AALBORG UNIVERSITY

Follow up of children born Small for Gestational Age without catch-up growth at 4 years old at Aalborg University Hospital

Masters project
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Abstract

Baggrund
Børn født med en fødselsvægt eller længde sv.t mindre end -2 standard deviationer defineres som Small for Gestational Age (SGA) (1,2). Hvis disse børn ikke opnår „Catch-Up Growth" inden 4 års alderen, kan de henvises og vurderes m.h.p. behandling med væksthormon (2,3). Hvis disse børn ikke henvises, er der risiko for at de kan udvikle forskellige følgesygdomme som er associerede med at blive født SGA. De har desuden en øget risiko for at blive afvist af jævnaldrede, have lavt selvværd, mangle selvtillid og har større risiko for social isolation (2,4–6).

Formål
Vi undersøger hvor mange børn der blev født SGA i Region Nordjylland mellem 1. Oktober 2016 og 30. September 2017, der ikke opnåede catch-up growth, og hvilke af disse børn, der blev henvist til pædiatrisk undersøgelse i fire årsalderen.

Metode
Vækstkurver, udgivet af Maršál et al. (7) blev anvendt til at evaluere fødselsvægten af alle børn født i Region Nordjylland mellem 1. Oktober 2016 og 30. September 2017. Data var udtrukket fra regionale databaser og efter ekskludering af udlandske borgere, afdøde børn, børn med syndromer samt fjernelse af alle dobbeltregistrerede CPR-numre, fik 213 familier tilsent et digitalt spørgeskema, hvor de blev spurgt ind til barnets højde ved forskellige aldre og forældrenes målte højde i voksenalderen.

Resultater
Ud af de 213 som fik tilsendt spørgeskema, svarede kun 40. 37 svare var brugbare og 7 af dem viste sig at være børn der ikke havde nået catch-up growth. Ud af de 7 fandt vi 2 der kunne eventuelt kvalificeres til GH behandling som ikke var henvist til pædiatrisk evaluering

Fra børnenes journaler fandt vi, 116 børn der ikke var henvist og deres højde ved 4 års alderen var ukendt. 81 børn som havde nået catch-up growth var ikke henvist. 11 børn med catch-up growth var henvist, 4 børn uden catch-up growth var henvist og 8 børn uden catch-up growth var ikke henvist (table 1)(figure 2).

Har børnene været henvist?		
Henvist, med catch-up	11	5%
Henvist, uden catch-up	4	1,8%
Henvist, ukendt højde	0	0%
Ikke henvist, med catch-up	81	36,8%
Ikke henvist, uden catch-up	8	3,6%
Ikke henvist, ukendt høje	116	53%

Table 1: hvor mange børn var henvist og registrering af catch-up growth

Konklusion
Denne undersøgelse bekræfter, at nogle børn født SGA, ikke er henvist til pædiatrisk vurdering. Men antallet af disse børn og årsagen bag de manglende henvisninger er stadig ukendt. Denne undersøgelse giver ikke en tilstrækkelig repræsentation af undersøgelsespopulationen p.g.a. den lave svarprocent på spørgeskemaet. Registreringen og deling af vækstdata mellem forskellige områder af sundhedsvæsenet er utilstrækkeligt til at monitorere disse børn ordentligt.

Abstract

Background

Children born with a birth weight or lenght less than -2 standard deviations are defined as small for gestational age (1,2). If these children do not reach catch-up in growth before the age of 4 they might qualify for treatment with growth hormone (2,3). If the children that would qualify for the treatment are missed by health care professionals the risk is that these children might develop various comorbidities, have a hard time coping with the physical environment, are at increased risk of being rejected by peers, have low self esteem, lack confidence and are more prone to social isolation (2,4–6).

Aim

In this study we investigate children that were born SGA in the Northern Jutland region of Denmark between 1. October 2016 and 30. September 2017. We want to find out how many of them that did not reach catch-up in growth and might therefore qualify for treatment with growth hormone, were referred to pediatric evaluation by the age of four.

