reported to track through life (87). Sayer et al. (151) found that birth weight was in fact associated with sarcopenia in men and women, independently of height and weight, though gestational age was not reported in this study. It could therefore be important to see how the grip strength in SGA men develop as they grow older.

In the current study, the participants' physical fitness was assessed objectively. It could be useful to examine how the participants experience and evaluate their own physical fitness. If adults born SGA feel that their fitness is poor, this could still affect their health, even if the objective assessments did not reveal any major differences. In addition, we were not able to adjust for the participants' physical activity level, which is strongly correlated with physical fitness. This could be relevant to investigate further, to see whether adults born SGA are equally active as their peers, and if their physical activity level is associated with their physical fitness. Data on self-rated fitness, physical activity level measured with accelerometer and other outcomes has been investigated in the larger NTNU LBW Life study, but has yet to be analysed.

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PART II

9 ARTICLE

Physical fitness in adults born small for gestational age at term: a prospective cohort study

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The article is written for submission to, and according to the guidelines of, the journal Early Human Development: https://www.elsevier.com/journals/early-human-development/0378-3782/guide-for-authors.

ABSTRACT

Background: Low birth weight has been associated with reduced physical fitness in adulthood, but less is known about physical fitness in adults born small for gestational age (SGA) at term.

Aim: To investigate whether physical fitness differ between term-born SGA adults and term-born adults with normal birth weight.

Study design: Prospective cohort study.

Participants: In all, 107 32-year-old adults born at term (gestational age ≥37 weeks) participated; 46 were born with a birth weight <10^{th} centile (22 women, 24 men), and 61 were born with a birth weight ≥10^{th} centile (35 women, 26 men).

Outcome measures: Primary outcome measure was grip strength measured with a Jamar hand dynamometer. Secondary outcome measures were number of push-ups in a modified push-up test and heart rate after Åstrand-Ryhming step test. Results were compared between the two groups, stratified by sex and differences were adjusted for covariates.

Results: Maximal grip strength in the dominant hand was 37.0 (SD 8.2) kg in the SGA group, and 38.7 (SD 10.2) kg in the control group (p=0.348). Men born SGA had an average of 4.8 kg lower grip strength in both the dominant (95% CI: -9.0, -0.6, (p=0.025)) and non-dominant (95% CI: -9.2, -0.4, (p=0.035)) hand compared with men in the control group. The difference was no longer significant when adjusted for height. Secondary outcome measures did not differ between groups or stratified by sex.

Conclusion: Reduced grip strength in men born SGA indicates reduced muscular fitness, which may predispose them to future morbidity and mortality.

Trial registration: ISRCTN77533991

Keywords: Small for gestational age, physical fitness, grip strength, modified push-up test, step test

Abbreviations: SGA, small for gestational age (birth weight <10^{th} centile); BMI, body mass index; SES, socioeconomic status; SD, standard deviation; CI, confidence interval

Introduction

Individuals born small for gestational age (SGA) are often defined as having a birth weight below the 10^{th} centile for their gestational age, adjusted for sex and parity [1]. SGA is the most frequently used indicator of intrauterine growth restriction, which is a state where the foetus does not reach its genetic growth potential [2]. This involves an extra vulnerability for later diseases, such as metabolic syndrome, cardiovascular disease, diabetes type 2, even when born at term (i.e., gestational age ≥37 weeks) [3]. Globally, approximately 10% of term-born infants in developed countries are born SGA, and according to the 1991 US national reference population, 20% of term-born infants in developing countries are born SGA [4]. Hence, the high prevalence represents a major concern for public health.

Physical fitness is defined as a set of attributes that people have or achieve that relates to the ability to perform physical activity [5]. Muscular and cardiorespiratory fitness are two important health-related components of physical fitness [6], that both have been reported to be associated with all-cause mortality, as well as non-communicable diseases [7, 8]. Several studies have found associations of birth weight with muscular and cardiorespiratory fitness in adulthood [9-11]. However, these studies have either included adults born preterm or not specified the gestational age of their participants. This makes it difficult to distinguish if the result is due to factors related to premature birth or low birth weight.

Three relatively small studies found no difference in cardiorespiratory fitness, measured by maximal oxygen uptake (VO_{2max}), between young (i.e., 18-24 years old) adults born at term where one group had birth weight below the 10^{th} centile and the other a birth weight at or above the 10^{th} centile [12-14]. On the other hand, two recent Swedish registry studies that included a large number of 18-year-old men born at term, found strong associations of birth weight with grip strength and cardiorespiratory fitness, measured by maximal workload on a cycle ergometer [15, 16]. Each standard deviation (SD) increase in birth weight, approximately 450-455 g for a baby born at 40 weeks, was associated with 1.8 kg increase in grip strength force [15] and 7.9 watt increase in maximal workload [16].

Thus, the research available concerning physical fitness in young adults born SGA at term shows inconsistent results. Furthermore, there is a lack of research regarding physical fitness in SGA individuals entering mid-adulthood, at an age where non-communicable diseases may occur [17]. Grip strength, a simple and widely used measure of muscular strength, has in this case proven to be particularly relevant as it is a strong predictor of future physical function, morbidity and mortality [8, 18, 19].

The main objective of this study was to examine whether muscular and cardiorespiratory fitness differed between term-born SGA adults and term-born adults with normal birth weight. We hypothesised that adults born SGA at term would display lower level of fitness than the term-born control group. We also investigated physical fitness in women and men separately and whether any differences were affected by potential confounding factors.

MATERIAL AND METHODS

Study design

This is a prospective cohort study of two groups of adults born in 1986-88; one group born small for gestational age (SGA) at term, and one group born at term with birth weights ≥10th centile, which serves as a control group. This study is a part of the NTNU Low Birth Weight in a Lifetime Perspective study (NTNU Low Birth Weight Life), a Norwegian prospective cohort study, which objective is to create a better understanding of how birth weight affects physical and mental health, amongst others, throughout life. The participants took part in a larger data collection and underwent a selection of tests and examinations throughout the testing day. In addition to physical fitness tests, examinations included anthropometric measurements, examination of lung function, visual function as well as fine and gross motor function. Data were collected from September 2019 to October 2020.

Participants

The participants were initially included to a multicentre study investigating the aetiology and consequences of intrauterine growth restriction [20, 21]. Pregnant women living in the Trondheim region were enrolled before week 20 of pregnancy based on referral from general practitioners and obstetricians. The participants were eligible if they had a singleton pregnancy and had been pregnant one or two times before (n=5722). A 10% random sample of the eligible women were selected to serve as a control group, using a sealed envelope method. The SGA group was selected from the remaining women if they fulfilled one or more defined risk criteria for SGA birth; a prior low birth weight birth, maternal cigarette smoking at conception, low pre-pregnancy weight (<50 kg), a previous perinatal death, or the presence of chronic maternal disease (chronic renal disease, essential hypertension, or heart disease) (n=1384). The two groups were thoroughly followed through pregnancy and examined at birth.

