Detection of specific language impairment in young children in well-child healthcare

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Early detection of children with specific language impairment using language milestones and risk factors

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Voor mijn vijf mannen

Contents

Chapter 1

General introduction and outline of the thesis

Normal language development is essential for all aspects of the child's development. Acquiring the ability to understand and use language is an indispensable prerequisite to allow a child to grow up to become a social all-round healthy member of society.

In 1989 the World Health Organization (WHO) defined mental health as "*a state of well-being in which the individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to his or her community*" (1). Being able to achieve this depends, to a large extent, on adequate language skills. Language development is a crucial element for social-emotional, behavioral and personality development as well as the achievement of academic skills (2). Therefore, language development ultimately determines the child's future place in society.

It is remarkable that the majority of children develop in a harmonious manner, where every aspect of development is at about the same stage at each age in most children. For instance, most children start talking around one year, start walking around the age of 14 months, can talk in sentences of three or more words at the age of three years and at the age of four they can tell a little story. However not all children develop as expected and some may be affected by complex abnormalities of many aspects of development. But sometimes just one aspect of development is delayed. Such an isolated developmental disorder may be restricted to only motor, cognitive or language development.

Language development does not follow the regular, expected pathway in all children. Language development can be delayed or inadequate due to several reasons. The following categories may be distinguished (3, 4):

1. Language delay due to lack of exposure
2. Secondary developmental language disorder
3. Primary developmental language disorder or specific language impairment (SLI)

One cause may be that the child is exposed to insufficient or inadequate language input. For instance, when children grow up in a home where parents mostly speak in only one or two word comments, it is difficult to learn to speak in longer sentences and acquire a feeling for syntax. This is usually called "language delay due to lack of exposure". When language development is delayed due to hearing loss, neurological damage or low intelligence, this is called a secondary developmental language disorder. When the cause of the language disorder is not obvious it is generally considered a primary developmental language disorder or specific language impairment (SLI) (2). It is complicated to differentiate between a language delay and a language disorder (5). The term "language delay" is mostly used when the sequence of acquiring language is normal, but the rate is slower than normal. The term "SLI" is used when language acquirement is not only slower than normal but also qualitatively different from that of normally developing children.

Specific language impairment is regarded as a neurodevelopmental disorder. Recently some debate has started about the criteria which should be used to identify and classify language impairments as well as about the most appropriate terms to use. The CATALISE

(=Criteria and Terminology Applied to Language Impairments: Synthesising the Evidence) study which used the outcome of a Delphi procedure with experts in ten disciplines, has recently recommended using the term Developmental Language Disorder (DLD) for children with severe language problems (4). It was concluded that these language problems are so severe that they pose a handicap in everyday life, have a poor prognosis and have no known biomedical etiology. A new development was that it was agreed that risk factors or other neurodevelopmental disorders, such as attention deficit hyperactivity disorder (ADHD) do not need to be excluded when making the diagnosis of DLD (4).

The subject of this thesis is children with a deviant language development which is not caused by a lack of language input or due to another known impairment.

Various terms are used in studies of young children with language developmental problems. Because it is usually stated in the literature that the diagnosis of SLI cannot be established before the age of four years (2,6) the term "late talker" is often used for young children with language delay at the age of two years old. Some of these children are late in starting to talk, but when older their language skills are within the normal range. These children are sometimes called “late bloomers” (7).

In this thesis we have used the term Specific Language Impairment because until recently SLI was the term most commonly used in the literature for a primary language developmental disorder.

Prevalence

The prevalence of SLI cited in the literature ranges from 2-12%, due to differences in definition, age when diagnosed and cutoff values used. The most quoted prevalence of 7% comes from the population study of Tomblin (8). Even though SLI is the developmental disorder with the highest prevalence, it attracts much less attention than other developmental disorders. This was remarked upon by Bishop, who noted that other developmental disorders, like ADHD or autism, get more attention in social media and research funding (9). She reached this conclusion after comparing a publication index of 35 neurodevelopmental disorders. The difference could be partly explained by other disorders being more severe and the fact that SLI is not a very visible disorder. Another reason may be that many different disciplines are involved in diagnosing and caring for children with SLI. In the medical field speech therapists, pediatricians, otorhinolaryngologists, audiologists, child neurologists, psychiatrists, child healthcare professionals and public healthcare workers are all confronted with children with language developmental problems and consider this to be within their work field. It is possible that as a result, the focus on this issue is dispersed and less interest is paid to fundamental medical research on this subject.

Long-term consequences of late talking/SLI

Attainment of normal language skills is to a great extent influenced by motor, neurological, sensory, and social-emotional development, as well as quality and quantity of language input. The other way round, when language skills are inadequate this may also affect other developmental areas.

The long-term consequences of SLI on language skills have been studied by Rice (10). In a longitudinal study where children were followed from 2 ½ to 21 years of age it was found that children with SLI had persistent language problems. Children with SLI were compared with unaffected children at several ages and it was concluded that children with SLI had lower receptive vocabulary skills over the whole investigated age range. In a study by Rescorla it was also found that late talkers identified at 24-31 months of age, with normal nonverbal capacities, had poorer language and reading skills than normally developing peers at the age of 17 years (11).

Long-term consequences of SLI on emotional and behavioural problems were the subject of a review published by Yew et al. (12). Using 19 follow-up reports from eight cohorts, they found that when children with SLI were compared with non-language-impaired children that they had more overall emotional, overall behavioural and ADHD problems later in life and that these problems were more severe. In their mid-thirties people with SLI still struggle with the consequences of poor social adaptation, such as prolonged unemployment and a paucity of close friendships and love relationships (13). When a group of children with SLI were followed using the Strengths and Difficulties Questionnaire (SDQ) from the age of seven to 16 years it was found that they had poorer long term social and, to a lesser extent, emotional outcomes (14). In a long-term follow-up study on children with SLI it has been reported that, in addition to SLI, they have social, emotional and behavioural problems in adolescence (15).

As society becomes more demanding concerning communication skills, it is clear that when language development is deficient this has a great impact on the child's opportunities for using its potential skills and for its future place in society. People with SLI will increasingly face more challenges in the future than has been the case up to now (16).

Importance of early identification of SLI

The American Academy of Pediatrics (AAP) stated in 2006 that "early identification of developmental disorders is critical to the well-being of children and their families" (17). They described early identification as an integral function of primary medical care and a responsibility of all pediatric healthcare professionals. They advised that developmental surveillance should be part of every well-child preventive care visit from birth to three years of age. This recommendation also applies to developmental disorders such as SLI.