Method

A growth curve published by Maršál et al. (7) was used to evaluate the birthweight of all children born in the Northern Jutland region between 1. October 2016 and 30. September 2017. Data was extracted from regional databases and after exclusion of foreign citizens, deceased children, children with identifiable syndromes and CPR numbers that were double registred, 213 mothers of children born SGA were sent a digital questionnaire asking about the child‘s height at various ages and the parents‘ measured height as adults.

Results

Out of the 213 questionnaire candidates, only 40 answered. 37 answers were useable and 7 of them included children that have not reached their catch-up growth. Out of the 7, we found 2 that might be eligible for GH treatment and have not been referred for paediatric evaluation.

From the children’s medical journals, we found that 116 children were not referred and with unknown height. 81 were not referred but with catch-up, 11 children were referred and with catch-up, 4 were referred and without catch-up and 8 children were not referred and had not reached catch-up (table 2)(figure 2).

Have the children been referred?		
Referred, with catch-up	11	5%
Referred, without catch-up	4	1,8%
Referred, unknown height	0	0%
Not referred, with catch-up	81	36,8%
Not referred, without catch-up	8	3,6%
Not referred, unknown height	116	53%

Table 2: how many children were referred and registration of catch-up growth

Conclusion

Although this study confirms that some children that might qualify for growth hormone treatment are missed by health care professionals, the number of children and the reason for this missed oppurtunity is still unknown. The study does not offer a sufficient representation of the study population due to poor participation. The registration and flow of growth data between different fields of the health care system is inadequate to properly monitor these children.

Introduction

Children born with a birth weight or length less than 2 SD (standard deviations) are defined as Small for Gestational Age (SGA) (1,2). It is important to ensure that these children obtain catch-up in growth by the age of four(1). „Catch-up growth“ is a term used for a physiological process where the child‘s growth rate accelerates causing the standard deviation score (SDS) to improve to above -2SD (2,3,8). If catch-up growth is not reached by this age the child should be assessed by a pediatrician and evaluated for possible treatment with growth hormone (GH). Until that age there is a possibility of spontaneous catch-up growth, especially in premature children (9). The aim of therapy with GH is to increase the height velocity (HV) and normalization of height standard deviation (9,10). The suspicion might be raised that children born SGA without catch-up growth are missed by health care professionals and therefore miss the opportunity of GH treatment and might have short stature as adults. SGA children are in the care of several doctors during their childhood – some of them see a neonatologist, their general practitioner or go to the pediatric department for different reasons. This can easily cause the exchange of information between healthcare professionals to be inadequate and can result in children being referred to a pediatric endocrinologists too late.

Causes and comorbidities

Causes of SGA vary but have been associated with maternal lifestyle, obstetric factors and placental dysfunction (2,11). Consequences for the child born SGA can be disturbances in glucose and lipid metabolism, poor bone density and abnormal onset of puberty (2,4). SGA has also been associated with fetal abnormalities such as a number of syndromes and congenital malformations (5) and a number of comorbidities later in life (12,13). Comorbidities such as obesity, hypertriglyceridemia, non-alcoholic fatty liver disease, hypercholesterolemia, diabetes and hypertension are all challenging metabolic alterations that are associated with SGA (12,13). It is though equally important to take into consideration the psychosocial distress that short stature in young people and adults can bring. Researchers have shown that young adults with significant short stature have a difficult time coping with the physical environment, are at increased risk of being rejected by peers, have low self esteem, lack confidence and are more prone to social isolation (6). The impact of treatment with growth hormone in children born SGA on factors other than their height such as metabolic alterations and type 2 diabetes has been studied (14,15), some researchers have found that further investigation is needed to confirm the benefits fully on these factors. In other studies, GH has proven to improve lipid, protein and glucose metabolism (14). The results from previous studies are promising and produce an urge for further research (15).

Treatment

At birth, the babies‘ weight, birth length and head circumference are registered. The measurements are evaluated using standardized growth curves (8). About 3,3% of all babies born in Denmark are SGA (3) and by the age of four, 90% of these children have reached catch-up in growth. The 10% that remain small, should be referred for pediatric evaluation where treatment with GH might be considered (2,16).

