Hearing loss, otitis media with effusion and obstructive sleep apnea in children with Down syndrome

Marit Erna Austeng

University of Oslo, 2013
To Zoe’ and Noah

A child's laughter could simply be one of the most beautiful sounds in the world.

-unknown
Contents

Summary ............................................................................................................. 5
Acknowledgement ............................................................................................. 7
List of papers ....................................................................................................... 9
Abbreviations ..................................................................................................... 10
Introduction ....................................................................................................... 11

Background ....................................................................................................... 13
  Predisposing factors for otorhinolaryngologic disease .................................. 14
  Otorhinolaryngologic disease in children with DS ........................................ 15
  Hearing loss .................................................................................................. 16
  Otitis media with effusion (OME) ................................................................. 19
  Obstructive sleep apnea (OSA) ................................................................. 20
  Treatment guidelines and follow up ......................................................... 22

Aims .................................................................................................................. 23

Material and Methods ....................................................................................... 24
  Study design ................................................................................................. 24
  Study population ....................................................................................... 24
  Investigations ............................................................................................... 25
  Parental questionnaire ............................................................................... 25
  Prevalence .................................................................................................. 25
  Definitions of hearing loss ......................................................................... 26
  Pure tone audiometry ................................................................................ 26
  Play audiometry ........................................................................................ 26
  Definition of otitis media with effusion (OME) ....................................... 27
  Definition of obstructive sleep apnea (OSA) ........................................ 27
  Polysomnography (PSG) .......................................................................... 28
  Statistics ...................................................................................................... 28
  Ethical considerations ............................................................................... 29

Results .............................................................................................................. 30
  Summary paper I ........................................................................................ 30
  Summary paper II ....................................................................................... 31
  Summary paper III ...................................................................................... 32

Theoretical issues .............................................................................................. 33
  Hearing loss ................................................................................................. 34
  Otitis media with effusion (OME) ............................................................ 34
  Obstructive sleep apnea (OSA) ............................................................... 35
  Developmental issues ............................................................................... 36
  Ethical issues .............................................................................................. 36
<table>
<thead>
<tr>
<th>Methodological issues</th>
<th>38</th>
</tr>
</thead>
<tbody>
<tr>
<td>The design</td>
<td>38</td>
</tr>
<tr>
<td>Study population</td>
<td>38</td>
</tr>
<tr>
<td>Random errors</td>
<td>39</td>
</tr>
<tr>
<td>Systematic errors</td>
<td>39</td>
</tr>
<tr>
<td>Selection bias</td>
<td>39</td>
</tr>
<tr>
<td>Selection bias of the OSA study</td>
<td>40</td>
</tr>
<tr>
<td>Recall bias</td>
<td>40</td>
</tr>
<tr>
<td>The problem of volunteers in a study</td>
<td>41</td>
</tr>
<tr>
<td>Unmeasured confounders</td>
<td>41</td>
</tr>
<tr>
<td>Conclusion and contributions of this study</td>
<td>42</td>
</tr>
<tr>
<td>Future aspects</td>
<td>44</td>
</tr>
<tr>
<td>References</td>
<td>46</td>
</tr>
</tbody>
</table>
Summary

Down syndrome (DS) is the most common chromosome abnormality in humans. It is typically associated with a particular set of facial characteristics due to the altered craniofacial anatomy, and with cognitive retardation. The hypotrophy of the craniofacial anatomical structures in combination with soft tissue alterations is suggested to increase the susceptibility to certain otorhinolaryngologic diseases.

The overall aim of this thesis was to investigate the prevalence of hearing loss, otitis media with effusion (OME) and obstructive sleep apnea (OSA). These otorhinolaryngologic disorders may have a discernible impact on the cognitive development, in addition to hearing impairment, language development and sleep quality in children with DS, hence associated communication disorders.

Hearing is crucial for language development, social integration and participation in daily activities of life. Hearing impairment adds to the difficulties of understanding social setting and verbal communication particularly in children with DS, already affected by a cognitive retardation. Furthermore, OME contributes to hearing loss and may therefore also be associated with disorders in cognitive development and communication disorders. OME may cause long-term squeals with sclerosis of the ossicular chain, mastoid cells, and the tympanic membrane or perforation of the latter. OSA has received attention not only due to its impact on cardiovascular disease, metabolic syndromes but also the impact on cognitive capacity and school performance. Reduced sleep quality also affects the quality of life for the child itself and the families affected.

A national population based cross sectional study was initiated and children born in 2002 with DS were invited to participate. The prevalence of hearing loss, OME and OSA was assessed in these children at the age of 8.

We found a high prevalence of hearing loss, OME and OSA in children with DS born in 2002. Significant hearing loss was found in 35 % of the children, 40 % percent had OME and 63 % of the children showed moderate to severe OSA. We concluded that the children in this present study were under-diagnosed.

The study presented here reports high prevalence of hearing loss, OME, OSA and also lack of medical follow up during the first 8 years of life. Treatment guidelines, which encourage close monitoring of diseases in children with DS, are published in the international literature. The implementation of national guidelines concerning these otorhinolaryngologic related disorders in children with DS in Norway may lead to a greater focus and cooperation among health...
professionals; improve the medical follow up and ultimately somatic outcome of the children with DS.
Acknowledgement

This project was made possible by generous support and funding by the Association for the Hearing Impaired (HLF) through the Norwegian Extra Foundation for Health and Rehabilitation and Ostfold Hospital Trust.

My gratitude goes to Ostfold Hospital Trust Fredrikstad, my employer, Department of Research and Department of Head and Neck Surgery for the financial support during the initial period of the project and the practical support throughout the project period.

I would like to express my gratitude to the 8 Departments of Otolaryngology geographically spread throughout Norway for their positive attitude and for enabling the ENT examination of the respective children.

This work would not have been possible without the friendliness and professionalism offered by employees of the Otorhinolaryngology - Department of Lovisenberg Diakonale Hospital.

I would like to express my sincere gratitude to my primary advisor, Kari J Kvaerner, for your good spirit, persistence and for the encouragement. Thank you for sharing your academical knowledge and competence with me. I would also like to express my gratefulness for the invaluable friendly advice, understanding and patience on a personal level which has enabled me to appreciate these years and to complete my work.

I would like to thank to my second PhD advisor, Harriet Akre for being the door opener and introducing me to sleep medicine. Thank you for making the interesting clinical diagnostics possible and for the determined support throughout the clinical examination period. I am grateful that you have for shared your expertise, and attitude, for being a role model and letting me profit from your admirable focus on the patients combined with the strong will and capacity to enable research.

I want to express my gratitude for the expertise offered by Britt Øverland in the management of the sleep recordings and for sharing your outstanding knowledge and for the collaboration.

I am grateful for the kindliness and competent audiological examination conducted by Jorunn Solheim and colleagues and for the excellent cooperation with the staff members at the TAKO – Centre, especially by Els-Mari Andersson, and Stefan Axelson.

I will always be thankful to my former Head of Department, chief and college Lars Sponheim for support, and for believing in this project. I am grateful for the opportunity to
learn from you, I thank you for your understanding and patience and for teaching me the basics of otolaryngologic surgery.

I would like to thank Kari Anne B. Næss PhD –ISP, UiO for the collaboration in the initial phase of the project and the encouragement throughout the PhD period. Also Eva-Signe Falkenberg for the fruitful work and help with funding of the project, and for your kind advises critical remarks and cooperation in the writing process.