An infant was defined as SGA if the birth weight was below the 10^{th} centile according to each specific gestational week, and the reference standards were sex-specific based on data from the Norwegian Medical Birth Registry [22]. The control participants had birth weight at or above the 10^{th} centile. Gestational age (GA) was based on the first day of the mother's last menstruation if this was accurately recalled +/- three days. Ultrasound based GA was used if last menstrual period was not recalled, or if there was a discrepancy of more than 14 days. Both groups were born at term (GA ≥37 weeks) [20, 21].

Initially, 104 participants born SGA and 120 control participants were included (Figure 1). At birth, two SGA infants and two control infants were excluded due to congenital syndromes or multimorbidity. Of the total sample, 22 SGA individuals and 23 controls were not invited because they previously had refused to participate, were living abroad, had no contact information or did not answer the phone. Thus, a total of 174 potential participants were invited to the current study, 79 in the SGA group and 95 in the control group. Due to practical reasons related to the Covid-19 pandemic, six SGA individuals and seven controls that initially agreed to be assessed were not able to participate. Furthermore, 27 individuals in each group did not consent to clinical assessment. Thus, 46 SGA individuals and 61 control individuals agreed to participate, which corresponds to 61.5% of those who were invited.

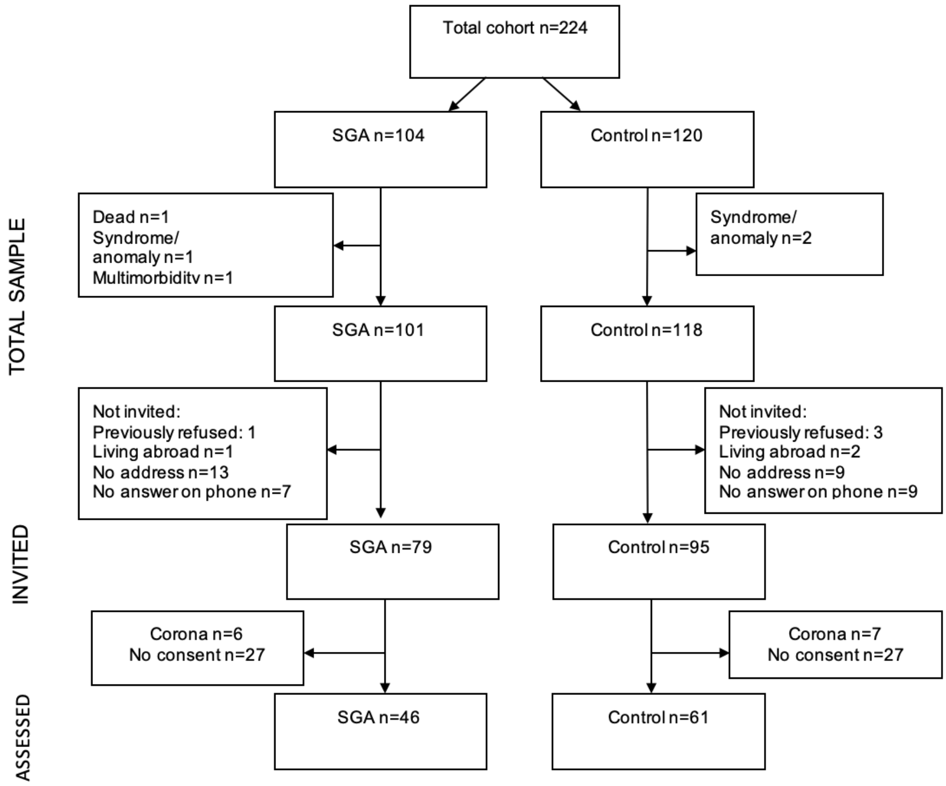

Figure 1: Flowchart of the study population. SGA = small for gestational age (i.e., birth weight <10th centile).

Non-participants

There were no statistically significant differences between participants and non-participants regarding gestational age, birth weight, body length, ponderal index or socioeconomic status (SES).

Methods

Assessments were carried out at NTNU/St. Olavs Hospital in Trondheim, Norway. A brief medical interview was conducted prior to testing. If the participant had a condition that made them unable to perform a physical test or that could be worsened by testing, they were excluded from that particular test. All examinations were carried out by experienced and specially trained examiners, blinded to birth weight group. Anthropometric measurements were performed by a nurse and physical fitness tests by two physiotherapists and a medical research student. The examinations were carried out in the same order for each participant.

Anthropometric measurements

At birth, the infants in both groups were weighed to the nearest 10 g on a standard scale, and crown-heel length was measured with both legs extended to the nearest mm [21]. Ponderal index (g/cm^3) was calculated based on these measurements.

At follow-up, the participants' height, waist and hip circumference were measured to the nearest mm. Waist circumference was measured at the mid-point between the lowest rib and the crista iliaca, and hip circumference at the maximal circumference over the buttocks. Weight was measured by bioelectric impedance analysis (Seca mBCA 515) with a 100 g accuracy. Body mass index (BMI, kg/m^2) and waist-to-hip ratio (WHR, waist circumference/hip circumference) was calculated based on the anthropometric measurements.

Socioeconomic status

Socioeconomic status (SES) was calculated according to Hollingshead's Two Factor Index of Social Position [23], based on participants' education and occupation. This gives a social class rating from 1 (lowest) to 5 (highest).

Primary outcome measure

Muscular fitness measured by the maximal isometric grip strength of the hands and forearm muscles was considered the primary outcome. A Jamar (Smith and Nephew, Memphis, TN) hand dynamometer was used. The dynamometer has 5 handle positions; position 3 and 4 were used for women and men, respectively. The participants were seated during the test, with shoulder abducted, a 90-degree angle in the elbow and a neutral position in the wrist, without support of the forearm [24]. Measurement was repeated three times in both the dominant and the non-dominant hand with 30 seconds recovery in between each attempt. Grip strength was measured in kg force and the maximal grip strength of the three measurements for dominant and non-dominant hand was used in the analysis. One participant in the control group could not perform the grip strength test in the dominant hand due to a wrist fracture.