Criteria for growth hormone treatment of SGA children in Denmark (17)
1. **Absence of catch-up growth at 4 years of age**
2. **Height <2,5 SD**
3. **Height >1 SD under the target height SD**

Table 3: Criteria for growth hormone treatment in Denmark

When evaluating eligibility for treatment in children with absence of catch-up growth, there are factors that should be looked at e.g birth weight and rate of growth. Possible gene mutations such as Turners- or Downs syndrome should also be investigated as many syndromes are associated with short stature. Other causes of short stature such as delayed growth and puberty, hypothyroidism and coeliac disease should be excluded (18). Parents' height as adults is also of great importance when evaluating eligibility for treatment with growth hormone, because the genetic growth potential of the child could be lower than the average target height (19). Criteria for growth GH in Denmark are listed in table 3 (Table 3).

The desired effect of treatment of SGA children with GH is to increase GH levels and for the children to reach their target height, and potentially normalizing metabolism and psychosocial wellbeing. A Swedish study found that 86% of children that received GH treatment reached their target height (20). To compare, only 56% of untreated SGA children reached their target height (20). Another study showed that the increase in predicted adult height after 5 years of treatment with growth hormone ranged from 6,3 - 19,5 cm if the treatment was started before puberty (12). The treatment has proven to be more effective in younger, shorter and lighter children (20). This again confirms the importance of referring the children to pediatric evaluation at an early age.

A child's target height can be calculated using a simple formula (Equation 1). The predicted adult height, which is a more detailed estimation of the child's target height, can be calculated using the child's actual height, the parents' final height and the growth reserve (19). Growth reserve is assessed by taking an x-ray of the child's left hand to evaluate the bone age that corresponds to the child's biological age(19).

$$Girl\ target\ height = \frac{Father's\ height\ in\ cm + \ mother's\ height\ in\ cm - 13}{2}$$

$$Boy\ target\ height = \frac{Father's\ height\ in\ cm + mother's\ height\ in\ cm + 13}{2}$$

Equation 1: Calculation of target height(19).

Side effects of growth hormone treatment such as edema, pain at injection site and a rash have been reported (22). Other more serious side effects like early onset of puberty (21) and insulin resistance (23) are uncommon but the patient should be monitored closely with follow-up consultations during the treatment (21,24). In the follow-ups there should also be a registration of height, weight and compliance (18).

Although it is highly beneficial to find all the children that possibly need help with GH there is no guarantee that the parents accept treatment for the child. A recent study also shows that a large part of parents do not feel that they are involved in the process of making treatment decisions. This has led to poor adherence to the therapy and the children missing doses (25). Even if the treatment is accepted, an effective treatment can not be guaranteed, as variability of responses between individuals to GH is to be expected (26).

Aim

To our knowledge there is no study that has investigated how many SGA children without catch-up growth are referred in due time for pediatric evaluation of their growth. In this study we investigate how many children, born SGA in the Northern Jutland Region between 1. October 2016 and 30. September 2017 - that did not reach catch-up growth were referred to pediatric evaluation by the age of four.

Method

Inclusion criteria for this study were children born between 1. October 2016 and 30. September 2017 with birth weight or length less than -2 SD for their gestational age (27). A growth curve published by Maršál et al. (7) was used to evaluate the birth weight. These growth curves are based on data from 4 Scandinavian centers and 759 ultrasonically estimated fetal weights (7).

Source and study population

Data was extracted from regional databases. 5562 babies were born in the region in the one-year timespan from 1. October 2016 until 30. September 2017. From that population 247 children were born SGA (Figure 1) according to their weight and/or height and 5 children were born SGA only according to their height. After excluding foreign citizens and exclusion of those not able to receive the questionnaire (Figure 1), the parents of the remaining children were sent an electronic questionnaire (Appendix 1) asking about the children's height and weight at 2, 3 and 4 years of age. They were also asked if the children had any known illnesses and asked to provide the parents' measured height. 213 families were sent the digital questionnaire.