I want to express my gratitude to Michael Abdeelnoor PhD for the statistical expertise and for sharing your epidemiological thoughts and aspects with me.

Further I would like to thank parents and children who have volunteered to participate and to make this project possible.

I am most grateful for the academical advice from my brother, Andreas Austeng, my sister Dordi Austeng and brother in law Hans Stenoien, and also for your persistent support and care for my family. I also thank my parents for providing unconditional support and encouragement.

I am grateful for good laughs, enjoyable lunch meetings, and fruitful discussions throughout the PhD period with Hege, Stine, Lise, Lars Petter, Anders; former and present Phd students at Ostfold Hospital Trust, and the colleagues at the department of Quality and Research.

A very special thank you to colleague and PhD student Hege Hølmo Johannessen for the shared hours, caring attitude and academical discussions.

I appreciated the support of friends in Oslo and Fredrikstad, over the last three years. I feel a special gratitude to those who have given the children extra attention and care; Anne and Morten Holum, and Lene and Morten Oksmo. Thank you.

I would like to express my gratitude to Will, for supporting my wish to conduct this work, believing in me and reminding me that the profitable way to reach a goal is to do so step by step.

And last but not least, Thank You Zoe and Noah for being the best of all children. You have been patient and I am grateful.
List of Papers

This thesis is based on the following papers which are referred to in the text by their roman numerals.

I. Hearing level in children with Down syndrome at the age of eight
   Marit Erna Austeng, MD, Harriet Akre, MD, PhD, Eva-Signe Falkenberg, PhD, Britt Øverland, MSc, PhD, Michael Abdelnoor MPH, PhD, Kari Jorunn Kværner, MD, PhD, MHA

II. Otitis media with effusion in children with Down syndrome
    Marit Erna Austeng, MD, Harriet Akre, MD, PhD, Britt Øverland, MSc, Eva-Signe Falkenberg, PhD, PhD, Michael Abdelnoor MPH, PhD, Kari Jorunn Kværner, MD, PhD, MHA

III. Obstructive sleep apnea in younger school children with Down syndrome
    Marit Erna Austeng, MD, Britt Øverland, MSc, PhD, Kari Jorunn Kværner, MD, PhD, MHA, Els-Marie Andersson, DDS, PhD, Stefan Axelsson, DDS, PhD, Michael Abdelnoor, MPH, PhD, Harriet Akre, MD, PhD.
# Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI</td>
<td>Apnea Hypopnea Index</td>
</tr>
<tr>
<td>AOM</td>
<td>Acute Otitis Media</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>CPAP</td>
<td>Continuous Positive Airway Pressure</td>
</tr>
<tr>
<td>DS</td>
<td>Down Syndrome</td>
</tr>
<tr>
<td>dB HL</td>
<td>decibel Hearing Level</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>kHz</td>
<td>kilo Hertz</td>
</tr>
<tr>
<td>OAI</td>
<td>Obstructive Apnea Index</td>
</tr>
<tr>
<td>ODI</td>
<td>Oxygen Desaturation Index</td>
</tr>
<tr>
<td>OME</td>
<td>Otitis Media with Effusion</td>
</tr>
<tr>
<td>OSA</td>
<td>Obstructive Sleep Apnea</td>
</tr>
<tr>
<td>PSG</td>
<td>Polysomnography</td>
</tr>
<tr>
<td>PTA</td>
<td>Pure Tone Average</td>
</tr>
</tbody>
</table>
Introduction

Down syndrome (DS) is a craniofacial syndrome caused by an aneuploid genetic disorder with an extra chromosome 21. This third chromosome is either translocated to chromosome 14, or found as triplet of chromosome 21. A mosaic of cell lines appears in 1 - 2% of the children and these children presents with a milder appearance of syndrome associated features (1). DS occurs once in every 600 to 750 births (2-4), making it the most common genetic disorder in newborn children. During the last decades, new therapies in the management of cardiac and intestinal malformations have been implemented, and neonatal care has developed with provisions of intensive care unit treatment. This has improved the outcome in somatic health and increased life expectancy in children with DS (5, 7).

![Down syndrome, translocation and trisomy.](image)

Owing to the longer life expectancy, otorhinolaryngologic related diseases, amongst others, have gained importance in the management of DS. Some otorhinolaryngologic diseases such as hearing loss, otitis media with effusion (OME) and obstructive sleep apnea (OSA) are associated with communication disorders. Children with DS have a special need for optimal hearing, due to the presence of language disability with phonological difficulties of conversational speech,
and cognitive impairment (1, 8-12). Disorders like hearing loss, otitis media and OSA have a negative effect on the ability to concentrate, the child’s capacity to learn and to achieve knowledge through the education offered to them (13-17). Treatment recommendations that have been published advocate a close follow up of hearing ability, OME and OSA (1, 11-12, 18-22).

We initiated this study to investigate the prevalence of hearing loss, OME and OSA in 8 year old children with DS to provide knowledge utilizable for health professionals. We also aimed to provide documentation of follow up for hearing loss, OME and OSA during the first 8 years of life.
Background

DS involves a set of common features due to the genetic abnormalities, however the children show great variation in somatic disease, language- and cognitive skills (1, 12, 23). Social and cognitive development and also behavior, is thought to be influenced by the load of somatic diseases, as well as the child’s environment at home and at school (24). In addition to medical follow up to ease the burden, and prevent further development of disease, it is important for children to develop communicative means to benefit from the social interaction involving shared activities. This is believed to trigger the further development of language and social skills, and prevent communication- and social impairment (8, 25).

In Norway, most children with DS attend regular schools to profit from integration and interact with typically developed children of same age. Many children with DS graduate from highschool, can do paid work, and some participate in post-secondary education (26). Education and proper care could improve quality of life significantly. Since education is highly dependent on speech acquisition in the primary education and thus on the ability to hear and concentrate, a high prevalence of hearing impairment, OME and OSA may contribute considerably to poor outcome.

Some factors may allow for improved cognitive and social development:
- Comprehensive learning conditions through improved ability to concentrate
- Optimized hearing capacity
- Social integration
- Thrive for regular kindergarten and school attendance through prevention of recurrent infectious disease and avoidance of frequent hospital appointments.

A higher prevalence of hearing loss, otitis media, OSA, and also other otorhinolaryngologic related diseases are reported in children with DS (1, 19). Hearing loss, OME and OSA have uncertain prevalence-estimates of 30 - 80 % depending on diagnostic methods and study design (19, 27, 28). However, the age related prevalence of disease in school children has not been studied and there are no interdisciplinary national guidelines or consensus of treatment and follow up of otorhinolaryngologic related diseases in children with DS in Norway. Hence we do not know to what extent school children with DS are burdened with hearing loss, OME and OSA, and the regularity and quality of medical care is not known.
Predisposing factors for otorhinolaryngologic disease

DS is a craniofacial syndrome with particular facial characteristics due to the anatomical alterations. In combination with hypertrophy of soft tissue these structural changes are suggested to predispose for otorhinolaryngologic related diseases (18).

Hypoplastic low set ears are often observed, and the external ear canals are narrow. The angle between the ear canal and the eardrum is oblique compared to angle in otherwise healthy children, in addition alterations to the ossicular chain are observed (19, 29-32). Hypotrophy of the bone structures of the upper and lower jaw causes a smaller oral cavity. In addition the hard palate in children with Down's syndrome appears narrow and vaulted and contributes also to a decrease in the volume of the oral cavity.

Mid-face hypoplasia with a contracted nasopharynx in combination with often observed hypertrophy of the adenoids causes a posterior obstruction of the nose. The nose is shorter with a flat nasal bridge, which provides to a flattened facial profile.