There are several reasons why it is important to identify children with developmental disorders as early as possible. First a treatable cause of the developmental problem may be found, e.g. a hearing deficit causing a language delay. Secondly, it may be possible to implement intervention programs which have been shown to be beneficial. An early diagnosis followed by appropriate interventions could possibly improve the child's prospects and prevent or limit secondary problems. It is generally believed that benefits from these intervention programs will be greatest if children with developmental disorders start as early as possible, although more studies on this issue are recommended (18,19). In the case of developmental language problems Capone Singleton recently stated that the "wait and see" approach for late talkers is outdated, because it is debatable whether late talkers who catch up later will all have a normal development in all aspects (20). A major benefit of early identification of a developmental problem is that it can give parents and co-educators insight into the child's problems, so they are aware of the child's strengths and weaknesses. In this way their hopes and expectations can be adjusted accordingly. They can adapt their approach towards the child, which could improve the social-emotional well-being of the child by avoiding inappropriate demands and helping the child in difficult situations. Unnecessary parental feelings of guilt can be decreased by providing clarity about the child's problems.

A disadvantage of an early diagnosis could be that parents feel it necessary to have their child further investigated even in cases when they were not aware of any developmental abnormality. Especially in situations when the concerns later turn out to have been unnecessary it may give the organization a bad reputation and parents may avoid further visits.

Difficulties in identification

Although we consider it important to identify children with SLI as young as possible, there are some major difficulties involved. The younger the child the less specific the symptoms of SLI are. Not talking or beginning late with talking is an obvious symptom, but this is not always recognized as being a language developmental problem. Some children start talking late, but catch up and their language skills are within the normal range when entering school (21,22). Other children start talking at a normal age, but later on it becomes obvious that their language development is inadequate and they are diagnosed as having SLI. Whereas a delay in motor development is generally obvious to parents and educators, it is more difficult for parents to notice a language delay.

Another problem in identifying children as having SLI is that symptoms of SLI may resemble those of psychiatric and learning disorders. For instance, it can be very frustrating for a young child of 2 ½ years not to be able to tell his parents what he would like to eat in a sandwich. The ensuing frustration can be interpreted as a temper tantrum or as not being able to find the right words to express oneself (SLI). Another example is

when a child, of for instance three years of age, is unable to tell another child he wants to play with the toy the other child is playing with. Because he cannot find the right words, he has to express himself in another way and this could involve snatching the toy or using violence to get what he wants. This could be seen as a conduct disorder. When a child does not pay attention when the teacher is telling a story it could be because the child does not understand the words, but it could also be interpreted as ADHD. Not being able to read can be labelled as dyslexia, but can also be related to a language disorder. Also, not understanding a verbal explanation can be associated with SLI or not being able to carry out the task because of lower intellectual capacities. When a child does not make eye contact it can be because the child is aware that his or her words are not understandable (SLI), but it can also be related to a contact disorder (Autism Spectrum Disorder (ASD)). Also, difficulties in narrative skills can be associated with language disorders but can also be related to poor pragmatic skills associated with ASD.

Another major problem is that the natural history of language delay is unknown. The development of a child is an ongoing process, with accelerations and delays which may possibly be caught–up with later on. Several studies have shown that language delay in early life is not a stable developmental characteristic. Duff et al. recently reported that starting to talk relatively late at the age of 18 months is not an early signal of language difficulties later in life (23). Language delay up to the age of two years has been reported as having limited predictive value for having a language delay at the age of three to six years (7). However, these children may continue to have significantly weaker language skills at age 17 (11).There are also reports that some children whose language skills started in the normal range scored in the abnormal range at a later age (24).

Interventions/treatment after detection

Until recently it was debated whether treatment of SLI was effective. In a large meta-analysis of the efficacy of treatment for children with developmental speech and language delay/disorder Law reported that the evidence for effectiveness of interventions for these children was mixed (25). In 2016 the United States Preventive Services Task Force (USPSTF) stated in their new review that even though interventions for speech and language difficulties vary widely that there was adequate evidence available that treatment is associated with improvement in some speech and language fields (5). However, up to now, due to the paucity of research on the subject, there is little evidence to support the hypothesis that children with SLI have better outcomes when they are diagnosed earlier and interventions are begon promptly afterwards.

In the Netherlands treatment for SLI mainly consists of guidance by a speech and language therapist, on an individual basis, in group setting or through parental guidance. Special needs schools are available for children who, due to their severe SLI, are not able

to keep up with the other children in mainstream schools. In these special schools children can receive the expert attention they need.

Various methods to detect developmental disorders

The methods described most frequently to detect the presence of developmental disorders are (1) screening and (2) developmental surveillance (also referred to as monitoring).

In 1951 the United States Commission of Chronic Illness defined screening as "the presumptive identification of unrecognized disease or defect by the application of tests, examinations, or other procedures which can be applied rapidly. Screening tests sort apparently well persons who probably have a disease or disorder from those who probably do not" (26). Screening involves using uniform tests in a standardized procedure. This method is mostly used for large populations and therefore a suitable tool is needed, preferably one not needing too much time or highly trained users. The proportion of false positive and false negative outcomes which is acceptable is an important factor in selecting a screening tool. A false positive outcome of a screening means that a child is incorrectly considered as having the disorder, resulting in unnecessary worry for parents and may lead to further diagnostic procedures which are not required. A false negative outcome reassures parents incorrectly and may delay necessary appropriate guidance and interventions. Acceptable proportions of false positive and false negative outcomes of a screening test are related to the prevalence, the seriousness of the disease, the consequences of not detecting the disease, the importance of early detection and the amount of needless parental concern.

Another way to detect a developmental disorder is developmental surveillance or monitoring, where well educated, experienced professionals observe children as part of an ongoing process. Developmental surveillance is defined as a continuous process in which a health professional observes the child, takes a developmental history and explores any concerns that the caregiver might have. The development of the child is viewed in the context of the child's overall well-being and other domains pertaining to child health and welfare (19). The AAP recommends that developmental surveillance should be part of every well-child preventive care visit (17). Because a significant number of children with developmental delay are not detected by developmental surveillance it is often less effective than desired (19). A disadvantage is that it requires quite a lot of time and such a continuous and ongoing process needs a healthcare system where children are examined at frequent regular intervals (19). To be carried out well, developmental surveillance also needs experienced and trained professionals.

Reviews concerning methods to detect speech and language delay or disorder in various countries.

Research is carried out in many countries on speech and language problems in young children and reviews on the efficacy of screening for speech and language development are regularly published. However, this research covers many different aspects of the subject: some publications are on speech and language problems, some only on language, some on speech and/or language delay, other are focused on speech and/or language disorders.

In 1998 the National Coordination Centre for Health Technology Assessment in the United Kingdom reported that early speech and language delay is an important health problem, but the epidemiology and natural history is not fully known and there is no adequate and validated test available (27). The conclusion was that the need for screening for speech and language disorders is obvious, but there are problems with the effectuation of this screening and more research is needed.