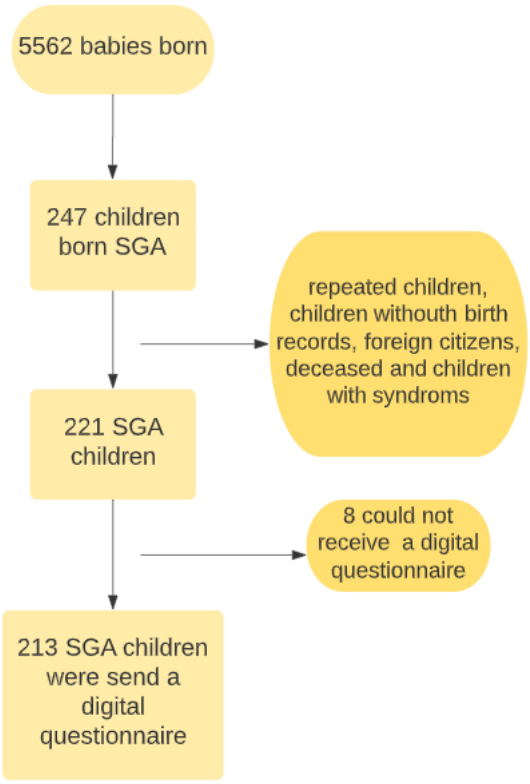

Figure 1: Flowchart of SGA children that qualified for the study

Data collection

Added to the information from the digital questionnaire, data was also retrieved from the children's medical journal that is accessible to hospital personnel. Redcap was used to manage and store the database and for designing and collecting answers from the digital questionnaire. In the medical journal it is stated if the child has been referred to the paediatric department for evaluation of growth parameters. For some children precise height and weight measurements, measured at the hospital was registered in the medical journal (figure 2). When the children are born, they are diagnosed SGA according to their weight and/or height. When assessing if the child was eligible for evaluation for GH treatment at 4 years old, only their height was evaluated.

Statistics

The results were obtained by manually calculating the percentages of each subgroup from our 2 sources – the questionnaire and the medical journals. The statistics from the questionnaire are described in Table 4 and the statistics from the medical journals are shown in Figure 2.

Results

In our study there were 247 children born SGA in the Northern Jutland region in the time span from 1. October 2016 – 30. September 2017. This means that 4,4% of all children born in the region were SGA. A digital questionnaire was sent to 213 families of children born SGA. Out of those 213 candidates only 40 answered the digital questionnaire. 37 answers were complete. From the 37 answers, 6 had various conditions such as asthma and gastric symptoms - though none of the children had the same condition. The growth information from the questionnaire was crosschecked with the measurements from the health journal and were found to match.
The answers show that 7 children have not reached their catch-up growth (-2SD) which makes out 18,9 % of usable answers (table 4). Out of those 7 that remain small, 2 might have been eligible for GH treatment (height less than -2,5SD) and neither of them had been referred for paediatric evaluation. The answers also revealed that only 2 of the 37 children had been referred but both of them had reached catch-up growth before the age of 4 (table 4).

Adding to the data we obtained from the digital questionnaire, the children‘s medical journals were also looked at to see if we would find how many of the SGA children were referred for evaluation with a pediatric endocrinologist (figure 2). The data in the medical journal was not sufficient to answer all the questions we needed for this survey. The height and weight of some children was registered at various ages and information on how many children were referred to the pediatric department for evaluation of growth parameters. From this information we found a few children that had registered height that showed they had reached catch-up growth before the age of 4 (figure 2). Most of the them or 116 children (53%) did not have sufficient, if any, registered height and had not been referred. 81 children (36,6%) had registered height that showed they had reached catch-up growth before the age of 4 and were never referred. 11 children (5%) had been referred and obtained catch-up before they reached 4 years of age. 4 (1,8%) had not reached catch-up before the age of 4 and had been referred. Finally 8 children (3,6%) had not reached catch-up before the age of 4 and had not been referred for reasons unknown (Figure 2).