Secondary outcome measures

As secondary outcome measures, muscular and cardiorespiratory fitness was assessed by the 40-second modified push-up test and Åstrand-Ryhming step test. The 40-second modified push-up test measures the muscular strength and endurance capacity of the upper body [25] and is modified to improve standardisation. The participants started laying prone on a mat with their hands close to the shoulders and feet hip-width apart with their toes on the mat [25]. Before every push-up they had to clasp hands behind their back before pushing themselves to a straight leg push-up. In the top position they had to touch either of their hands with the other hand before returning to the push-up position and returning to the down-position. The number of correctly performed push-ups in 40 seconds were registered. One participant in the control group could not perform the push-up test due to a wrist fracture.

The Åstrand-Ryhming step test is a four-minute submaximal step-test that measures cardiorespiratory fitness [26]. The participants stepped on and off the step for four minutes paced by a metronome set to 46 beats per minute (i.e., 23 times up on the step/min). The height of the step was adapted to sex: 33 cm for women and 40 cm for men. Heart rate was observed during the test using a heart rate monitor (Firstbeat Technologies Oy) and recorded after 4 minutes of stepping and after being seated for 2 minutes. If participants were not able to complete the test, the heart rate when they ended the test was recorded and used in the analysis.

Statistical analysis

The analyses were conducted in SPSS version 27 (IBM Statistics). A p-value of less than 0.05 was considered statistically significant. Participant characteristics were examined using descriptive statistics. Differences in continuous data between groups were examined using independent samples t-test or Mann Whitney U-test based on whether the data were normally distributed or not. Differences in categorical variables were described using Chi square test.

Difference in muscular and cardiorespiratory fitness between the SGA and the control group was examined using independent samples t-test. The assumption of normally distributed variables was checked by visual inspection of histogram, Q-Q-plot and boxplot. As physical fitness differs between women and men [27, 28], we also performed analysis stratified by sex.

Differences in physical fitness between groups were adjusted for potential confounding factors in a univariate general linear model. Height, waist-to-hip ratio and socioeconomic status were chosen as these variables have been reported to correlate with both being born SGA [3, 29, 30] and physical fitness in previous literature [10, 31, 32]. Normal distribution of the standardised residuals was checked by visual inspection of Q-Q-plot.

Sensitivity analyses were performed to investigate whether any physical conditions affected the result of the physical fitness assessments. Participants were excluded if they had any pain, musculoskeletal diagnosis or recent injuries that could affect the specific physical fitness tests. Furthermore, we excluded outliers, pregnant women and participants who did not manage to do any push-ups or complete the step test in separate sensitivity analysis.

A sample size calculation was performed based on a grip strength difference of 5 kg, as this has been reported to impact all-cause and cardiovascular mortality [18, 19]. We used a standard deviation (SD) of 7.8 based on reported SD's for men and women aged 30-39 years in a Norwegian study by Kjær et al. [27]. With an alpha-level of 0.05 and desired power of 80% we needed 39 participants in each group.

Ethics

The study is approved by the Regional Ethical Committee (REC number 23879). Written informed consent was obtained from all participants. The data was anonymised and stored securely on a remote server with a two-step identifier. All methods were non-invasive and entailed low risk for injury or adverse events. An appointed doctor was medically responsible during data collection. Participants in need of health services were referred as appropriate.

RESULTS

Background characteristics

Participants' characteristics at birth are shown in Table 1. As expected by study design, the SGA group had significantly lower birth weight, body length and ponderal index at birth compared with the control group. All participants were born to term, and there was no difference between the groups regarding gestational age. There were 22 (47.8%) women in the SGA group and 35 (57.4%) in the control group (p=0.433).

Table 1 Characteristics at birth of adults born small for gestational age (SGA) at term and adults born at term with normal birth weight (control).

	SGA n=46 (women n=22)		Control n=61 (women n=35)		
	Mean	**(SD)**	**Mean**	**SD**	**p-value**
Gestational age (weeks)					
Girls	39.6	(1.3)	39.7	(1.2)	0.550
Boys	39.6	(1.1)	39.9	(1.2)	0.439
Total	39.6	(1.2)	39.8	(1.2)	0.351
Birth weight (g)					
Girls	2841	(253)	3622	(479)	<0.001
Boys	2988	(151)	3772	(445)	<0.001
Total	2918	(216)	3686	(467)	<0.001
Body length (cm)[a]					
Girls	47.8	(2.1)	50.5	(1.8)	<0.001
Boys	49.2	(1.5)	51.8	(1.9)	<0.001
Total	48.5	(2.0)	51.1	(1.9)	<0.001
Ponderal index[a]					
Girls	2.6	(0.3)	2.8	(0.2)	0.001
Boys	2.5	(0.2)	2.7	(0.3)	0.009
Total	2.6	(0.2)	2.8	(0.3)	<0.001

[a]Data missing for 5 SGA participants (2 women, 3 men) and 3 control participants (women). SD = standard deviation

At follow-up, participants' weight and BMI were similar in the two groups (Table 2). Mean height was significantly lower in the SGA group compared to the control group, both when comparing the total group and when stratified by sex. SGA women were also slightly younger than women in the control group, and SGA men had higher waist-to-hip ratio than men in the control group.

The participants' socioeconomic status was similar in the two groups, and both groups had median scores in the upper part of the scale.

Table 2 Characteristics at follow-up of adults born small for gestational age (SGA) at term and adults born at term with normal birth weight (control).

	SGA n=46 (women n=22)		Control n=61 (women n=35)		
	Mean	**(SD)**	**Mean**	**(SD)**	**p-value**
Age at examination (years)					
Women	32.3	(0.5)	32.6	(0.5)	0.016
Men	32.8	(0.6)	32.5	(0.5)	0.154
Total	32.5	(0.6)	32.6	(0.5)	0.618
Height (cm)					
Women	163.4	(6.6)	168.2	(6.5)	0.009
Men	177.6	(5.6)	183.2	(6.1)	0.001
Total	170.8	(9.4)	174.6	(9.8)	0.045
	Median	**(IQR)**	**Median**	**(IQR)**	**p-value**
Weight (kg)					
Women	62.3	(55.7-67.6)	65.7	(59.3-78.4)	0.079
Men	81.8	(76.1-88.7)	83.4	(76.4-91.6)	0.705
Total	74.6	(62.7-84.0)	75.7	(65.0-86.2)	0.443
BMI					
Women	22.5	(21.5-25.5)	23.7	(20.6-26.4)	0.646
Men	26.0	(23.8-28.2)	24.9	(22.4-26.8)	0.187
Total	24.8	(22.4-27.3)	24.3	(21.8-26.7)	0.489
Waist-to-hip ratio					
Women	0.78	(0.76-0.83)	0.78	(0.77-0.82)	0.922
Men	0.89	(0.87-0.93)	0.86	(0.83-0.92)	0.034
Total	0.85	(0.78-0.90)	0.82	(0.78-0.87)	0.120
Socioeconomic status					
Women	4.0	(4.0-5.0)	4.0	(4.0-5.0)	0.092
Men	4.0	(3.0-5.0)	4.0	(3.0-5.0)	0.671
Total	4.0	(3.0-5.0)	4.0	(4.0-5.0)	0.119

SD = standard deviation. IQR = interquartile range (25 quartile-75 quartile). Socioeconomic status (values 1-5, 5 = highest social class).