The main feature of the pharyngolaryngeal abnormalities is a reduced airway space (20, 29, 33-39).

Picture 1. Cephalogram of child with DS. Hypotrophy of the anatomical structures of the mid-face and hypertrophy of the adenoids in the epipharynx is shown.
A common symptom of DS is the general muscle hypotonia, which also involves the muscles of the upper airways (40, 41). This hypotonia affects the soft palate and combined with hypertrophy of lymphatic tissue also contributes to a reduction of the airway space. Eustachian tubes are suggested to be affected and may be a contributor to inadequate ventilation and drainage of the middle ears (31, 42, 43). The hypotonic tongue muscles combined with the relative macroglossia leads to a protrusion of the tongue which is also facilitated through the often observed obstructed nose and presence of mouth breathing (19, 44-47). Physiotherapy may strengthen the tongue muscles, prevent protrusion and improve the ability to produce oral language. Rapid maxillary expansion has been suggested to reduce the symptoms of OSA and the yearly rate of upper airways infections (48-49).

Otorhinolaryngologic disease in children with DS

Otorhinolaryngologic diseases are common in children with DS (8, 18, 19). The risk of hearing impairment is increased and is, amongst others, closely linked to the higher prevalence of otitis media (28, 50-53). Recurrent upper airway infections are observed and may be facilitated by the suggested immune-system development delay (54, 55). Chronic nasal drainage or rhinorrhea is also a frequent clinical finding, as well as chronic mouth breathing (19, 29, 56). The prevalence of OSA is high and the rate of thyroid disease is also higher than in otherwise healthy children (19, 27, 57-60).

Figure 2  Common otorhinolaryngologic disease in children with DS
**Hearing impairment**

The newborn hearing-screening program has been introduced to ensure early detection of impairment and to introduce hearing rehabilitation before the age of 6 months. Early rehabilitation is recommended to ensure adequate development of language- and cognitive skills, and is associated with 20 - 40 % better outcome in language, social adaption and social behavior in children compared to those with hearing losses which remains undetected (16, 25, 61-63). Mild hearing loss and unilateral hearing loss may also have an impact on speech development and perception (63, 64). Hearing impairment have an impact on language development, cognitive and social development is believed to depend on language (11, 25, 65-67). Due to the increased risk of hearing loss, hearing rehabilitation and follow up is of importance in children with DS. Children with DS have a lag in expressive language skills, amongst other language difficulties and cognitive disabilities (9, 68, 69).

Hospital- and community based prevalence studies on hearing loss in older children with DS has reported uncertain estimates of 31 - 79 % (28, 31, 51, 52). The prevalence of hearing loss in newborn with DS exclusively, based on screening data, is reported in less wider range of 34 - 46 % (51, 51, 53).

Common risk-factors which may act on the hearing ability in children with DS are pinpointed below:

- Congenital sensorineural hearing loss (4, 13, 14, 51, 53)
- Intensive care unit treatment in the neonatal and perinatal period due to heart disease and nutrition problems in addition to infections and disorders which demand newborn intensive care (25)
- Otitis media (28, 51-53)
- Stenotic ear canals with earwax, persistence of mesenchymal tissue in the tympanic cavity (19, 29-32)
- Structural and functional alterations in the middle and inner ear including nasopharynx and auditory canal (30, 42, 70)

Hearing loss is estimated to be present in 1 - 2/1000 of infants, with an increase up to approximately 4 / 1000 by school age (61, 71-73), see table 1. An increase in prevalence during childhood might be caused by inerative progressive hearing loss, infections, tumors, head trauma and temporal bone fractures, ototoxic drugs, amongst other (25, 74-79). The increase in prevalence of hearing loss in children with DS throughout childhood is not known.
Early hearing rehabilitation in profound hearing loss is important to improve the acquisition of language, phonological characteristics and conversational speech, improve the life quality ability to interact with others, and might affect the final outcome (80).
Table 1. Austeng et al. 2012. Hearing level in children with Down syndrome at the age of eight. (Paper I)

<table>
<thead>
<tr>
<th>Author</th>
<th>Prevalence</th>
<th>N (total)</th>
<th>N (responders)</th>
<th>Country</th>
<th>Age (years)</th>
<th>Definition of hearing loss</th>
<th>Design</th>
<th>Diagnostic methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fortnum, Summerfield, Marshall, Davis, and Bamford (2001)</td>
<td>0.91/1000</td>
<td>26,000</td>
<td>17,160</td>
<td>UK</td>
<td>3-16</td>
<td>40 dB</td>
<td>Retrospective, community based</td>
<td>Questionnaires to health professionals/authorities</td>
</tr>
<tr>
<td>Cone, Wake, Tobin, Poulakis, and Rickards (2010)</td>
<td>6.5/1000</td>
<td>6581</td>
<td>6240</td>
<td>Australia</td>
<td>2 and 5 grade</td>
<td>16-40 dB</td>
<td>Cross sectional, School children</td>
<td>Pure tone audiometry</td>
</tr>
<tr>
<td>Bamford et al. (2007)</td>
<td>3.47/1000</td>
<td>225 Service institutions</td>
<td>185 Service institutions (85.2%)</td>
<td>UK</td>
<td>5 years</td>
<td>40 dB</td>
<td>School screening</td>
<td>Pure tone audiometry</td>
</tr>
</tbody>
</table>

*p < 0.001 comparing prevalence in children with Down syndrome (35%) to otherwise healthy children (0.112-0.34%).

a Sensorineural hearing loss.
b Slight mild conductive loss; 6.3/1000 > 15 dB.
c Sum of 3 years birth cohort.
**Otitis media with effusion (OME)**

OME is a middle ear disorder characterized through the persistence of serous fluid in the middle ear. This fluid state may follow an acute otitis media (AOM) for 4 - 6 weeks and resolve as part of the natural healing process. However OME may also persist for a longer period with or without episodes of AOM (11, 81).

In otherwise healthy children OME has a high cumulative prevalence up to 90 % at school age and is reported to be inverse proportional with age. The prevalence estimates of bilateral OME in children less than one year of age is estimated to 34 % in the winter season and decline to 10 % at the age of five. By the time the children reach 10 years of age the prevalence is reported reduced to 3 - 4 % (82-85).

The diagnosis of OME is confirmed with otomicroscopy, which would uncover serous fluid in the middle ear, a possible thickened tympanic membrane with or without retraction. The tympanometry measurements would produce an altered tympanometry curve (82, 86). OME affects hearing thresholds decline of 15 - 40 dB (87).

Children with craniofacial syndromes, like DS, are at high risk of OME with prevalence estimates up to 80 % (28). The nasopharyngeal hypertrophy of lymphatic tissue and dysfunction of the eustachian tubes has been suggested to contribute to a lack of sufficient ventilation of the middle ear. In addition, the immature immunologic development frequently seen in children with DS may further contribute to the higher prevalence of ear infections, (54, 88, 89) and also a persistence of higher infection rate past the observed peak years in otherwise healthy children.