After 1998 several large reviews have been carried out to investigate the feasibility of universal screening for a primary speech and language delay or disorder. One of these was by Law et al. (2000) who reported that data in the literature suggested that there is a need to identify early language delay as soon as is practicable (28). However, even though there are many screening tests for language development, they found no consensus regarding the relative values of the various screening procedures. Therefore, the conclusion of the review was that the introduction of universal screening for speech and language delay could not be recommended. Possible alternatives suggested were (1) "clinical examination" (2) "confirmatory screening" or staged approach, (3) "risk management" or (4) "primary prevention". These options are not free from practical problems. Option 1 means that all children should be examined by a medical practitioner. This requires the services of highly trained professionals. Option 2 is described as screening in stages; a first step is to investigate whether parents have concerns about the language development of their child. These children will then be seen by a professional and appropriately classified. This would require using questionnaires for parents to select children who need extra examinations. Option 3 involves using risk factors to select a population with higher risk levels. This requires insight into such factors and their predictive properties. Option 4 places the accent on developing health-promotion techniques to reduce the incidence, such as alerting parents and giving advice to the general population on stimulating children's language development. However, the possible effects of these suggestions are unknown.

A systematic review from the US Preventive Services Task Force in 2006 concluded that several aspects of screening for speech and language delay have not been sufficiently studied to determine which methods are optimal, including which instrument to use, the age at which to screen and which age interval is most useful (29). They concluded that there was not enough evidence on the effectiveness of screening in primary care settings,

or on the role of enhanced surveillance by primary care physicians. They also found that there was limited evidence on the benefits of interventions and on the possible adverse effects of screening and interventions (29). The report was updated in 2016 and again the conclusion was that screening for speech and language delay and disorders in children aged 5 years or younger in an asymptomatic population could not be recommended, mainly because the balance between benefits and harm could not be sufficiently assessed (5). A review from Kasper et al. (2011) on the German situation also concluded that, even though they could not exclude a potential benefit, the benefit of population-based screening for specific speech and language impairment for preschool children has not been proven (30). They stated that this was mainly due to a lack of controlled studies evaluating language screening. In 2007 vd Ploeg et al. also concluded that, in the Netherlands, screening for language disorders was not advised mainly because of the lack of adequately investigated screening tools (31).

Situation in the Netherlands

The current situation in the Netherlands is that practically all young children are regularly seen at the well-child healthcare clinics and their development is regularly monitored using the Dutch Developmental Instrument (DDI or “van Wiechen” instrument). Identification of a language problem and the decision to refer the child to a special center for diagnostic evaluation and intervention is mainly based on the assessment of the individual youth health medical practitioner. When further diagnostics are advised this can be provided at the Speech and Hearing Centers (SHC) or "audiologische centra" (32). Teams consisting of speech therapists, psychologists, audiologists and social workers work at these centers and they have appropriate facilities for diagnosing and evaluating referred children. These services are free of charge to parents.

Despite this, we have the impression that in the Netherlands many children with developmental language disorders are not correctly identified or could be identified at an earlier age. It is reported that 1.7% of children attending the regular well-child healthcare in the Netherlands are referred for further investigation because of speech and language problems (33). The large gap between the number of children being referred from the well-child clinics (i.e. 1.7%) and the generally mentioned prevalence of 7% suggests that not all children with SLI are detected at an early age or are not identified at all.

When our study started in 2012 only 0.4% of school-aged children in the Netherlands were attending special needs schools for children with severe speech and language difficulties, according to the statistics of the Dutch government department for education, culture and science (34). Even though only children whose very severe SLI prevents them from attending mainstream education attend these special needs schools, these figures are much lower than the generally mentioned prevalence of 7% of children

with SLI. This could also suggest that not all children with very severe SLI are identified in the Netherlands. A study carried out in Amsterdam in 2009 revealed indications that children with SLI were not detected or detected late (35). The recently published study by Uilenburg et al. showed that the mean age for referral to SHCs in the Northwest of the Netherlands, when using the normal care procedure as described above, was 4 years and 2 months for boys and 5 years and 1 month for girls (36). This means that many children with SLI are diagnosed after they have entered school which is at the age of four years in the Netherlands.

Conclusions

It may be concluded that SLI is a developmental problem, with a large and long-lasting impact on a child's development. Although the evidence that treatment for SLI is effective is slight, it is generally recognized that early identification is preferable to later. However, there is no agreement on how this could best be achieved. Despite frequent regular developmental monitoring of young children in the Netherlands it appears that most children with SLI are recognized late or not at all. This means that parents are not aware of the extent of the developmental problem of their child and commencement of appropriate guidance and treatment is delayed or is not provided.

Insight into the characteristics of children with SLI could improve the understanding of the etiology and provide tools for improving early detection of children with this developmental disorder.

Aims and outline of the thesis

The aim of this thesis is to establish an optimal method to detect children with SLI at the youngest possible age using language milestones and/or characteristics of these children. This should be achieved using methods which are feasible within the Dutch healthcare system. A secondary aim was to gain more insight into the etiology of SLI by studying characteristics of these children.

The studies in this thesis had a nested case-control design. The study population consisted of 253 children with SLI as cases and 253 normally developing children as controls. Cases and controls were pair-wise matched for sex and date of birth. Compared with most other studies concerning SLI this is a large sample size. A major advantage of the study design was that the diagnosis of SLI in the cases was undisputable according to the internationally used criteria for SLI. The cases were children aged four years or older, attending special needs schools for children with severe language problems who had been fully diagnosed as having SLI and who met the very strict criteria for admission to these schools. The data used to compare the group of children with SLI with the group of

normally developing children were retrospectively retrieved from the files of the well-child healthcare. These data were recorded according to a uniform protocol by trained professionals and registered before the diagnosis of SLI was made and confirmed.

A pilot study was performed to test whether the used study design was appropriate. The pilot study was a limited project where only data on perinatal risk factors were investigated. The outcomes of this are described in chapter 4. In chapters 2, 3, 5 and 6 the outcomes of the studies using the data of the major study are presented. The major study had the same study design as the pilot study, but more children were included and data on more variables were used.

In the general discussion (chapter 7) the various methods for detecting children with SLI are discussed using the outcomes of the performed studies and applied to the healthcare system of the Netherlands.

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Chapter 2

Failure to meet language milestones at two years of age is predictive of specific language impairment

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Abstract

Aim: This study established predictive properties of single language milestones for specific language impairment (SLI) after the age of four, as these had not previously been reported in the literature.

Methods: In this nested case-control study, children attending special needs schools for severe speech and language difficulties were matched with children attending mainstream schools. Data covering the ages of 0-4 years were retrieved from well-child care clinics and the outcomes of 23 language milestones in the Dutch Developmental Instrument were analysed. The predictive properties were expressed as positive likelihood ratios, sensitivity and specificity.

Results: We included 253 pairs of children with and without SLI, aged from 4-11 years. The mean age was eight years and three months and 77% were boys. From the age of 18 months, cases and controls differed significantly on all milestones ($p < 0.01$). After 24 months, the language milestones had positive likelihood ratios ranging from 6-108. In general, language milestones had a high specificity (range 77-100%), but the sensitivity was relatively low (range 0-68%).