Physical fitness

The results of the physical fitness tests are shown in Table 3. Overall, there were no group differences in grip strength, modified push-up test or step test. However, stratified by sex, men in the SGA group had significantly lower grip strength in both hands compared with men in the control group. The mean difference was 4.8 kg (95% CI: -9.0, -0.6, p=0.025) and 4.8 kg (95% CI: -9.2, -0.4, p=0.035) in the dominant and non-dominant hand, respectively. The distribution and difference in grip strength between the men is shown in Figure 2. There was no difference in grip strength between the women in the two groups.

Table 3 Grip strength, 40-second modified push-up test and Åstrand-Ryhming step test in adults born small for gestational age (SGA) at term and adults born at term with normal birth weight (control).

	SGA n=46 (women n=22)		Control n=61 (women n=35)				
	Mean	**(SD)**	**Mean**	**(SD)**	**Mean difference**	**(95% CI)**	**p-value**
Maximal hand grip strength, dominant hand (kg)							
Women	31.0	(5.0)	32.1	(5.6)[a]	-1.1	(-4.0, 1.9)	0.462
Men	42.5	(6.4)	47.4	(8.1)	-4.8	(-9.0, -0.6)	0.025
All	37.0	(8.2)	38.7	(10.2)[a]	-1.7	(-5.3, 2.0)	0.348
Maximal hand grip strength, non-dominant hand (kg)							
Women	28.1	(4.9)	29.2	(5.5)	-1.1	(-4.0, 1.8)	0.433
Men	39.7	(7.0)	44.5	(8.4)	-4.8	(-9.2, -0.4)	0.035
All	34.2	(8.4)	35.7	(10.2)	-1.6	(-5.2, 2.1)	0.398
Number of modified push-ups in 40 seconds							
Women	9.5	(4.4)	8.1	(4.1)[a]	1.4	(-0.9, 3.8)	0.217
Men	12.5	(4.7)	11.7	(3.0)	0.9	(-1.4, 3.1)	0.447
All	11.1	(4.8)	9.6	(4.1)[a]	1.5	(-0.3, 3.2)	0.093
Heart rate after 4 min. step test							
Women	150.8	(17.1)	150.4	(18.9)	0.4	(-9.6, 10.4)	0.936
Men	160.8	(19.1)	160.0	(19.1)	0.8	(-10.1, 11.7)	0.885
All	156.0	(18.7)	154.5	(19.4)	1.5	(-5.9, 8.9)	0.685
Heart rate after 2 min. rest							
Women	98.5	(17.5)	98.0	(17.2)	0.5	(-8.9, 9.9)	0.916
Men	105.9	(21.5)	106.5	(24.9)	-0.6	(-13.8, 12.7)	0.935
All	102.4	(19.8)	101.6	(21.1)	0.8	(-7.2, 8.7)	0.849
Difference in heart rate from end of 4 min. step test and 2 min. rest							
Women	52.3	(9.6)	52.4	(13.2)	-0.1	(-6.2, 6.0)	0.974
Men	54.8	(13.7)	53.5	(16.5)	1.3	(-7.3, 10.0)	0.758
All	53.6	(11.8)	52.9	(14.6)	0.8	(-4.5, 6.0)	0.774

[a]1 missing due to fracture in the arm. SD = standard deviation. CI = confidence interval

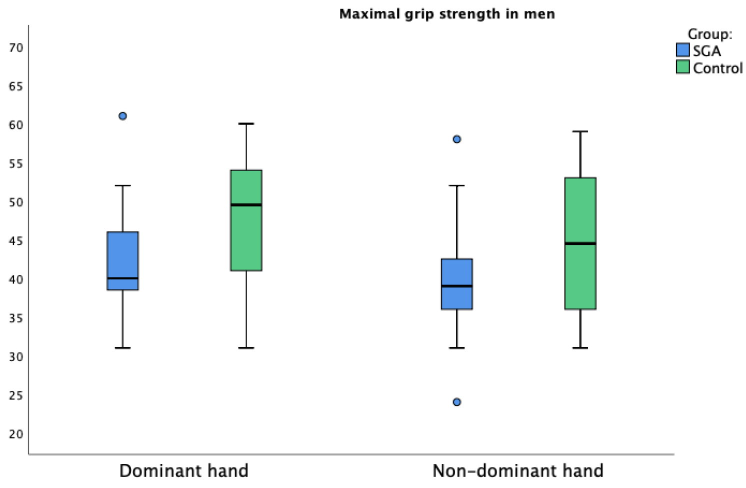

Figure 2 Distribution of grip strength in the dominant and non-dominant hand for men born small for gestational age (SGA) at term and men born with normal birth weight (control). The box contains 50% of the cases. Circles indicate outliers; thick horizontal line in each box, median value; and limit lines, the highest and lowest values (except for the outliers).

Potential confounding factors

When we adjusted height at follow-up, the difference in maximal grip strength among men decreased to 2.8 (95% CI, -7.3, 1.7, p=0.214) in the dominant hand and 2.8 (95% CI, -7.6, 2.0, p=0.248) kg in the non-dominant hand and were no longer significant (Table 4). When we adjusted for waist-to-hip ratio, the difference between the groups was essentially the same and still significant in both hands. Likewise, the difference was essentially unchanged when adjusting for the participants' socioeconomic status.

Table 4. Difference in maximal grip strength (kg) between men born small for gestational age (SGA) at term (n=24) and men born with normal birth weight (control) at term (n=26), unadjusted and adjusted for potential confounding factors.