The decision of appropriate treatment might prove to be a challenge to clinicians. Studies conducted on treatment of OME in otherwise healthy children find no significant difference in outcome of verbal comprehension and expressive language skills in surgical treatment compared to watchful waiting (90). However, OME with hearing impairment may affect the development of cognitive function and language skills in younger children (85). Although treatment recommendations are leaning towards a less aggressive surgical approach in children with satisfactory language development, OME guidelines urge a close follow up of children with craniofacial syndromes in risk of language delay (1, 11, 12, 25).
Obstructive sleep apnea (OSA)

In OSA periods of partial or complete obstruction of the upper airways leads to cessation of airflow. This respiratory disturbance may cause oxygen desaturations, awakenings, increased pulse and blood pressure (91, 92). OSA in children is associated with cardiovascular disease, (93, 94) and metabolic syndrome (95). OSA may present with symptoms of breathing difficulties, snoring, and disturbed sleep. Daytime symptoms like concentration difficulties and mood changes may appear in children with OSA. OSA affects the ability to learn through concentration deficiency, the affected produce lower scores in school achievement tests and quality of life questionnaires (13, 14, 22, 91, 95-99).

Children with DS are at high risk of developing OSA due to craniofacial anatomy and soft tissue alterations, hypotonia and glossoptosis (19, 37, 91). The prevalence of OSA in children with DS is estimated to be 10 - 30 times higher than otherwise healthy children. Prevalence estimates in children with DS are in the range of 30 – 80 % (table 2) whereas in otherwise healthy children the estimates are in the range of 0 - 5.7 % (22, 27, 59, 60, 100-102). These uncertain estimates in children with DS may be a reflection of the different diagnostic tools, diagnostic criteria for OSA and/or the age range in the populations studied.

Polysomnography (PSG) is the gold standard diagnostic tool for OSA, and PSG with video recording is especially valuable in children to report on the child’s movement and behavior during sleep (22, 91). Children with DS may have day time symptoms of poor sleep quality without OSA which may be revealed through the video recording during PSG; they may assume a peculiar sleep position with awakening, be flopped forward or sitting cross-legged, or have longer periods without sleep (103). Children with DS do not necessary snore, and parental reports on OSA do not necessary correspond to PSG recordings (27, 104, 105). The treatment of choice in pediatric OSA in children without risk factors concerning surgery or general anesthesia is adenotonsillectomy, whereas others may benefit from continuous positive airway pressure (CPAP) treatment (22). As mentioned above, OSA is associated with significant morbidity and may, amongst other, impact cardiovascular systems and lead to hypertension. Left heart hypertrophy arrhythmias are also associated with OSA (93, 94, 106, 107).

Diabetes, high blood pressure, elevated cholesterol and higher body mass index (BMI) known as metabolic syndrome is associated with childhood OSA, as well as thyroid disease (95,108-110). Publications have shown a higher prevalence of these conditions in children and adults with DS, however the inter-connection with OSA is not known (111,112).
Table 2. A selection of published studies on prevalence of obstructive sleep apnea in children with Down syndrome.

<table>
<thead>
<tr>
<th>Author</th>
<th>Prevalence</th>
<th>Design¹</th>
<th>Country</th>
<th>n</th>
<th>Age (years)</th>
<th>Diagnostic</th>
<th>Definition of OSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marcus et. al 1991</td>
<td>44%</td>
<td>Hospital based</td>
<td>USA</td>
<td>51</td>
<td>1-18</td>
<td>16 PSG, nap studies</td>
<td>AHI&gt;1</td>
</tr>
<tr>
<td>Stebbens VA et. al 1991</td>
<td>31%</td>
<td>Population based, healthy children</td>
<td>UK</td>
<td>32</td>
<td>1-4.9</td>
<td>Polygraphy</td>
<td>UARS SaO2</td>
</tr>
<tr>
<td>DeMiguel-Diez J et. al 2003</td>
<td>55%</td>
<td>Volunteers</td>
<td>Spain</td>
<td>108</td>
<td>1-18</td>
<td>PSG</td>
<td>AHI&gt;3</td>
</tr>
<tr>
<td>Dyken et. al 2003</td>
<td>79%</td>
<td>Hospital based</td>
<td>USA</td>
<td>19</td>
<td>3-18</td>
<td>PSG</td>
<td>AHI &gt;1</td>
</tr>
<tr>
<td>Mitchell RB et. al 2003</td>
<td>48%</td>
<td>Diagnose registry retrospective</td>
<td>USA</td>
<td>23</td>
<td>1-10.2</td>
<td>Not stated</td>
<td>Not stated</td>
</tr>
<tr>
<td>Shott S et. al 2006</td>
<td>57%</td>
<td>Hospital based</td>
<td>USA</td>
<td>56</td>
<td>3-5</td>
<td>PSG</td>
<td>AHI &gt;1</td>
</tr>
<tr>
<td>Ng DK et. al 2006</td>
<td>59%</td>
<td>Volunteers</td>
<td>Singapore</td>
<td>22</td>
<td>0-18</td>
<td>PSG</td>
<td>AHI &gt;1.5</td>
</tr>
<tr>
<td>Fitzgerald DA et. al, 2007</td>
<td>97%</td>
<td>Hospital based, retrospective</td>
<td>Australia</td>
<td>33</td>
<td>2-19</td>
<td>PSG</td>
<td>AHI &gt;1</td>
</tr>
</tbody>
</table>

PSG = polysomnography, AHI = apnea hypopnea index, UARS = upper airway resistance syndrome, SaO2 = oxygen saturation
Treatment guidelines and follow up

Internationally published clinical practice guidelines encourage follow up and treatment of OME in children at risk of speech, language and learning problems, and emphasize the need to follow up any possible hearing impairment in children with DS. Substantial recommendations of referral to clinical otorhinolaryngologic examination and audiological tests have been published, however these are not interdisciplinary integrated and withheld some variation (19). Accordingly, the management of speech and language delay and assessment of cognitive development function in these children at risk is suggested routinely, included hearing tests and an evaluation of the need for hearing devices (1, 11, 113, 114). Recommendations and reported practice patterns on diagnostics and follow up of pediatric OSA are published (19, 22, 27, 115-118). In Norway, no interdisciplinary national guidelines on the management of OSA or any otorhinolaryngologic disease in children with DS exist.

We have little knowledge on what has been done to optimize otorhinolaryngologic disease in children with DS. In Norway, there is no national registry on children or adults with DS, nor any intercommunal or interregional governmental organization or resource centre to coordinate teaching resources, education, language development or somatic health of children with DS in Norway. The Norwegian patient treatment registry hold data on surgery conducted in children, however these data is not necessarily linked to the DS diagnose.
Aims

The main aim of this study is to contribute to increased knowledge on the prevalence of three defined otorhinolaryngologic related diseases in children with DS. Main domains of interest are the auditory function, OME and OSA. In addition to prevalence, we aimed to describe current routines for the diagnosis and follow-up of hearing loss OME and OSA during the first 8 years of life of children with DS born in 2002. These diseases may influence development of cognitive functions.

Main aims
1. Study the prevalence of hearing loss in children with Down syndrome (Paper I)
2. Study the prevalence of OME in children with Down syndrome (Paper II)
3. Study the prevalence of OSA in children with Down syndrome (Paper III)
Material and Methods

Study design

We chose the design of a cross-sectional population based study to estimate the prevalence of hearing loss, OME and OSA in this study population.

Study population

Children born with DS in Norway in 2002 with a present home address in Norway were enrolled in this study. These children were recruited through departments of Medical Genetics in 2010. The national pedagogical resource centre were contacted to ensure that there were no left outs or children with DS who had moved to Norway after 2002, not initially included. Those children who had more than one parent with another mother tongue than Norwegian were not included due to language and communication difficulties.

The children were invited through a letter of consent and both caregivers and children signed. Fifty-seven children met the inclusion criteria. Three pair of parents did not accept the invitation to participate in the study. One child has moved and is lost to follow up.