Conclusion: Failure to meet language milestones from the age of 24 months was predictive of SLI, but the use of separate milestones had limited value due to low sensitivity.

Introduction

Speech and language disorders are among the most prevalent developmental disabilities. If language impairment is part of another condition, such as a hearing impairment or intellectual disability, language impairment is regarded as secondary to the child's other disorder. However, a relatively large group of children have a primary language disorder, for example when they have normal hearing and no obvious signs of cognitive, neurological or socio-emotional impairment. These children have what is usually called specific language impairment (SLI), even though this term has recently been the subject of some debate (1). The reported prevalence of SLI varies from 2-12% due to differences in the definition and the methods of investigation (2) and a figure of 7% is usually quoted (3). Normal communication skills are essential for optimal development and this may be hindered by SLI (4). Identifying SLI at an earlier stage may lead to early and adequate intervention and may help parents to understand what is wrong with their child.

The American Academy of Pediatrics recommended that all children should be regularly screened for developmental disorders (5). Parental questionnaires or screening tools are often used to monitor language development in well-child care, general practice or paediatrics. Examples of such questionnaires or tools are the Early Language Milestone Scale, the Parents' Evaluation of Developmental Status: Developmental Milestones and the Language Developmental Survey (6-8). These questionnaires or tools are often based on items called milestones. However, in daily practice these instruments tend to be time consuming and professionals often use so called red flags, the milestones of the National Institute on Deafness and other Communication Disorders (NIDCD) or just single milestones for assessing a child's language development, instead of a complete screening tool (9,10). An example of a language milestone is that the child *says two-word sentences* at the age of two years.

The validity of complete language tests was reviewed by Nelson et al and the general conclusion was that no optimal screening method was available to identify children with speech and language delay (11). The predictive validity of single milestones to identify children with SLI has not previously been reported in the literature.

The goals of our study were to assess the predictive validity of single language milestones for SLI and to evaluate the earliest age at which the predictive properties were satisfactory. Having SLI from the age of four years onwards was used as the gold standard.

Methods

Design

This study was designed as a prospective nested case-control study. The design was prospective because language milestones were registered before the diagnosis of SLI was known (12).

Cases

Children attending special needs schools and diagnosed with SLI provided the cases in this study. The schools were located in the service area of the Municipal Health Services of Nijmegen and Arnhem, which is a mixed rural and urban area in the eastern part of the Netherlands.

The criteria for admission to special needs schools for children with severe speech and language problems are very strict in the Netherlands. One of these criteria is a score of more than a 1.5 standard deviation (SD) below the mean on two or more validated language tests, with regard to auditory processing, speech production problems, grammatical problems and lexical-semantic problems (13,14). A special committee selects the language tests used (15). In addition, the disorder should not be due to hearing impairment or limited cognitive skills, as established by validated tests. These requirements correspond with the internationally used criteria for diagnosing SLI. Children were diagnosed by a multidisciplinary team of specialists, including an audiologist, a psychologist, an educational specialist and a speech therapist. The diagnostic report was subsequently examined by an independent, government-controlled committee. However, a child could sometimes be admitted to a special needs schools for children with severe speech and language problems, even though the criteria were not fully met, for example if a more appropriate special needs school was too far away from the child's home. Therefore, we examined the records of all cases to check whether they met the inclusion criteria. We excluded cases who were adopted, because reliable data on their earlier milestones were not available, and cases with a cleft palate.

Information on language milestones was collected from the files of the well-child care clinics of the Municipal Health Services of Nijmegen and Arnhem, which provides this care for all children in this region.

Controls

A matched control was selected for each case child. Controls were recruited from the files of the Municipal Health Services of Nijmegen and Arnhem. To ensure that cases and controls were similar, a control child of the same gender and date of birth was selected for each case. When no control was found with exactly the same date of birth, a maximum

difference of two days was accepted. Only controls who attended mainstream schools were selected. Children who had been adopted or had a cleft palate were excluded.

Language milestones

In the Netherlands all children are invited for 11 visits to well-child care facilities at regular age-points from birth to the age of four years. Almost 95% of children attend these services and during each visit developmental data are collected in a uniform manner using the Dutch Developmental Instrument, which is also known in Dutch as the Van Wiechenschema (16,17). This instrument is used to monitor child development. The Dutch Developmental Instrument is a modification of the Gesell test. It consists of 75 milestones covering five developmental fields and 23 of these are called language milestones and cover language development and communication. All milestones are assessed at an age when the chance of passing is at least 90%, which is referred to as the age norm. The Dutch Developmental Instrument is considered to have adequate measurement properties (18). Child health professionals are trained to administer and register each separate milestone according to a uniform protocol. The results are registered in the child's personal file of the well-child care system. For this study we used the data from the files of case and control children recorded during their well-child care visits from birth to the age of four years. No information concerning later developmental milestones was used, only the information that the child had been assessed and attended a special needs school for children with severe speech and language problems or that the child was attending a mainstream school.

Statistical analysis

Pairs of cases and controls were treated as independent groups in the analyses, because there was no reason to assume that the scores from each pair would correlate on the language milestones, because they were measured when the children were much younger. Differences between the groups in mean age at each well-child care visit were tested by independent *t*-tests. Proportions of failures on a language milestone, such as not passing a milestone at the age norm, were compared between the groups, using logistic regression analyses. In these analyses, the group variable (one = case; zero = control) was used as the outcome variable and each language milestone (one = fail; zero = pass) and the age at the well-child care visit were used as predictors. The age variable was included to test differences between cases and controls at each language milestone adjusted for the effect of age. Because these tests were performed 23 times, once for each milestone, a Bonferroni correction was used to guarantee that the overall significance level α was 0.05. In addition, sensitivity and specificity values were computed. Furthermore we computed the positive likelihood ratio (LR+), its confidence interval and the positive predictive value (PPV), assuming a prevalence of 2% and a prevalence of 7% (19).

Informed consent

In the Netherlands all parents of children who attend the Municipal Health Services are informed that their child's anonymous data may be used for scientific research.

The Dutch Central Committee on Research Involving Human Subjects assessed the research project. They concluded that individual parent's approval at the time of the study was not needed, because anonymity of the data was guaranteed. Despite this, parents of the cases were informed about the study and were asked for their consent for their child's participation, even though it was not legally required.

Results

We found that 330 children attended a special needs school for children with severe speech and language problems in the study region in 2012. They were born between 2000 and 2007 and their ages ranged from four to 11 years. Of these, 42 did not meet our inclusion criteria, 25 were excluded because of missing well-child care records and four were excluded because parents did not give consent for participation (Figure 1). The records of six matching controls were missing, leaving 253 cases and 253 controls available for analysis. The mean age of both groups was eight years and three months, with a standard deviation of one year and 10 months, and 77% were boys.