	Unadjusted		**Adjusted for height**		**Adjusted for waist-to-hip ratio**		**Adjusted for SES**	
	B (95% CI)	**p**	**B (95% CI)**	**p**	**B (95% CI)**	**p**	**B (95%CI)**	**p**
Dom hand	-4.8 (-9.0, -0.6)	0.025	-2.8 (-7.3, 1.7)	0.214	-4.6 (-9.0, -0.3)	0.038	-4.7 (-8.9, -0.5)	0.029
Non-dom hand	-4.8 (-9.2, -0.4)	0.035	-2.8 (-7.6, 2.0)	0.248	-4.7 (-9.3, -0.1)	0.047	-4.7 (-9.1, -0.2)	0.039

SES: socioeconomic status, Dom hand=dominant hand, Non-dom hand=non-dominant hand

Sensitivity analyses

Results were unchanged when we excluded one woman and one man in the SGA group and two women in the control group in the grip strength analyses, and likewise excluded 5 women and three men in the SGA group and three women and five men in the control group from the step test analyses due to musculoskeletal diagnoses or recent injuries. When we excluded three women and three men in the SGA group and three women and two men in the control group from the push-up analyses, there was a small increase in number of push-ups to 1.8 (95% CI: 0.05, 3.5; p=0.044) in favour of the SGA group. The difference was not significant when stratified by sex (data not shown).

Results were unchanged when we excluded two pregnant women in each group, and when we excluded one man in the SGA group and two women in the control group that were not able to do any push-ups or two men in the SGA group that could not complete the test.

When we excluded one man in the SGA group and two men in the control group who were outliers in the grip strength tests (Figure 2), the difference in grip strength increased to 5.6 kg (95% CI: -9.6, -1.7, p=0.006) in the dominant hand and to 4.9 kg (95% CI: -9.0, -0.8, p=0.021) in the non-dominant hand. When we excluded two SGA outliers (men) in the push-up test, the difference between the groups decreased to 0.9 (95% CI -0.7, 2.5, p=0.263). The step test results were essentially the same when excluding two SGA outliers (men).

DISCUSSION

Main findings

Overall, and contrary to our hypothesis, we found no difference in physical fitness between adults born SGA and the control group, measured by grip strength, a 40-second modified push-up test and a 4-minute submaximal step test. However, men in the SGA group had significantly lower grip strength in both dominant and non-dominant hand compared with men in the control group. The difference was not affected by adjustments for waist-to-hip ratio and socioeconomic status, but was no longer significant when we adjusted for height.

Strengths and limitations

A strength of this study is the prospective population-based design, where participants were recruited and followed from mid-pregnancy. The participation rate of 61.5% of the invited represents a substantial loss to follow-up. Nevertheless, follow-up rates of 50-80%

participation have been suggested to be acceptable in cohort studies [33]. Individuals performing worse may have a stronger tendency to drop out [33, 34], which could have led to a selection bias toward physically fit participants. However, there were no differences in background variables between participants and non-participants, and assessment of physical fitness was only a part of a larger follow-up examination. Thus, it seems unlikely that the results are affected by selection bias. However, loss to follow-up limits the sample size and may have affected the power of the study. Nevertheless, the non-significant differences in crude test results were small, indicating that type II-errors are unlikely.

In this study, SGA was defined as birth weight below the 10th centile. This may also comprise individuals who are genetically small and not necessarily growth restricted. At the same time, the control group may comprise individuals who are growth restricted, but still have a birth weight above the 10th centile. This could possibly contribute to smaller differences between the groups in this study. Nevertheless, the 10th centile is a common cut-off used to identify SGA individuals [4].

The SGA women were on average 0.3 years younger than the control women. This is believed to have little impact on the result, as physical fitness is seen to be quite stable across the thirties before gradually declining from midlife [27, 28].

The use of objective measurement tools to assess physical fitness is a strength of this study, as self-reports may be biased by over- or underestimation [35]. Furthermore, the measurements were conducted in the same order and with the same equipment for all participants. Additionally, the measurements were carried out by three experienced and specially trained examiners who were blinded to birth weight groups. This strengthens the internal validity of the results. Both grip strength measured by a dynamometer and the modified push-up test have been reported to be valid instruments for assessing muscular fitness [36, 37]. A limitation of the study was the measurement of cardiorespiratory fitness by a submaximal test with heart rate as the outcome, as heart rate is largely individual [38], and a maximal exercise test measuring maximal oxygen uptake would more accurately evaluate cardiorespiratory fitness [6]. However, a submaximal test is less time consuming and more comfortable for the participants to perform and was considered more feasible in this study.

The difference in number of push-ups performed was slightly increased in favour of the SGA group when we excluded participants with pain, musculoskeletal diagnosis or recent injuries. There was, however, no difference in analyses stratified by sex, indicating that the difference might not be of great importance. Additionally, when excluding two SGA outliers in the total sample, the difference in push-ups decreased substantially. In this study we were able to adjust for anthropometric measurements and socioeconomical factors, but we cannot exclude the possibility that hereditary factors and physical activity level or other lifestyle habits may have affected the results.

Physical fitness

Our hypothesis that adults born SGA would display a lower fitness level than their peers was not confirmed in this study. The only significant difference in physical fitness was found between SGA and control men in grip strength, where men born SGA had approximately 5 kg lower grip strength in the unadjusted analyses. However, the result must be interpreted with caution, as the 95% CI was rather wide. The difference in grip strength is consistent with the recent Swedish study that found strong associations between birth weight in men born at term and grip strength at 18 years of age [15]. It is also in accordance with other studies that have found strong associations between lower birth weight and reduced grip strength in adulthood, regardless of gestational age at birth [9]. The reduction in grip strength found for SGA men in this study could indicate an increased risk of negative health outcomes, as increased hazard ratio of all-cause mortality ranging from 1.08 [19] to 1.16 [18], and for cardiovascular mortality of 1.17 [18], have been reported for every 5 kg reduction in grip strength.

Adjusting for socioeconomic status or waist-to-hip ratio did not affect the difference in grip strength between men. When we adjusted for height, the difference in grip strength was no longer significant, indicating that the difference was mediated through a lower height in men born SGA. This is in accordance with previous research reporting that height is associated with grip strength [10]. However, as many adults born SGA are characterised by shorter height than adults born with normal birth weight [39], this may be an inherent part of being born SGA, and one may therefore argue that the results should not be adjusted for height. Moreover, individuals not experiencing catch-up growth after being born SGA have been reported to be at higher risk of poorer health compared with those who achieve their growth potential [40, 41]. Additionally, even when adjusted for height, the grip strength of SGA men was lower than the 59 kg normative value for men of the same age in Norway [27, 42]. This underlines the relevance of the lower grip strength finding in our study.

The differences in grip strength among men only, may be related to motor development, as associations between motor development and grip strength in adulthood have been documented [10]. Growing up, boys in the general population are reported to have motor problems more often that girls [43]. In the SGA population, several studies also show that boys are more vulnerable to growth restriction in utero than girls, possibly because of a higher growth velocity [44]. Thus, SGA boys and men may be more susceptible to unfavourable development outcomes. In support of this, we have previously reported reduced manual dexterity at 14 years of age in the SGA boys, and not girls [45]. This may be related to the findings of reduced grip strength in the present study.