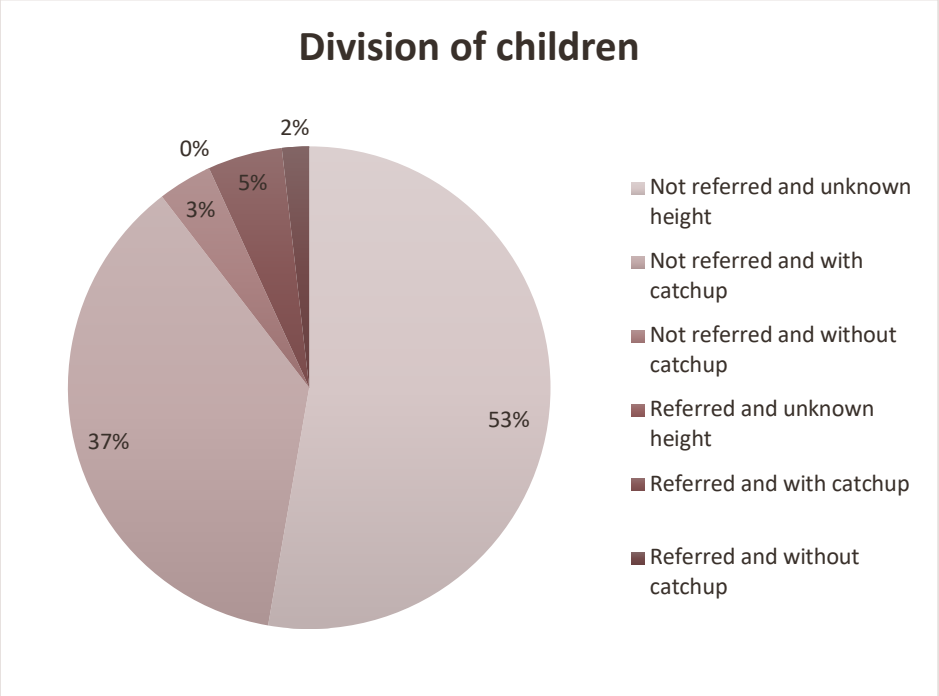

Figure 2: Not referred, unknown height: 116 children (53%), Not referred, without catch-up: 8 children (3,6%), Referred, with catch-up: 11 children (5%), not referred, with catch-up: 81 (36,8%), Referred, unknown height: 0, Referred, without catch-up: 4 children (1,8%)

	SD	Did not reach Catch-up growth?	Referred to a pediatric endocrinologist?	Might Qualify for treatment?	Received gowth hormone treatment?
1	+0,64		X		
2	-0.61				
3	+0,35				
4	+0,46				
5	+0,39				
6	+0,9				
7	-1,15				
8	-2,45	X			
9	+1,14				
10	+0,64				
11	-0,38				
12	-1,15				
13	-0,38				
14	-1,66				
15	-2,42	X			
16	-1,5		X		
17	-3,04	X		X	
18	-0,89				
19	+1,66				
20	-1,11				
21	+1,66				
22	+0,13				
23	-2,17	X			
24	-1,61				
25	+1,15				
26	+1,66				
27	-2,48	X			
28	+1,15				
29	-0,64				
30	+0,64				
31	-2,61	X		X	
32	-2,17	X			
33	-1,53				
34	-0,64				
35	+1,41				
36	+0,39				
37	-0,89				
Total:		7	2	2	0

Table 4: Results. 7 children did not reach catch-up growth (>-2 SD) and non of them had been referred. 2 children were referred but both of them had reached catch-up growth. 2 children might qualify for GH treatment (>-2,5 SD) and no child had received GH treatment.

Discussion

The strength of this study is the completeness of the cohort, as we were able to include every child born in the Northern Jutland region from 1. October 2016 – 30. September 2017. The validity of the data was substantial, because we based it on the personalized Danish identification number (CPR number) (3). A survey method (digital questionnaire) was favorable in this research as the purpose was to gather precise and quantitative information from the parents relatively quickly (28). When asking parents about height and weight of their children at different ages, the survey method gave the parents time to gather this information, making it more accurate than if asked in an interview. One of the limitations of this study is the small number of participants. In the beginning, the aim was to use a data set of 5 years but 1 year had to suffice due to lack of data authorization and the criteria that the children had to have reached the age of 4 to be included. This being a quality assurance project that only allowed us to collect data from the past 5 years. Another limitation of this study is the low number of answers to our questionnaire, we only received 40 answer sheets, some of them only partially answered. It can also be put into question if the growth data we asked for in the questionnaire was accessible enough to the participants, and if they were motivated enough to answer (29). When asking the participants something that is not easily accessible, in a non-mandatory and in a non-incentive survey – the risk is non-response bias (30). Meaning that a poor participation, can lead to a less representative sample of the population (31). Even though the participation and thus number of answers were low, the results are striking. If we hypothetically apply the numbers to the rest of children born SGA, assuming that the non-responders have the same height distribution as the responders, we would expect that about 47 children would not have reached catch-up growth by the age of 4 and about 13 children might qualify for a treatment they are not offered. For Denmark this would mean that annually around 3294 children born SGA, that might qualify for GH treatment, are missed by health care professionals. These are just speculations but certainly a reason to investigate this matter further.