To obtain reference data in 8 year old Norwegian children, we enrolled 57 otherwise healthy children born in 2002 who underwent audiological testing, clinical examinations and their parents responded to the questionnaire on anamnestic data. This group were volunteers of a larger cohort of 220 children (26 %) who had been selected and considered socio-demographically representative for the Norwegian population, and who had served as a control group in a larger study on language skills, “The Nature and Development of Language and Communication Skills in Children” by the research group Child Language Learning, Department of Special Needs Education, University of Oslo.
**Investigations**

The clinical examinations and the audiological test performed in children with home address within the South-East Health Region were conducted at Lovisenberg Diakonale Hospital, Oslo. These children underwent PSG, in addition to dental examination at the TAKO-Centre, Resource Centre for Oral Health in Rare Medical Conditions, Lovisenberg Diakonale Hospital, Oslo. The reference group of otherwise healthy children who were investigated with the aim to yield reference data was also examined at Lovisenberg Diakonale Hospital.

The children who had home addresses in the remaining three health regions were examined at the nearest otorhinolaryngologic department, all in all 8 locations.

**Parental questionnaire**

Information regarding psychiatric and somatic medical history of all children was collected through a parental questionnaire. The questionnaire was divided into three parts; follow up of otorhinolaryngologic diseases, medical history of otorhinolaryngologic diseases and conducted surgical treatment, and the last part covered history of other diseases such as ophthalmology diseases, gastrointestinal diseases, heart diseases and medication. The questionnaire was designed during the early phase of the project, and piloted with the parents of the reference group as responders.

**Prevalence**

Prevalence is defined as the number of people or the proportion of a population who has a disease at a given time.

We studied the prevalence of three defined otorhinolaryngologic diseases in children with DS born in 2002, at the age of 8.
Definitions of hearing loss

Hearing loss is commonly classified as sensorineural, conductive, or mixed. Pure-tone air-conduction average (PTA) was calculated as the mean of the pure-tone hearing thresholds at 500, 1000, 2000 and 4000 Hz. Hearing loss was categorized using PTA according to World Health Organization criteria (120) in the better hearing ear: normal ($\leq$ 25 dB HL), mild (26 – 40 dB HL), moderate (41 – 60 dB HL), severe (> 60 dB HL).

In the absence of bone-conduction thresholds, the following criteria were used to categorize hearing loss. Definition of conductive hearing loss: PTA hearing level $>$ 26 dB HL, type B or C2 tympanograms, the absence of tympanic membrane movement and/ or otomicroscopic signs of OME.

Definition of sensorineural hearing loss: PTA $>$ 50 dB HL in the better hearing ear, tympanometry A curve, a mobile tympanic membrane, and without microscopic verified middle ear fluid.

Definition of mixed hearing loss: PTA $>$ 50 dB, visible middle ear effusion, tympanometry B curve and discretionary masked bone conduction performed with failing air bone gap.

Pure tone audiometry

Pure tone audiometry is used to test the hearing ability. Hearing ability is tested at different frequencies and the loudness of the test sound is measured in decibel. The audiogram represents the hearing ability measured in pure tone audiometry. Normally, humans can detect frequencies from 20 - 20,000 Hz. Speech is found between 250 and 8000 Hz with low frequency sounds in vocals and the consonants like t, s, f and k represent higher frequencies. PTA is the average of hearing ability measured at 4 frequencies; 500, 1000, 2000 and 4000 Hz. Otherwise healthy children at the age of 8 would cooperate during conventional pure tone audiometry.

Play audiometry

The play audiometry also measures the child’s ability to discriminate between intensities of sound, performed in a soundproof room. The child is presented a game, a play task like
throwing marbles in a box, or a pc-computer program with animations of animals. The child is allowed to throw a marble or make the animals in the computer game move, when he or she hears a sound presented through the earphones on the right or left side. The results are marked in an audiogram. Some of the children with DS were tested using play audiometry.

**Definition of otitis media with effusion (OME)**

OME is defined as the presence of fluid in the middle-ear without signs or symptoms of acute ear infection. The definitions of otitis media are being discussed.

The OME causes a decreased mobility of the tympanic membrane, cause conductive hearing loss and diagnosed through otomicroscopy, pneumatic otomicroscopy (11, 121).

**Definition of obstructive sleep apnea (OSA)**

OSA in children is defined as the presence of clinical symptoms of OSA and the diagnosis is confirmed with PSG values above the estimated normal values of sleep in otherwise healthy children without OSA, OAI < 1 or AHI < 1.5 (22, 91).

Whereas the diagnosis of moderate to severe OSA is defined through a moderate increase in PSG values and the presence of day and nighttime symptoms, the definitions of mild OSA is more difficult to define due to the lack for universal agreement on normal PSG values in children. Hence there is no agreement on the definition and cut to values to define mild OSA in children (91, 92).

Recent recommendations indicates cut off values for OSA in children to AHI > 1.5 or OAI > 1. Through a thorough analysis of the PSG with video recordings, nighttime symptoms in children can be confirmed (22, 91).
**Polysomnography (PSG)**

All patients underwent attended overnight PSG (Embla, Resmed, Norway) with simultaneously video and audio recordings at the Sleep Laboratory, Lovisenberg Diakonale Hospital, Oslo, Norway. The PSG recordings included a six-channel electroencephalogram (C3/M2, C4/M1, O2/M1, O4/M2, F3/M2, F4/M1), right and left electrooculogram and submental electromyogram. Ribcage and abdominal wall movements were measured using respiratory inductance plethysmography. Flow was measured with nasal pressure transducer and the arterial oxygen saturation was monitored via pulseoximetry. Electrocardiogram, body position and EMG from both legs were also included.

Sleep was scored for sleep stages according to the guidelines from American Academy of Sleep Medicine (92). An obstructive apnea was defined as at least two breaths with more than 90% reduction in flow in the presence of ribcage and abdominal movement. A central apnea was defined as at least two breaths with more than 90% reduction without absent respiratory effort with subsequent oxygen desaturation of at least 3% or an arousal, or if the event lasts for more than 20 seconds. Hypopneas were defined as a more than 50% decrease in flow for at least two breaths with subsequent oxygen desaturation of at least 3% or an arousal (92). The hypopneas were not classified further.

Apnea hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour of sleep, while oxygen desaturation index (ODI) was defined as the number of oxygen desaturations ≥ 3% per hour of sleep.

**Statistics**

Statistical analyses were performed using a commercially available software program (SPSS 17.0 for Windows). Descriptive statistics was applied to define frequencies of gender, mean hearing loss, and mean of PSG values and prevalence of disease ranges and the standard deviation. Chi square test was applied to compare the prevalence of disease between groups with testing of significance and the establishment of p-value to test the null-hypothesis. P-values < 0.05 were used as an indication of a significant difference. The independent Student T-test was used to compare the mean hearing levels between subgroups. To measure the strength of association between two variables the Pearson’s correlation coefficient was applied (119,122).
**Ethical considerations**

The project was conducted in accordance to the Helsinki declaration and common ethical accepted values. The protocols and the questionnaires were approved by Regional Committee for Medical Research Ethics (nr 2010/1950, S-07496b).

In accordance with rules set by the Data Inspectorate, a permission application is submitted through the office of Norwegian Social Science Data Services.