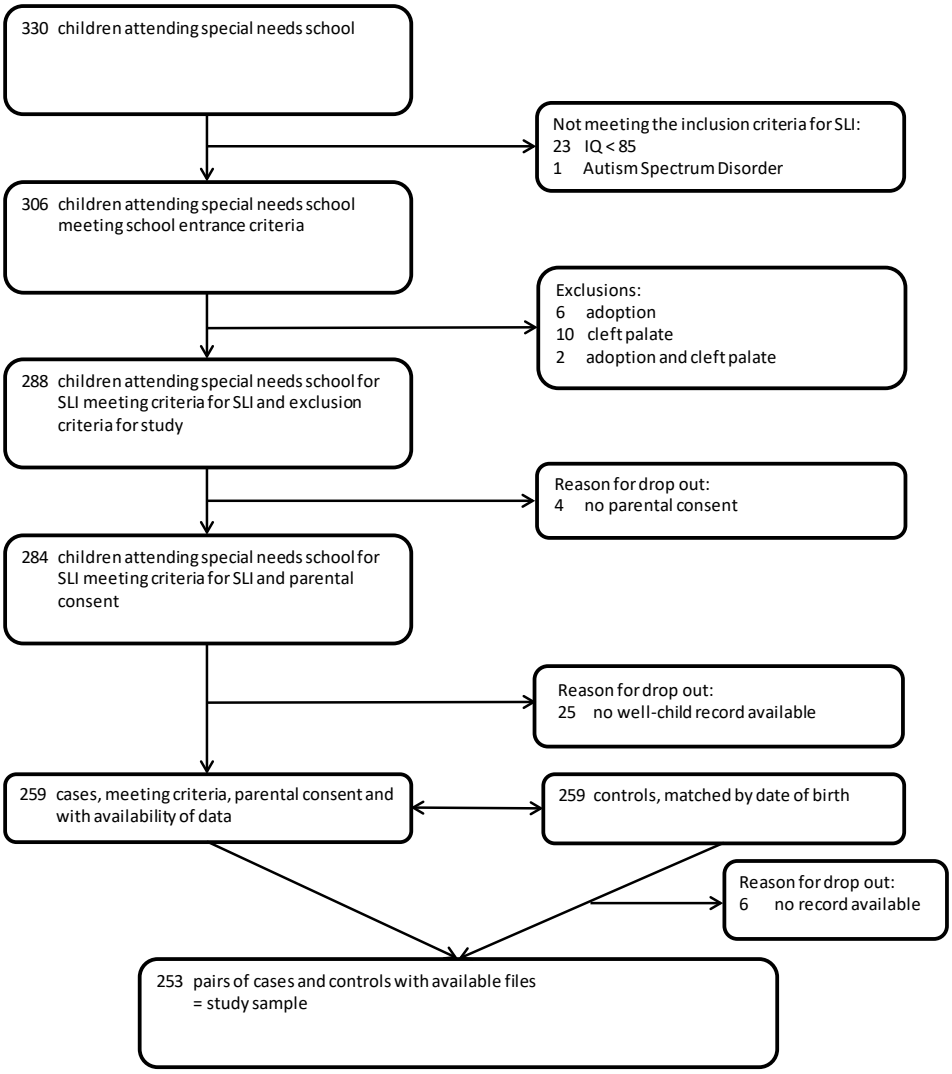

Figure 1 Study Sample

The mean age of cases and controls were similar for most well-child care visits (Table 1). The mean age showed statistically significant differences at three age norms, but these differences were small and without a general pattern. The number of children attending at two months and 30 months was considerably lower. This was due to the fact that children are sometimes not invited to these visits, depending on the policy of specific healthcare services.

Table 1. Sample sizes and mean age (in months) of cases with specific language impairment and controls. The age norm in months closely approaches the age recommended for regular visit to the well-child clinic.

Regular visit	Age norm in months	cases			controls			*P*[a]
		N	*mean age*	*SD*	*N*	*mean age*	*SD*	
1	1	232	1.1	0.3	231	1.1	0.2	0.84
2	2	167	2.1	0.3	188	2.1	0.3	0.55
3	3	230	3.3	0.4	242	3.2	0.3	0.04
4	6	229	6.2	0.4	241	6.1	0.3	0.23
5	9	231	9.3	0.5	237	9.4	0.5	0.01
6	12	222	11.5	0.6	240	11.7	0.6	<0.01
7	15	241	14.6	0.7	244	14.6	0.6	0.75
8	18	195	18.4	0.9	221	18.4	0.9	0.48
9	24	222	24.7	1.2	245	24.5	0.9	0.07
10	30	146	30.2	1.5	118	30.4	1.4	0.34
11	36	216	36.7	1.4	250	36.5	1.1	0.25
12	42 & 48[b]	205	45.8	1.3	222	45.6	1.2	0.07

Notes. n = sample size. SD = Standard deviation.

[a] Result from independent *t*-test for the difference between the mean ages of cases and controls.

[b] In practice, the language milestones with an age norm of 42 and 48 months were measured only at one regular visit (i.e., around 45 months).

Before the age of 18 months, cases and controls differed in the percentage of failures on one specific milestone, *waves bye-bye,* after it was adjusted for age with an overall $p < 0.05$, after Bonferroni correction (Table 2). From the age of 18 months onwards, cases and controls differed in the percentage of failures on all milestones, after adjustment for age, with an overall $p < 0.05$, after Bonferroni correction (Table 2). From the age of 24 months, all odds ratios were higher than 10. For example, children not passing the language milestone *says two-word sentences* at the age norm of 24 months were 21 times more likely to have severe specific language impairment, and be a case, than those passing the language milestone, with an adjusted odds ratio (OR) of 20.96 (Table 2). A specificity of ≥ 95% was found for 18 of the 23 milestones at the age norm. Sensitivity was < 50% for 19 of the 23 milestones at the age norm (Table 3). Furthermore, from the age of 24 months onwards, the estimated LR+ of all milestones was six or higher and from the age of 30 months onwards it was higher than 10 (Table 3). The positive predictive values were above 30% from the age of 18 months onwards when a prevalence of 7% was assumed, indicating that the chance of having SLI was higher than 30% when the milestone was not passed at that age. When a prevalence of 2% was assumed, the chances were lower, but still above 10%.

Table 2. Result from logistic regression analysis with group (one = case; zero = control) as outcome and language milestone and age at visit as predictor variables.