The fact that we did not find any differences between the groups in the push-up test or step test, deviates from our hypothesis. Our findings are also in contrast to the study by Ahlquist et al. [16], reporting a strong association between 1 SD decrease in birth weight and reduced cardiorespiratory fitness in term-born men, and other studies reporting associations between birth weight and cardiorespiratory fitness when including adults born preterm [10, 46, 47]. However, our results are consistent with three other studies that found no differences in VO_{2max} between young adults born SGA and controls born with normal birth weight [12-14]. The results of this study may therefore contribute to strengthen the evidence that adults born SGA at term may not have lower cardiorespiratory fitness than those born with normal birth weight.

Clinical implications

Overall, the lack of differences between SGA and control individuals found in this study is promising with regards to future health. However, reduced grip strength is an established predictor of future physical function, morbidity and mortality [18, 19, 48]. Research also shows that grip strength tracks through life [48]. Thus, having reduced grip strength at younger ages increases the risk of having even lower grip strength at older ages, which can increase the risk of functional problems [48]. It is therefore worrying that men born SGA already at 32 years of age had reduced grip strength compared with men in the control group. Consequently, promoting a physically active lifestyle in men born SGA may be advantageous. A physically active lifestyle has been shown to form early in life [49], indicating that promotion of physical activity, especially concerning activities that enhance muscular strength, should be a focus from childhood.

CONCLUSION

Overall, we found no difference in physical fitness between individuals born SGA at term and individuals born with normal birth weight at term, entering mid-adulthood, which are promising results. However, men born SGA had significantly lower grip strength than men born with normal birth weight. This may predispose them to reduced future physical function, morbidity and mortality. Adequate physical activity levels may therefore be particularly important for this group. Nevertheless, there are few studies concerning physical fitness in term-born SGA individuals entering mid-adulthood. Further research is therefore needed to determine whether adults born SGA have lower physical fitness than others.

Declaration of interest: none

Acknowledgements

This study is part of the NTNU Low Birth Weight in a Lifetime Perspective Study (NTNU LBW Life) at Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology. We thank the participants for their cooperation and interest in this study. We thank Dr. Anna P.M. Jørgensen for invaluable help with recruitment and organising examinations, research assistant Siv Anita Myhre for anthropometric assessments, physiotherapist Bjørg Liabakk and medical research student Cathrin Vano Mehl for assessments of physical fitness.

Funding sources

This study was funded by the Joint Research Committee between St. Olavs Hospital and the Norwegian University of Science and Technology.

Author contributions

MM analysed the data and drafted the manuscript. KAIE designed the study, organised the data collection, supervised data analyses and contributed to drafting the manuscript.
Others that have contributed to the design of the study and data collection will be co-authors and involved in the final stage of the manuscript preparation. They will receive the

manuscript for review after submission of this Master thesis. All author(s) will read and approve the final manuscript before submission to a scientific journal.

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APPENDIX

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK midt	Hilde Eikemo	73597508	29.01.2021	23879
			Deres referanse:	

Kari Anne Indredavik Evensen

23879 Lav fødselsvekt og hjerneutvikling - Psykisk og fysisk helse, kognisjon og genetikk

Forskningsansvarlig: Norges teknisk-naturvitenskapelige universitet

Søker: Kari Anne Indredavik Evensen

REKs vurdering

Vi viser til søknad om prosjektendring mottatt 26.01.2021. Søknaden er vurdert på fullmakt av komiteens sekretariatsleder, med hjemmel i helseforskningsloven § 11 og forskrift om behandling av etikk og redelighet i forskning § 10 annet ledd.

Omsøkte endringer

Du har søkt om følgende endringer:

1) oppdatert medarbeiderliste hvor seks medarbeidere (Berdal, Karlsen, Eriksen, Mehl, Matre og Benum) har kommet til, mens tre andre har trått ut av prosjektet.

2) data skal lagres på UiO og TSD-løsningen, og ikke NTNU.

Vurdering

Til endring 1: REK har ingen innvendinger mot oppdatert medarbeiderliste. Samtlige delprosjekter vurderes som nært relatert til prosjektets overordnede formål, og er således dekket av tidligere avgitt bredt samtykke. REK kan derfor ikke se at endringen reiser nye forskningsetiske spørsmål.

Til endring 2: Komiteen tar informasjonen til orientering.

Vilkår for godkjenning

Du må sende inn forskningsprotokoll for Berdal, Karlsen og Eriksen straks de foreligger. Vennligst bruk skjemaet "Generell henvendelse".

Vedtak

Godkjent med vilkår

Med vennlig hilsen

Hilde Eikemo
Sekretariatsleder, ph.d.
REK midt

Klageadgang
Du kan klage på komiteens vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes til REK midt. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK midt, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag (NEM) for endelig vurdering.

NTNU

Fakultet for medisin og helsevitenskap
Institutt for klinisk og molekylær medisin

Vår dato 07.06.2019
Deres dato

Vår referanse Kari Anne I. Evensen
Deres referanse

FORESPØRSEL OM DELTAKELSE I FORSKNINGSPROSJEKTET

LAV FØDSELSVEKT I ET LIVSTIDSPERSPEKTIV

Vi ønsker å finne ut hvordan det går med voksne som ble født med lav fødselsvekt. Dere som får dette brevet ble enten født for tidlig, eller til rett tid – med lav eller vanlig fødselsvekt. Mange av dere har deltatt i undersøkelser hos oss tidligere. Dette er et spørsmål om å delta nok en gang for å undersøke din helse og fungering. Studien vil gi ny kunnskap om voksne som er født for tidlig eller med lav fødselsvekt, som kan bidra til å forbedre tilbudet til de som trenger hjelp.

HVA INNEBÆRER PROSJEKTET?

Studien innebærer å besvare spørreskjema (ca. 1,5 time), ett oppmøte ved St. Olavs hospital (ca. 4 timer) og utføring av noen oppgaver for reaksjonsevne og hukommelse hjemme på pc/nettbrett (ca. 35-45 min). Spørreskjemaene handler om psykisk og fysisk helse, familie, utdanning og arbeid. Oppmøte ved St. Olavs hospital innebærer en kort medisinsk undersøkelse (30 min) for måling av høyde, vekt, kroppssammensetning og blodtrykk og en undersøkelse av lungefunksjon (30 min). Videre vil synsfunksjon, bilde av øyets netthinne og hornhinne samt måling av nerveaktivitet i netthinnen og synsbanene bli undersøkt av en øyelege (1-1,5 time). For de av dere som ble født for tidlig ønsker vi å hente opplysninger om øyeundersøkelse i nyfødtperioden fra sykehusjournalen. En fysioterapeut vil undersøke fin- og grovmotorisk funksjon (1 time), og sette på en aktivitetsmåler på forsiden av låret og en på øvre del av ryggen som du skal ha på i en uke. Disse vil ikke begrense din daglige aktivitet, og du kan dusje som normalt.