This study was approved by the Regional Committee for Medical Research Ethics required an informed consent signed by parents and the child.
Results

Summary paper I

Hearing level in children with Down syndrome at the age of eight

In paper I we identified the prevalence of hearing loss in this study population of 8 year old children with Down syndrome (DS). This cross sectional study was national wide, and all children born in Norway in 2002 were invited to participate. These children are considered at high risk for developing hearing impairment. The reported prevalence estimates of hearing loss in children with DS are uncertain and in the range of 34 – 81 %.

Fifty-six children met the inclusion criteria and 53 (94 %) children accepted the invitation to participate.

We found that 35 % percent had a hearing loss according World Health Organization criteria with a cut of values for hearing loss defined as hearing levels lower than 25 dB HL in the best hearing ear. Mild hearing loss was found in 13 children (26 %) moderate in 3 children (6 %) and severe hearing loss was found in 1 child (2 %). All children but three were undiagnosed prior to the study.

Considering hearing impairments great influence on learning and development of cognitive and social functions, this study shows the importance of examine children with DS for hearing loss throughout childhood and also in the early school years.
**Summary paper II**

**Otitis media with effusion in children with Down syndrome**

We performed a national wide cross sectional clinical and audiological population based study, to determine the prevalence of otitis media with effusion (OME) in 8 year old children with Down syndrome (DS) born in Norway in 2002. The data on otitis media were obtained through otomicroscopy and tympanometry in 52 out of the 56 children (92 %) who accepted the invitation to participate.

OME was found in 38 % (20 / 52) of the children at the time of examination. All children were undiagnosed prior to the study except for two. We found that hearing loss greater than 25 dB HL in the better ear was present in 60 % of the children with effusion. The DS syndrome children with OME had significantly lower hearing threshold than those without effusion. Approximately two in three children with a history of acute otitis media or repeated periods of OME in the past had current OME.

This study indicates that OME is very prevalent even among school children with DS and is associated with significant hearing loss. This is an important finding that has clear implications for clinical care of these children.
Summary paper III

Obstructive sleep apnea in younger school children with Down syndrome

Obstructive sleep apnea (OSA) in children with Down syndrome (DS) is considered to be common as the children are at high risk due to the altered craniofacial anatomy, however prevalence estimates are uncertain and in the range of 31 – 79 %. These estimates are based on children with a wide age range using various diagnostic tools. Children born within the geographical area of the South East Health Region with DS in 2002 were included in the study. The response rate was high (90 %). This health region comprises more than 52 % of the children born with DS in Norway that year.

We found that 28 out of 29 children (96 %) had an apnea hypopnea index (AHI) > 1.5 and 24 out of 29 children ( 88 %) had an obstructive apnea index (OAI) > 1. Nineteen children (66 %) had an AHI > 5 and 17 children (59 %) had an OAI above 5 which indicate moderate to severe OSA.

The mean AHI was 10 (SD 8.8), with minimum and maximum values of 1.1 and 37.0 respectively. Mean AHI in girls was 12.6 and in the boys 7.7, with no significant difference between the genders. The mean ODI (oxygen desaturation index) was 13.8 (range 2.4 - 53.9). Corresponding ODI values were 16.6 and 10.7 for girls and boys respectively, a non-significant difference. One third of the children were within the range of normal weight (n = 9), and two thirds (n = 18) were classified as overweight or obese. No difference in ODI or AHI between normal weight and overweight children were found. Five out of 10 children who had adenoidectomy or tonsillectomy performed in the past had an OAI of 5 or more.

We found a high prevalence of moderate to severe OSA in these 8 year old children. OSA is known to affect concentration, learning ability and somatic health and therefore managing OSA at an early age is important. All children were undiagnosed prior to this study.
Theoretical issues

The thesis extends the knowledge of three otolaryngology related diseases that may have an influence on the cognitive development processes and effect the learning ability in 8 year old school-children with DS; hearing loss, OME and OSA. At this age, these children are particularly vulnerable to hearing loss and concentration difficulties as they are in the process of learning the basics of how to read and write.

To our knowledge, the prevalence of hearing loss, otitis media and OSA in children with DS has not been reported on a population-based level prior to the present thesis. Previous reports are based on clinical hospital samples, community based studies and studies based on volunteers, amongst other methodical differences. Some of these earlier reports found higher prevalence estimates of disease in children with DS than in the current study. These studies support our findings of a very high prevalence of hearing loss, otitis media and also of OSA in children with DS. Although some earlier reports on prevalence of OME, OSA or hearing loss are lower than the prevalence found in the present study, these prevalence estimates of disease in children with DS are still very high. These present study findings warrants the importance of medical follow up throughout childhood as these diseases may impact on the final outcome in terms of language development and cognitive development.

Studies performed in otherwise healthy children and overall clinical shared experience indicate that the prevalence of OSA in children who are not overweight and also the prevalence of OME decline after the preschool years, whereas the prevalence of hearing loss increases (60, 70-72, 82, 86). The age specific prevalence of these diseases in children with DS and prevalence alterations throughout childhood is not known. A high prevalence of hearing loss, OME and OSA has been suggested in preschool children with DS (19). The sum of the findings reported by Shott et al. and our observed prevalence of hearing loss, OME and OSA implies that the prevalence of OSA and OME in children with DS is high in the preschool years and remains high up to the age of 8. However, as we chose a cross sectional design, we are not eligible to predict the nature of disease throughout preschool years and school years, but can only rely on our data to estimate the prevalence at the age of 8.
**Hearing loss**

Hearing loss is common in children with DS. We found that 35% of the children with DS had impaired hearing with hearing thresholds below 26 dB in the better hearing ear (Paper I). Hearing is important to maximize the acquisition and development of language and speech, (62, 123) and the hearing rehabilitation in children with DS is encouraged as reported in the literature (19). Only two children had been offered hearing devices during the first 8 years of life. The treatment and follow up of the children in this population has potential of improvement.

The rate of estimated sensorineural hearing loss in the present study of 8 year old children with DS of 16% is in line with the findings by Hess and al. who found hearing loss with sensorineural component in 15.5% in children up to the age 8 years (124). Park et al. reports a much lower prevalence of sensorineural hearing loss in children younger than one year (3%) with data obtained from newborn hearing screening program (53). These study reports suggests an increase of sensorineural hearing loss throughout childhood. Early onset of presbyacusis and hair cell dysfunction affect adults with DS (125). Nevertheless, these observed high rates of sensorineural losses in school children warrant the need of audiological rehabilitation in addition to the mechanical hearing losses caused by OME.

In addition to the hearing loss in 35% of the children, we found seventeen children (32%) with bilateral low frequency thresholds lower than 20 dB. Only one child in this study population with DS had bilateral hearing thresholds better than 15 dB. Also unilateral hearing loss, which was present in some of the children, has been suggested to affect language development (64, 126). Hence, a higher number of children than the reported 35% with hearing thresholds below 26 dB in the best hearing ear may have a degree of hearing loss, which affects cognitive development and language development.

**Otitis media with effusion (OME)**

Studies conducted in otherwise healthy Norwegian and Finnish children has reported an association between the history of OME in early childhood and the susceptibility for disease at the age of ten (127). Our data also showed a significant association ($p \leq 0.000$). Nevertheless we have to be careful to conclude on the association between past and current diseases as our data is limited, as only 23 of the 53 children (43%) studied had received medical follow up
including otorhinolaryngologic examination and audiological tests during the first 8 years of life.