Age norm in months	Language milestone	OR_{adj} *(95% CI)*	*P*
1	*Reacts when spoken to (no pass vs. pass)*	1.01 (0.14 – 7.23)	0.99
2	*Smiles in response (no pass vs. pass)*	0.38 (0.08 – 1.90)	0.24
3	*Vocalizes in response (no pass vs. pass)*	1.65 (0.27 – 10.00)	0.59
6	*Produces varying sounds (no pass vs. pass)*	1.11 (0.07 – 17.93)	0.94
6	*Reacts on calling his/her name (no pass vs. pass)*	0.25 (0.09 – 0.70)	0.01
9	*Says "dada","baba", or "gaga" (no pass vs. pass)*	2.88 (0.90 – 9.25)	0.08
12	*Babbles while playing (no pass vs. pass)*	4.37 (0.86 – 22.28)	0.08
12	*Reacts to verbal request (no pass vs. pass)*	1.96 (0.56 – 6.85)	0.29
12	*Waves "bye-bye" (no pass vs. pass)*	3.90 (2.10 – 7.25)	<0.01*
15	*Says 2 "sound-words" with comprehension (no pass vs. pass)*	1.53 (1.02 – 2.32)	0.04
15	*Understands a few daily-used sentences (no pass vs. pass)*	1.21 (0.43 – 3.40)	0.72
18	*Says 3 "words" (no pass vs. pass)*	6.31 (3.81 – 10.44)	<0.01*
18	*Understands "play instructions" (no pass vs. pass)*	9.42 (2.74 – 32.42)	<0.01*
24	*Says 2 word "sentences" (no pass vs. pass)*	20.96 (12.69 – 34.62)	<0.01*
24	*Points at 6 parts of a doll's body (no pass vs. pass)*	12.69 (6.44 – 25.02)	<0.01*
30	*Refers to self, using "me" or "I" (no pass vs. pass)*	42.57 (12.82 – 141.33)	<0.01*
30	*Points at 5 pictures in a book (no pass vs. pass)*	48.34 (6.48 – 360.73)	<0.01*
36	*Says "sentences" of 3 or more words (no pass vs. pass)*	232.60 (31.67 – 1708.50)	<0.01*
36	*Speech is understood by acquaintances (no pass vs. pass)*	51.60 (21.58 – 123.40)	<0.01*
42	*Talks spontaneously about events at home/playground (no pass vs. pass)*	38.28 (9.03 – 162.24)	<0.01*
42	*Asks questions about "who", "what", "where" and "how" (no pass vs. pass)*	27.36 (9.62 – 77.85)	<0.01*
48	*Speech is easily understood by examiner (no pass vs. pass)*	38.29 (16.35 – 89.66)	<0.01*
48	*Asks questions about "how much", "when" and "why" (no pass vs. pass)*	18.93 (7.75 – 46.21)	<0.01*

Notes. OR_{adj}, = Odds ratio adjusted for the effect of age; CI = confidence interval; * overall $p < 0.05$, using Bonferroni correction.

Table 3. Sensitivity, specificity, positive likelihood ratio (LR+) with 95% confidence interval (95% CI), and positive predicted values (PPV)

Age norm in months	Language milestone	Specificity (%)	Sensitivity (%)	*LR+*	95% CI		PPV[a] (%)	PPV[b] (%)
1	*Reacts when spoken to*	99	1	1.00	0.14	7.04	2	7
2	*Smiles in response*	96	1	0.35	0.07	1.64	1	2
3	*Vocalizes in response*	99	1	1.55	0.26	9.21	2	7
6	*Produces varying sounds*	100	0	1.09	0.07	17.3	-	
6	*Reacts on calling his/her name*	91	2	0.27	0.10	0.70	0	2
9	*Says "dada", "baba", or "gaga"*	98	5	2.29	0.81	6.48	5	16
12	*Babbles while playing*	99	3	3.34	0.68	16.36	6	18
12	*Reacts to verbal request*	98	3	2.01	0.60	6.77	3	10
12	*Waves "bye-bye"*	93	23	3.18	1.89	5.35	6	20
15	*Says 2 "sound-words" with comprehension*	77	32	1.39	1.03	1.88	3	9
15	*Understands a few daily-used sentences*	97	3	1.19	0.44	3.22	2	7
18	*Says 3 "words"*	88	46	3.80	2.58	5.59	7	22
18	*Understands "play instructions"*	99	12	8.47	2.57	27.93	20	47
24	*Says 2 word "sentences"*	88	73	6.11	4.30	8.67	11	31
24	*Points at 6 parts of a doll's body*	95	39	7.10	3.99	12.64	14	37
30	*Refers to self, using "me" or "I"*	98	53	23.79	7.68	73.62	35	67
30	*Points at 5 pictures in a book*	99	36	37.44	5.25	266.98	42	73
36	*Says "sentences" of 3 or more words*	100	48	108.48	15.27	770.88	100	100
36	*Speech is understood by acquaintances*	97	55	18.76	8.95	39.33	27	58
42	*Talks spontaneously about events at home/playground*	99	28	29.56	7.27	120.16	36	68
42	*Asks questions about "who", "what", "where" and "how"*	98	35	19.00	7.04	51.29	26	57
48	*Speech is easily understood by examiner*	95	68	13.89	6.68	28.87	22	51
48	*Asks questions about "how much", "when" and "why"*	96	44	10.01	4.73	21.19	18	45

Notes. [a] PPV assuming a prevalence of specific language impairment of 2%;

[b] PPV assuming a prevalence of specific language impairment of 7%;

Discussion

The main findings of this study were that developmental language milestones, especially from the age of 24 months onwards, were predictive of SLI. From the age of 24 months onwards, not passing a milestone at the age norm was an indication that the child might have SLI. In general, milestones had a very high specificity, but the sensitivity was relatively low at the age norm. The high specificity meant that a high percentage of children in our study who did not have SLI passed a milestone at the age norm. The lower sensitivity indicated that many children with SLI also passed a milestone at the age norm. Therefore, passing a milestone at the age norm should not lead to the conclusion that the child does not have SLI.

In a systematic review of the feasibility of universal screening for speech and language delay, Law et al (20) noted that, in general, even screening tests for speech and language delay that consisted of many milestones had a lower sensitivity than specificity. Lowering the age norm was very likely lead to higher sensitivities for the milestones, but this would also lead to a lower specificity. Higher specificity is often chosen to minimise false positive results and therefore avoid unnecessary parental concern and overuse of services.

In the recommendations on developmental screening tests from the American Academy of Pediatrics, sensitivity and specificity levels of 70-80% are regarded as acceptable (5). In our view, the following factors are relevant for the choice of satisfactory values for sensitivity and specificity in combination with the positive likelihood ratio: the prevalence, the seriousness of the disease, the consequences of not detecting the disease, the importance of early detection and the acceptance of needless parental concern (20-22). In the case of SLI, the consequence of not detecting the disorder at two years of age is not critical, as long as a system is in place to provide ongoing monitoring of the child's development. Therefore, lower values for sensitivity are acceptable, although early detection at two years of age is preferable. High specificity values and likelihood ratios are important to prevent unnecessary parental concern. When we take all these considerations for SLI together, we conclude that a high specificity of ≥ 90%, a relatively lower sensitivity of ≥ 70% and a high likelihood ratio or LR+ of > 10 are important. Because of the low sensitivity, the use of separate language milestones cannot be recommended for developmental screening purposes. An exception is the milestone *says two-word sentences* at the age norm of two years old, but here the specificity is below 90%.