When looking at children‘s medical journals, it can be hypothesized why some of the children’s measurements are missing and why there are so few referrals to the paediatric department. Due to the Covid Sars Cov-2 outbreak in Denmark in the year of 2020, there was a hiatus of physical checkups at some general practitioners for children and instead it was in the parent’s hands to measure their child at 3 and 4 years old. This could possibly have caused unreliable measurements and/or inadequate response of the responsible professional to the results, as the consultation was solely held over the telephone. Future research will undoubtedly take on the topic of diminished children's health-care during the Covid Sars Cov-2 pandemic. It is also plausible that because some of the children in the group have just turned 4, they have yet to be referred.

If this research should be repeated in the future we would like to include a larger number of children. Unlimited access to data from primary physicians and collaboration with other departments, other regions in Denmark or even other countries would give a better overview of the state of this matter (32). A better result could be obtained by seeking authorization to access health data from all healthcare facilities concerning the child. If the survey method would be repeated, it could be beneficial to follow up with a telephone call to clarify unclear survey responses (28) and it could also be beneficial to add some kind of incentive to increase response rate, for example a money prize or a lottery ticket (29).

Our hope for the future of children that are born SGA is that parents and health care professionals realize the importance of taking action and evaluating height and weight measurements of children. The measurements are easy and non time consuming but the value of them, especially for children born SGA, might be overlooked. In the process of retrieving data from the medical journals of the children for this study we often saw that children without catch-up at around 4 years of age were referred to a department for other issues than their height. The measurements of these children were taken and made available but there was no remark or interpretation of them from the health care professional that noted these measurements. The importance of growth curves should be emphasized as they are a clear indicator of whether there is a timely catch-up growth or not. It is also important to ensure the accessibility of growth information for both patients and physicians. As of today, hospitals in Denmark do not have access to data from primary care physicians and this can cause a big void in patient care. We feel a joint database with growth data of children would be highly beneficial to healthcare.

Conclusion

In concluding our research, we are still left with some questions unanswered. Although this study can confirm that there are SGA children who have not reached catch-up in growth, and are not being acknowledged - the reasons are unknown. We still do not know how many children are in fact missed by healthcare professionals. While the study does not offer a sufficient representation of the study population due to poor participation, the results confirm our suspicion of missed SGA children and lack of referral to the paediatric department when needed. By looking at medical journals we can see a need in monitoring the weight and height of the SGA children and/or an all accessible growth-database. It would be highly valuable to conduct further research on this matter.