Disse aktivitetsmålerne vil kunne fortelle hvordan du har brukt kroppen din denne uken, for eksempel hvor mye du har løpt, sittet eller ligget i ro, og er de samme som er brukt i HUNT-undersøkelsen. Du sender dem tilbake til oss i en ferdigfrankert konvolutt.

Du vil få en unik BrukerID og et passord (4 sifferet pinkode) for å logge inn på pc/nettbrett for å utføre pc-oppgavene hjemme.

MULIGE FORDELER OG ULEMPER

Oppgaven din er å svare på spørsmål om deg selv, utføre noen tester og gå med aktivitetsmålere i 7 dager. Alle undersøkelsene er ufarlige og vil ikke medføre ubehag. Du vil få tilbakemelding om resultater av undersøkelsene. Hvis du trenger og ønsker helsehjelp, kan du få henvisning til riktig helsetjeneste. Du vil få 500 kr for utfylling av spørreskjema, oppmøte og aktivitetsmåling i en uke, gratis undersøkelse hos øyelege, og ytterligere 200 kr for utføring av oppgaver hjemme på pc/nettbrett. I tillegg dekkes reiseutgifter.

FRIVILLIG DELTAKELSE OG MULIGHET TIL Å TREKKE SITT SAMTYKKE

Det er frivillig å delta i prosjektet. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side, og leverer det ved oppmøte hos oss. Selv om du samtykker, kan du la være å svare på enkeltspørsmål i spørreskjema. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke. Dersom du trekker deg fra prosjektet, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner. Dersom du senere ønsker å trekke deg eller har spørsmål til prosjektet, kan du kontakte Kari Anne I. Evensen, tlf. 977 33 635, karianne.i.evensen@ntnu.no.

HVA SKJER MED OPPLYSNINGENE OM DEG?

Opplysningene som registreres om deg skal kun brukes slik som beskrevet i hensikten med prosjektet. Du har rett til innsyn i hvilke opplysninger som er registrert om deg og rett til å få korrigert eventuelle feil i disse opplysningene. Du har også rett til å få innsyn i sikkerhetstiltakene ved behandling av opplysningene.

Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger gjennom en navneliste. Det er kun prosjektleder og prosjektkoordinator som har tilgang til denne listen. Det vil ikke være mulig å identifisere deg når resultatene offentliggjøres. Hvis du har deltatt tidligere i denne studien, ønsker vi å sammenholde tidligere og nåværende opplysninger.

DELING AV DATA OG OVERFØRINGER TIL UTLANDET

Ved å delta i prosjektet, samtykker du også til at opplysninger og bilder av netthinnen kan overføres til samarbeidspartnere nasjonalt eller i utlandet som ledd i forskningssamarbeid og publisering. Det kan gjelde land i Europa, og dessuten USA, Canada, Australia eller New Zealand. Dette kan være land med lover som ikke tilfredsstiller europeisk personvernlovgivning. Prosjektleder vil sikre at dine opplysninger blir ivaretatt på en trygg måte. Koden som knytter deg til dine personidentifiserbare opplysninger vil ikke bli utlevert.

FORSIKRING

Pasientskadeloven gjelder for din undersøkelse ved St. Olavs hospital.

OPPFØLGINGSPROSJEKT

Det kan bli aktuelt å invitere deg til nye undersøkelser i denne langtidsstudien.

ØKONOMI

Prosjektet er finansiert av NTNU og Felles forskningsutvalg St. Olavs hospital/NTNU.

GODKJENNING

Regional komité for medisinsk og helsefaglig forskningsetikk har vurdert prosjektet, og har gitt forhåndsgodkjenning (Saksnummer 2013/636).

Etter ny personopplysningslov har dataansvarlig instituttleder Torstein Baade Rø og prosjektleder Kari Anne I. Evensen et selvstendig ansvar for å sikre at behandlingen av dine opplysninger har et lovlig grunnlag. Dette prosjektet har rettslig grunnlag i EUs personvernforordning artikkel 6a og artikkel 9 nr. 2 og ditt samtykke.

Du har rett til å klage på behandlingen av dine opplysninger til Datatilsynet.

KONTAKTOPPLYSNINGER

Dersom du har spørsmål til prosjektet kan du ta kontakt med:

Prosjektleder: Kari Anne I. Evensen	e-post: karianne.i.evensen@ntnu.no	tlf: 977 33 635
Prosjektmedarbeider: Tora S. Morken	e-post: tora.s.morken@ntnu.no	tlf: 995 99 705
Prosjektmedarbeider: Asta K. Håberg	e-post: asta.haberg@ntnu.no	tlf: 902 59 146

Personvernombud ved institusjonen er Thomas Helgesen, thomas.helgesen@ntnu.no.

Vår dato Vår referanse

Norges teknisk-naturvitenskapelige universitet

JEG SAMTYKKER TIL Å DELTA I PROSJEKTET OG TIL AT MINE PERSONOPPLYSNINGER OG MITT BIOLOGISKE MATERIALE BRUKES SLIK DET ER BESKREVET

Sted og dato | Deltakers signatur

Deltakers navn med trykte bokstaver

Jeg bekrefter å ha gitt informasjon om prosjektet

Sted og dato | Signatur

Rolle i prosjektet

Physical fitness tests

Modified from ESTER study guide for physical fitness tests.

Updated 23.8.2019 by Marjaana Tikanmäki

Step test

Purpose:
To measure cardiorespiratory fitness with a submaximal test.

Exclusion from the test: See additional health questionnaire

Equipment:
2 bench steps (33 cm and 40 cm), metronome, stopwatch, heart rate monitor

Preparations:
- Set the bench on the appropriate height (women 33 cm, men 40 cm)
- Wind up and set metronome to 92 beats/min before each performance (the participant will be stepping on the bench 23 times/min)

Instructions:
"We measure cardiorespiratory fitness using step test during which the participant steps on and off a bench for 4 minutes paced by a metronome. Step on the bench using entire soles of feet. Heart rate is observed during the test."