By using the LR+ and the prevalence it is possible to calculate the positive predictive value (PPV) of a language milestone, which is the probability that subjects not meeting a language milestone truly have SLI. For example, failing the milestone *says two-word sentences* at the age of 24 months, and assuming a prevalence for SLI of 2%, the PPV is expected to be 11%. Although this is a rather low percentage, we must bear in mind that this is the risk for having a severe language disorder that requires special needs education.

Rescorla found that the milestones *fewer than 50 words* or *no word combinations* at the age of two years had very low false positive and false negative rates for language

delay at the same age (8). Although it was not exactly the same, this milestone was comparable with our milestone *says two-word sentences* at the age of two years. We also found that this milestone was strongly related to language delay.

Schum (23) proposed guidelines about when to be concerned about speech and language development and when a child should be referred for further evaluation. The author used milestones taken from different sources of developmental tests for these guidelines. The red flags in McLaughlin's paper (9) were based on these guidelines. When a child did not meet a red flag at a certain age, immediate evaluation was considered necessary. McLaughlin mentioned 15 red flags, six of which were similar to the milestones used in our study. The red flags, the milestones of the NIDCD and our milestones resembled each other in many aspects (Table 4). The milestone *says two-word sentences* and *points at six parts of a doll's body* were mentioned as red flags and as NIDCD milestones, but with different age norms of 30 months and 24 months, respectively. But there were also similarities: the NIDCD milestone *uses two-word or three-word phrases to talk about and ask for things* was almost the same as our milestone *says sentences of three or more words* and both mentioned three years as the corresponding age norm.

At the moment there is a substantial discussion about the concept of SLI. We want to stress the point that the cases in this study were children with such severe language problems that they needed special education for this problem. Our outcomes represented the predictive properties for having such severe language problems, that mainstream education was precluded.

A first limitation of our study was that the cases in our study were a subgroup of children with SLI, that is only children with more severe SLI who needed special education. In 2012, almost 6000 children, 0.4% of all school aged children in the Netherlands, attended special schools for severe speech and language problems (24). This meant that only a selection of children with SLI, presumably only the more severe cases, were admitted to these schools. Therefore, the sensitivity rates for the total population of children with SLI might have been somewhat overestimated. Furthermore, since sensitivity rates might have been overestimated, the positive predictive values we calculated, assuming SLI prevalence rates of 2% and 7%, might also have been overestimated. It is possible that some of the controls could have had a mild form of SLI, even though they attended mainstream schools. Therefore, the specificity rates we found might be somewhat underestimated. A second limitation of our study was the amount of missing values in our data, especially at the well-child care visits at two months and 30 months. However, the sample sizes that remained were sufficient to estimate unbiased coefficients in logistic regression analysis, that is the number of events per variable was higher than 10.

Table 4 Summary of the age norm of the red flags according to American Family Physician Website, language milestones of the National Institute on Deafness and Other Communication Disorders (NIDCD) and language milestones from the Dutch Developmental Instrument (DDI)

McLaughlin		NIDCD		DDI	
Age norm months	Red flags	Age norm months	Items	Age norm months	Items
12	Does not babble, point or gesture	6	Babbles when excited or unhappy, babbles in a speech-like way	12	Babbles when playing
15	Does not use at least three words			18	Says 3 words
18	Does not say “mama”, “dada” or other names	12	Babbles using long and short groups of sounds (tata, upup,bibibi)	9	Says “dada”, “baba”, or “gaga”
		24	Follows simple commands and understands simple questions	18	Understands “play instructions”
24	Does not point to pictures or body parts when named	24	Knows a few parts of the body and can point to them when asked	24	Points at 6 parts of a doll’s body
30	Does not verbally respond or nod/shake head to questions			12	Reacts to verbal request
30	Does not use unique two word phrases, including noun-verb combinations	24	Puts two words together (“more cookie” or “no juice”)	24	Says 2 word “sentences”
		36	Uses two- or three-word phrases to talk about and ask for things	36	Says “sentences” of 3 or more words

A strength of our study was that the data on language milestones were registered in a uniform manner by trained professionals. Another strong point was that all cases were thoroughly diagnosed. As the diagnosis of SLI was made after the age of four years, this meant that the impairment was likely to have been persistent and we considered it unlikely that slow starters were included in our case group. Also, the fact that SLI was diagnosed quite some time after the language milestones were recorded meant that there was no question of recall bias.

Conclusion

We conclude that from the age of 24 months onwards, children not meeting language milestones at the age norm are at risk of having SLI at school age. The use of separate language milestones has limited value as a screening test for SLI, because sensitivity at

the age norm is low. However, failure on a language milestone at the age norm, especially after the age of two years, was found to be a reason for concern. Professionals should be aware that not meeting language milestones after the age of two years may be a signal that a child is at risk of having SLI.

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Chapter 3

Concise tool based on language milestones identifies children with specific language impairment at 24 to 45 months of age

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Concise tool based on language milestones identifies children with specific language impairment at 24-45 months of age.

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Abstract

Aim: This study aimed to develop a concise tool with acceptable predictive properties to identify children with specific language impairment (SLI).

Methods: In this nested case-control study children with SLI attending two special needs schools for severe speech and language difficulties in the Netherlands were matched by date of birth and sex with control children attending mainstream education. This study analysed the predictive validity for having SLI at a mean age of eight years and three months (range 4-11 years) using combinations of six language milestones that were registered at 24, 36 and 45 months and retrieved from the children's healthcare files in 2012.

Results: We included 253 pairs of children with and without SLI. During a single visit, combinations of two milestones at one age achieved a specificity of at least 97% and sensitivities ranged from 32% to 64%. However, the concise tool, which combined five milestones at three different ages - 24, 36 and 45 months - had a specificity of 96% (95% confidence interval 94%-99%) and a sensitivity of 71% (95% confidence interval 66%-77%).

Conclusion: Combining milestones at different ages provided a concise tool that could help to detect children with SLI at a young age.

Introduction

Specific language impairment (SLI) is diagnosed in children who exhibit a significant deficit in language ability that cannot be attributed to hearing loss, low nonverbal intelligence or neurological damage (1). The reported prevalence of SLI varies from 2-12%, due to differences in definition or study method (2). The most cited prevalence is 7%, as reported in a study by Tomblin et al (3).

SLI has been associated with social, emotional, personality and learning problems (4-6). When SLI is identified early this can improve long-term outcomes and provide early parental insight into their child's problems (7,8). There have been some indications that early interventions may have a positive effect on a child's development and give them a better chance to develop their potential skills (9).