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Appendix 1

Kære forældre

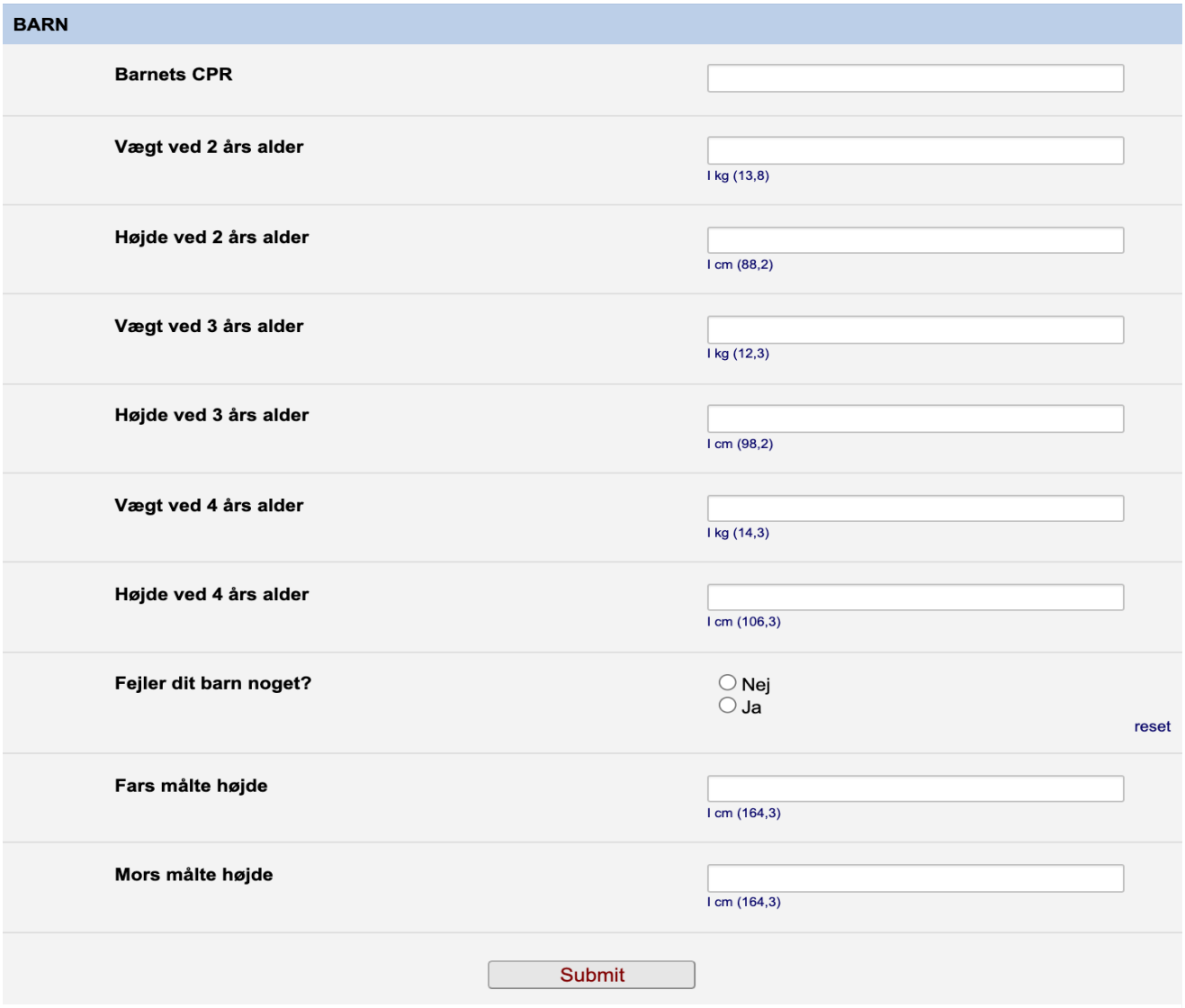
Vi er to medicinstuderende fra Aalborg Universitet, der arbejder med et kvalitetssikringsprojekt omkring børn født SGA (Small for Gestational Age). Det betyder man var meget lille da man blev født sammenlignet med gennemsnittet af børn født på dette tidspunkt i graviditeten. Ca. 3% af alle børn fødes små for alderen, og vi undersøger lige nu, om disse børn, har indhentet deres forventede højde ved 4 års alderen. Det gør langt de fleste børn.

Da I tilbage i 2016 eller 2017 fik et barn, der var lille ved fødslen, vil vi gerne bede om jeres hjælp.

Vi vil bede jer udfylde spørgeskemaet via nedenstående link. Det er nogle få spørgsmål omkring jeres barns højde ved 4-års alderen/indtil 4 års alderen samt jeres egen højde i voksenalderen. Alle oplysninger behandles helt anonymt.

På forhånd mange tak for jeres hjælp. I er velkomne til at kontakte os hvis I har nogle spørgsmål til projektet.

Med venlig hilsen



Appendix 1: The survey sent out to the parents