OME was significantly associated with hearing loss (Paper II). The language development in otherwise healthy children is thought not to be affected by periods of OME (90) as the children are found capable of compensating for periods of OME and slightly reduced hearing levels. However, OME and mild hearing loss may affect development in young children, especially those with a sensorineural hearing loss (128). Also young children at risk of language delay with OME are found to have lower scores on language ability than those without OME (129). Furthermore treatment with tympanostomy tubes in children with OME has been reported to cause an increase in quality of life in children and their caregivers (66). As the association between language development and OME in DS has not been studied, we do not know how language development is affected by OME related auditory deprivation.

**Obstructive sleep apnea (OSA)**

We did not find a significant association between OSA and BMI or gender, which is established risk factors for OSA in otherwise healthy children (130). However the limitation of studying disease in rare children with a rare syndrome, all of the same age, lies in the smaller number of children in the source population. The correlation analysis used for gender or BMI may not be valid due to low power when data on smaller study populations is divided into further subgroups. However the craniofacial alterations and hypotonia in DS may be the dominant influencing factor causing OSA in children with DS and not the BMI. Prevention of obesity is an important goal in children with DS not only for the possible impact on OSA but also for the impact on metabolic syndrome and associated diseases (95, 108-110).

The gold standard of diagnostic tools in paediatric OSA is PSG. Through a thorough analysis of the PSG with video recordings nighttime symptoms in children can be confirmed (22, 91). Although physical findings and the parent’s reports on snoring may prove helpful in making the diagnosis in children, studies on parental observations of nighttime symptoms in children with DS are not found to be reliable (27). Hence the evaluation by an experienced otolaryngologist in pediatric sleep is necessary if OSA is to be refuted.

Based on our findings we emphasise the importance of performing OSA diagnostics in children with DS at an early age. The diagnostic ought to be repeated in preschool and school age, as the airways-space alters with age. Under-treatment of these children probably involves the same risk of compromised learning ability and cardiovascular disease as in other children, and may inhibit the children to reach their full potential. Five out of 10 children who had
adenoidectomy or tonsillectomies performed in the past had an OAI of 5 or more. These children were referred to surgery without preoperative PSG diagnostic performed as they were operated on the indication of upper airways infection. We do not know to what extend performed surgery has had an impact on the outcome of OSA on these children studied.

We found a high prevalence of moderate to severe OSA in these 8 year old children. OSA is known to affect concentration, learning ability and somatic health and therefore managing OSA at an early age is important. All children were undiagnosed prior to this study.

**Developmental issues**

Inclusion in society and family-life is central in the social development of children (24). If we can assume that cognitive- and language development, concentration as well as development of social skills are affected by hearing loss, OME and OSA in DS children to the same extend as in otherwise healthy children, we have to assume that the risk of not treating DS children for the named diseases is equally grave as in otherwise healthy children. However, longitudinal studies on the association between these somatic diseases and development in DS have not been performed. Nevertheless smaller studies reported improvement of language skills, quality of life and emotional distress in children with DS who have been treated with bone anchored hearing aids (80, 131, 132, 175). This implies that in line with otherwise healthy children, adequate hearing rehabilitation of severe hearing loss is effective and furthermore, that treatment is likely to improve the outcome of children with DS. By the same rationale this can also be extended to OME and OSA as well implying that thorough otorhinolaryngologic diagnostics in DS children are warranted. This notion is supported by studies that show a positive effect of OSA treatment on sleep quality, neuro-cognitive behavior symptoms and quality of life in otherwise healthy children. (13, 133-142). There is reason to believe that children with DS would gain from treatment in the same way as otherwise healthy children and that the introduction of national guidelines of otorhino-laryngologic disease in children with DS ought to be considered.

**Ethical issues**

The ethical issues of involving children and their ability to give informed content have to be considered when conducting a study in children with DS. The decision to allow for research to
be conducted in a child is made by the caretaker with the child’s assent (143). To which degree a child of 8, and also a child with cognitive retardation, is able to understand the implications of taking part in a study, and how this assessment process is preceded for the good of the child, is difficult to assess. Furthermore, to what extent parents or other caregivers are able to obtain adequate information and understanding of the consequences of medical research and also the assessment of the parents’ ability and extent of psychological competence to inform the child is an ethical area of uncertainty (144).

International guidelines on research in children emphasize the importance of protective measures due to children’s vulnerability (144). No new experimental examinations were planned or pursued during this present study, nor did this study involve new medication or other experimental interaction in the children. The examinations conducted were well-known clinical procedures, following the ethical standards mandatory in any sleep- or audiological diagnostic procedures and in general otorhinolaryngologic examination of children.

The local data protection officer, who had great expertise and insight into research ethics in children, gave advice in the early stages of the design of this study. Under the condition that the anonymity of the children was ensured, the permit to publish prevalence rates and distribution of disease was given.

Further, when designing a study in children an intended benefit for the children involved ought to be a priority (144). One of the hypotheses while planning our study was that the children were under-diagnosed. The examinations offered were part of the expected diagnostic and follow up in any child at risk of disease during early childhood. Parents and caregivers were informed if diseases or disorders were diagnosed during the examination, and treatment and follow up were offered.
Methodological issues

The design

Few population-based studies on otorhinolaryngologic diseases in children with DS have been conducted. To best of our knowledge, this is the only population-based study of children with DS born in the same year. The participation rate was high, above 90% in all three studies, and the children were born in the same year. We had a cross-sectional design. This design is useful for descriptive studies and prevalence survey and provides early implication about a research hypothesis. Unfortunately there is no temporal sequence of exposure and outcome and assessing causality is difficult. Hence prevalence studies do not provide evidence of cause and effect, and also it is not possible to decide whether the cause followed the effect. Another limitation is that the cross-sectional study only provides information on the prevalence and does not provide information about the incidence or duration of the disease (119, 122).

Study population

The children were identified through the Departments of Medical Genetics at the Universities of Oslo, Bergen and Tromsø, who have complete national data in genetic registries. Eligibility criteria included a diagnosis of DS based on karyotypic information. The blood samples were collected during the perinatal period and the diagnosis was later also confirmed through physical examination. We believe that all children with DS born in Norway in 2002 who had a Norwegian address were localized. As the communication with bilingual children with DS and poor parental language skills was considered to make the cooperation difficult, children with more than one parent with other mother tongue than Norwegian, and still registered with a Norwegian home address were excluded from the study.

The findings of our study are likely to be generalizable to populations with DS of Nordic Caucasian background, who would have experienced the cultural and exposure experiences similar to those of the study participants.
**Random errors**

Clinical research strives for precision. Precision corresponds to reduction of random errors. Random errors is the divergence of the true sample value due to chance alone and occurs in the selection of the study participants, but is reduced by increasing sample size. Control of random errors was done via statistical tests.

**Systematic errors**

**Selection bias**

Selection bias is defined as a divergence in the association between exposure and disease observed in those who are included in the study and compared to those who are not. We believed to have kept the selection bias to a minimum in the in the study of hearing loss and otitis media by locating all children and achieving a high response rate of 53 / 57 (93 %). Hence the distribution of disease in this age band of children with DS in Norway is covered to a high extend. We reduced information bias and the inter-observer variability to a minimum by selecting a single physician to be in charge of all clinical examinations. The sources of information bias were carefully considered during the planning of the study.

Unfortunately, all children could not be examined at the same location. The group of otherwise healthy children and 29 of the 53 (54 %) children with DS were examined in the same otorhinolaryngologic department, using the same audiometric measures as the remaining 8 otorhinolaryngologic departments geographically spread throughout Norway. The group of children with DS and the otherwise healthy children examined at the same otorhinolaryngologic department would be expected to be affected equally if there were any modifications to the medical equipment used in the examinations.