- **Practice the sequence**: pace, posture (make sure knee and hip straighten out)

Test performance:
- Commands: READY – START! (0 min) …STOP! (4 min)
- Press split time button on the heart rate monitor at each of the three time points:
  1. The beginning of step test (0 min)
  2. The end of step test (after 4 min of stepping)
  3. The end of recovery time (after being seated for 2 min)
- Observe and instruct the participant on the right pace **(the right pace should be found during the first minute)**
- The end of step test (after 4 min of stepping): Record heart rate ___ ___ ___ beats/min into the forms and instruct the participant to be seated. The participant sits for exactly 2 min.
- After being seated for 2 minutes: Record heart rate ___ ___ ___beats/min into the forms.
- If the participant is not able to step on the bench for 4 minutes or fails to keep up the required pace, record heart rate and time at the end of stepping and write down comments to the clinical form.

Figure 1 Step test

Reference: Åstrand & Ryhming 1954. A nomogram for calculation of aerobic capacity (physical fitness) from pulse rate during sub-maximal work. J Appl Physiol 7(2):218-221.

Modified push-up test

Purpose:

To measure strength and endurance capacity of extensor muscles in arms and the ability of upper body muscles to stabilise the trunk.

Exclusion from the test:

Contraindications are symptoms of cardiorespiratory disease, difficult low back and arm pain that could be worsened by the test movement. Record them in the clinic form.

Equipment:

Stop watch, gymnastics mat

Instructions:

The examiner shows the performance (Figure 1). **The phases of the push-up are practiced once** before the 40-second test performance. One test performance is included in the test.

Starting position: The participant lay prone on a mat, places hands close to the shoulders, feet hip-width apart, toes firmly on a mat.

"Clasp hands behind your back (or your bottom if you don't reach your hands). Bring your hands to the shoulder-level. Push yourself to a straight leg push-up such that your arms and elbows are completely straight (hip and knees come off the floor simultaneously). In this position, touch either of the hands with the other and return to the push-up position and return down on the mat. Start a new push-up by clasping your hands behind your back. Make as many push-ups in 40 seconds as possible."

Test performance:

Stop watch is started when hands clasp behind the back for the first time. In the end of 40 seconds the last performed push-up is the one where the participant pushed arms and elbows straight up.

Test result:

The number of correctly performed push-ups in 40 seconds. The result is 0 if the participant cannot push up on straight arms at all.

Reference values:

Modified pushup (number of completed push-ups/40 s) women and men. There are no reference values for younger age group.

WOMEN	Age group (years)		
Fitness class	**31-40**	**41-50**	**51-60**
5	≥ 14	≥ 13	≥ 11
4	11 – 13	11 – 12	9 – 10
3	10	10	7 – 8
2	9	8-9	5 – 6
1	≤ 8	≤ 7	≤ 4

MEN	Age group (years)		
Fitness class	**31-40**	**41-50**	**51-60**
5	≥ 17	≥ 16	≥ 14
4	15 – 16	14 – 15	13
3	13 – 14	12 – 13	11 – 12
2	11 – 12	10 – 11	8 – 10
1	≤ 10	≤ 9	≤ 7

Fitness class:

5 = clearly above average
4 = somewhat above average
3 = average
2 = somewhat below average
1 = clearly below average

Reference: Testaajan opas. UKK-terveyskuntotestit keski-ikäisille. UKK-instituutti, 2005.
Suni J et al. (1996). Health-Related Fitness Test Battery for Adults: Aspects of Reliability. Arch Phys Med Rehabil. 77(4):399-405.

1. Starting position:
- Lie prone on a mat
- Hands close to the shoulders
- Toes on the mat
- Feet hip-width apart

2. Clasp hands behind your back (or your bottom, if you don't reach)

3. Return to starting position

4. Perform a straight-leg push-up with elbows completely straight in the vertical position
- Trunk straight
- Hip and knees come off the floor simultaneously

5. Touch one hand on top of the supporting hand,

6. Return to the up position

7. Return to the prone position

Make as many push-ups in 40 seconds as possible!

Figure 2 Modified push-up test

Hand grip strength

Purpose:

To measure maximal isometric strength of hand and forearm muscles.

Exclusion from the test:

Contraindications for the test are injury or disease that could be worsened by the test. If either or both of the hands are not tested, the reason is recorded in the clinical form.

Equipment:

Chair, hand dynamometer (Jamar)

Preparations and instructions:

Enquire which hand is dominant (the one participant uses for writing) and record it in the clinic form.

The handle size is being set at position 3 for women and position 4 for men.

Ask the participant to sit in a chair with:

- straight back
- feet flat on the floor
- upper arm unsupported and aligned with the trunk
- elbow flexed at 90° degrees
- forearm and wrist in neutral position

Test performance:

Grip strength will be measured in both hands starting with the dominant hand.

The participant squeezes the handle as tight as possible for 3-5 seconds. Every participant should be cheered similarly. During measurement, elbow and wrist position is maintained.

Commands: *"Are you ready? READY – START/NOW! SQUEEZE – SQUEEZE – SQUEEZE – that's enough".*

Measurement is repeated three times for after 30 second recovery.

Repeat similarly for the measurement of non-dominant hand.

Figure 3 Handgrip test

Test result:

The best of three measurements of dominant and non-dominant hands are used in analysis.

Reference: Suni J et al 2014. Retest repeatability of motor and musculoskeletal fitness tests for public health monitoring of adult populations. J Nov Physiother 4(1):1000194. Based on EHES Manual, Part B. Fieldwork Procedures, 2nd edition (2016), Available at: http://urn.fi/URN:ISBN:978-952-302-701-5.

EARLY HUMAN DEVELOPMENT

An international journal concerned with the continuity of fetal and postnatal life

AUTHOR INFORMATION PACK

TABLE OF CONTENTS

ISSN: 0378-3782

DESCRIPTION

Established as an authoritative, highly cited voice on **early human development**, *Early Human Development* provides a unique opportunity for researchers and clinicians to bridge the communication gap between disciplines. Creating a forum for the productive exchange of ideas concerning early **human growth** and **development**, the journal publishes original research and clinical papers with particular emphasis on the continuum between **fetal life** and the **perinatal period**; aspects of **postnatal growth** influenced by early events; and the safeguarding of the quality of **human survival**.

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Clinicians and Researchers concerned with the continuity of fetal and postnatal life.

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GUIDE FOR AUTHORS

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[dataset] [6] M. Oguro, S. Imahiro, S. Saito, T. Nakashizuka, Mortality data for Japanese oak wilt disease and surrounding forest compositions, Mendeley Data, v1, 2015. https://doi.org/10.17632/xwj98nb39r.1.
Reference to software:
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