To obtain reference data in otherwise healthy children of the same age as the study population, 120 of 220 (50 %) children of an established control group were invited to participate. Fifty-seven children, 26 % of the original control group of 220 children volunteered. We may have introduced a selection bias to these data due to the low response rate. However, the difference in prevalence of disease between this group of otherwise healthy children and children with DS was great. We found a prevalence of hearing loss and OME of 1.7 % (1 / 57)
in the group of otherwise healthy children. This prevalence is higher than reported in the literature; hence we believe that a larger reference group would have yielded a lower prevalence of disease.

**Selection bias of the OSA study**

The selection bias in the OSA study is not considered to have great impact on the internal validity to of the data. In the OSA study we chose an exhaustive population of children from a restricted geographical area to describe the distribution of disease. More than 50% of all children with DS born in 2002 in Norway who met the inclusion criteria were enrolled, 29 out of 32 eligible children volunteered to participate (92%) and we believe the study findings to be valid.

To exclude observer variability and reduce information bias the same experienced observer specialized on child PSG, who is also experienced in sleep recordings of children with other syndromes, performed scoring of all recordings.

The evaluation of the data was based on gold standard of sleep diagnostic in children and all children were examined in the same sleep laboratory with calibrated equipment. Hence we believe that information bias has not influenced the outcome.

**Recall bias**

Recall bias is caused by a miscellaneous recollection of the truth; either overestimated or underestimated, and is possible in any anamnestic response and is influenced by both memory and the recollection of the disease (122).

We designed this study to be prospective in respect to the data collection of hearing ability, present OME and OSA. However, the data on history of OME and AOM in earlier childhood and follow up and treatment of OSA was sought through a parental questionnaire. Hence this information is based on parent’s memory, notes, and in some cases consultation with a general practitioner.

The data on history of otitis media may represent a bias. The diagnose was either confirmed by a physician through otoscopy, or treated due to symptoms as part of an upper airway infection with increased infection parameter and symptoms like pain and distress, or discovered through eruption of the eardrum.

Recall bias is influenced by time, with a negative effect on accuracy, and the parents had to encounter for the child’s first 8 years of life. However, recall bias cannot be completely ruled out. Never the less, history of otitis media was not a main outcome.
The problem of volunteers in a study

The literature describes volunteers for studies to be more health conscious than non-volunteers (145). However, this might not be the case when parents are to consent to a study on behalf of their children (n = 3). Hence we do not know if the non-volunteers represent a selection bias, or if they would have influenced our data in a positive or negative way.

Unmeasured confounders

In all observational studies confounding can be thought of a mixing of the effect of the exposure under study on the disease with that of a third risk factor. This third factor must be associated with the exposure and independent of that exposure, be a risk factor of the outcome or disease. In this circumstance the observed relationship between the exposure and disease can be attributed totally or in part to the confounder. Confounder can lead to an overestimate or an underestimate of the true association. Unfortunately always in an observational study the possibilities of hidden confounders exist.
Conclusion and contributions of this study

The main contribution of this project can be summarized as follows:

- The present study adds important medical and audiological knowledge on hearing impairment, OME and OSA in school children with DS at the age 8. These findings suggest that the age related prevalence of hearing loss, OME and OSA is very high. Ear-disease and hearing loss is present in up to 40 % of the children whereas moderate to severe OSA affects 60 % of the children.

- Children with DS do not benefit from adequate medical treatment and follow up of hearing loss, OME and OSA. Only 50 % of the children had been through clinical otorhinolaryngologic exam and audiologic tests during childhood before the age of 8. None of the children had been referred to OSA-diagnostic, and although the children had suffered from OME in the earlier years, the follow up had seized before the age of 8. The infrequent medical and audiological follow up of otorhinolaryngologic disease throughout childhood revealed by this study unveil a potential for improvement.

- An adequate approach to the estimated mental age of the child, patience and the absence of hospital uniforms caused a relaxed atmosphere and facilitated the conduction of the clinical and audiological examinations. Audiological test and PSG is possible to conduct in children with DS at the age of 8.

Children with Down syndrome may have a special need for optimal hearing, due to their language disability and present cognitive impairment, which is believed to impact learning processes. Ear disease, hearing loss and OSA have a negative effect on the child’s ability to concentrate, capacity to learn and follow the education offered to them. Nevertheless, from clinical experience, and also through this project we have learned that not all children with DS will tolerate the use of masks and CPAP- treatment or hearing devices, hence we have to be careful to draw the conclusion that all children with DS may benefit from extended treatment. Clinical experience indicates that younger children may be more adaptable and tolerate treatment, however the individual differences are great.
These study findings may add to medical knowledge appreciated by general practitioners, pediatricians and otorhinolaryngologist and will hopefully lead to a higher-level of cooperation. Furthermore, this knowledge may increase priority and provide medical care, already in the younger years. Early treatment may prevent development of secondary disease and contribute to extended cognitive development through improved hearing and sleep quality.
Future aspects

This project focused on the prevalence of upper airway disorders; however a correlation analysis to look at possible associations between upper airways infections and OSA or the degree and presence of other concomitant diseases could increase understanding of otorhinolaryngologic disease in children with DS.

Our data suggests that medical follow up of children with DS in Norway is limited. Increased knowledge of present disease and the prevalence patterns may improve the medical care for children with DS throughout childhood and as young adults. A follow up study would reveal the age related prevalence of OSA in older school children and young adults with DS.

OSA is associated with metabolic syndrome in adults. The association in children is not clear, and has not been studied in children with DS. These children have an increased risk of thyroid disease, diabetes, cardiac disease and pulmonary hypertonia, which are all related to metabolic syndrome. Blood samples taken of those children who underwent PSG may be used to study the prevalence of these diseases isolated and also the association between markers of disease and OSA. A follow up study with blood samples and PSG controls would describe this association further.

From our clinical experience adjusting CPAP in older children with DS may prove challenging and in some cases we do not succeed. However, we have not studied the acceptance rate or compliance, nor which factors that may influence and increase the success rate. Children with DS may tolerate the initiation of CPAP to a greater extent in the first years of life. Since previous reports on younger children with DS found high rate of OSA, and as our study indicates that one third of the older children might be affected with serious OSA at the age of 8, a compliance study in younger children with comparative analysis to the present study would be of high interest.

The potential benefits of surgery on OSA in children should be further studied. Pre- and postoperative PSG measurements will be available for children referred to adenotonsillectomy. In addition the long-time efficiency of surgery could be assessed in a follow-up study.
Data on language skills is provided through the PhD project conducted by Kari Anne B. Næss, in a majority of the children with DS who participated in this study. Hence it would be possible to study the association between hearing loss, OME and also obstructive sleep apnea and language development. It would be interesting and unique as such studies are not reported in the literature.
References


(69) K. A. Naess. Language Development in Children with Down Syndrome. Article 2; A Longitudinal Study. Oslo. Norway: Oslo University, Faculty of Educational Science; 2011.


(91) Mindell JA OJ. A clinical guide to pediatric sleep Diagnosis and management of sleep problems. USA: Lippincott Williams & Wilkins; 2003.


(114) Generell veileder i pediatri
http://www.helsebiblioteket.no/retningslinjer/pediatri/nevrologi/down-syndrom.


(143) Concent paragraph 22

(144) Understanding Consent in Research Involving Children: The ethical Issues; A Handbook

(145) DHHS
(DHHS)http://www.hhs.gov/ohrp/policy/populations/children.html)