In 2015 the US Preventive Services Task Force reviewed the evidence on screening for speech and language delay and disorders (10) and found inadequate evidence on the accuracy of screening instruments for use in primary care settings. The Task Force also stated that the accuracy of surveillance by primary care clinicians was inadequate to identify children needing further evaluation for speech and language delays and disorders (11). It also considered that the benefits of early detection and intervention were not yet sufficiently proven (11). However, the American Academy of Pediatrics has stated that early identification of developmental disorders is an important task for paediatric healthcare professionals and it has recommended incorporating developmental surveillance at every well-child visit (12).

The fact that we do not currently have an adequate screening instrument for speech and language delay should not deter us from attempting to develop and refine what is available to try to identify children with SLI as early as possible.

In a previous study on data collected in 2012 we investigated whether children with and without SLI had reached language milestones at a specific age (13). A special feature of the study was that we used having SLI from the age of four years as the gold standard. The conclusion of that study was that single language milestones between two and four years of age were moderately predictive for SLI (13). Our hypothesis for the present study was that the predictive validity could be increased by using combinations of milestones.

The present study aimed to construct a concise tool to facilitate identifying young children with SLI using combinations of language milestones that could be administered between the ages of 24 and 45 months. We felt it was necessary that the tool should have acceptable predictive properties for detecting children with SLI in well-child clinics and paediatrics settings and should be quick and easy to administer.

Methods

Design and study population

This was a nested case-control study and the cases were 253 children (77% boys) with SLI who attended two special needs schools for severe speech and language difficulties in the eastern part of the Netherlands. They were matched by date of birth and sex with 253 control children who attended mainstream education. The current study analysed the predictive validity for having SLI, using combinations of six language milestones registered at 24, 36 and 45 months that were retrieved from the children's healthcare files in 2012. At the time of the data collection the ages of the subjects in this study ranged from four to 11 years, with a mean age of eight years and three months. A previous study on achieving language milestones at a specific age, published in 2016, was also based on data that the authors retrieved in 2012 and that study also covered the children who were included in the current study (13).

The study schools were located in Nijmegen and Arnhem, which is a mixed rural and urban healthcare area. The selection criteria for admission to these special needs schools are very strictly formulated by the Dutch Department of Education and include having a score of more than 1.5 standard deviations (SD) below the mean on two or more language tests concerning the following areas: auditory processing, speech production problems, grammatical problems and lexical-semantic problems (14-15).

In addition, the disorder should not be due to hearing impairment or limited cognitive skills, as established with a validated test. The tested non-verbal intelligence quotient should be at least 80. A special committee selects the tests used (16). Autism spectrum disorder should be excluded as a cause of the language disorder. These criteria correspond with the internationally generally used criteria for SLI (1). The children in our study were diagnosed by a multidisciplinary team of specialists, including an audiologist, a psychologist, a didactic specialist and a speech therapist. Their report was then examined by an independent, Government-controlled committee. Children were very occasionally admitted to these schools even though they did not fully meet all the admission criteria. We therefore examined the test scores of all cases and only included children who met all the inclusion criteria.

The controls were children attending mainstream education in the same region. Each case was matched with a control child of the same sex and same date of birth give or take two days.

A total of 330 children, aged between 4-11 years, attended the two special needs schools for children with severe speech and language problems in the studied region. Of these, 306 fully met the criteria for admission to these special needs schools. We excluded 18 children due to a cleft palate or because they had been adopted. Adoption was an exclusion criterion, because data on their earlier milestones were not always available or reliable. The parents of four children did not want their child to take part.

Fully documented child healthcare files were found for 259 of the remaining 284 children. We were able to include 253 children attending mainstream education who had fully documented child healthcare files and the study therefore comprised 253 matched pairs (Figure S1).

Informed consent

In the Netherlands, all parents of children who attend Municipal Health Services are informed at the start of their care that their child's anonymous data may be used for scientific research. The Dutch Central Committee on Research Involving Human Subjects assessed the research project and concluded that individual parental approval was not needed, because the anonymity of the filed data was guaranteed. Despite this, we still decided to inform the parents of the cases about the study and ask for their consent.

Dutch well-child care

In the Netherlands all children are invited to attend 11 visits to well-child care facilities from birth to the age of four years and the attendance rate is almost 95% (17). Child development data are collected at each visit in a uniform way using a Dutch instrument (18) that is a modification of the Gesell test. It consists of a set of age-appropriate items, also called milestones, which cover five developmental fields. A total of 23 milestones cover language development and communication and are called language milestones. All child health professionals are trained to administer and register the milestones in the well-child care system according to a uniform protocol. When a child passes or fails an item at a visit this is registered in the child healthcare file as a plus or a minus, respectively. Our previous study in 2016 reported on the predictive properties of all 23 language milestones. In that study, which used the same study population as the current study, we also established that the mean age of the cases and controls were not significantly different for most of the well-child care visits (13).

In this present study we used the six language milestones that are registered between the ages of 24 and 45 months in the child healthcare files.

The concise tool

The Dutch developmental instrument that we used includes the following six language milestones between the ages of 24 and 45 months: *says two-word sentences* and *points at six parts of a doll's body* at 24 months, *says sentences of three or more words* and *speech is understood by acquaintances* at 36 months, and *talks spontaneously about events at home or in the playground* and *asks questions about who, what, where and how* at 45 months of age. Our aim was to construct a tool based on these six language milestones between the ages of 24-45 months to facilitate identify children with SLI.

Statistical analyses and calculation

Multiple imputation was applied to adjust for missing values of the milestones. This simulation-based approach creates a number of imputed (completed) data sets by filling in plausible values for the missing data. The imputations were based on a model that uses information from other language milestones to achieve optimal estimates. Uncertainty about the model estimates is reflected in differences between imputations in the various completed data sets. We used multivariate imputation by chained equations to create 20 imputed data sets based on all language milestones between 24 and 45 months of age and the group variable, which was the case or control group (19). The averages of the outcomes of the language milestones over all 20 completed data sets are presented. All statistical analyses were performed in R Version 3.1.3 (The R Foundation, Vienna, Austria) and SPSS version 20.0 for Windows (IBM Corp, Armonk, NY, USA).

To construct the concise tool with the milestones, we calculated the proportion of children with a referral at one or more age visits. All possible combinations of outcomes, pass or fail, of the two milestones administered at each of the three ages were tested on their predictive validity in terms of specificity and sensitivity. To keep the number of false positives low, we preferred a specificity of at least 95%. We calculated 95% confidence intervals (95% CI) according to the method devised by Rubin (20) or the exact confidence interval from the binomial distribution.

Results

At the time of the data collection the mean age of the 253 children in the SLI group and the 253 in the control group was eight years and three months with a standard deviation of one year and 10 months, and 77% were boys. In another previous study, published in 2017 with the same study population, we established that the pregnancy characteristics and Apgar scores did not differ significantly between both groups (21). The numbers of cases and controls with available data on achieving language milestones between the ages of 24 and 45 months are documented in Table 1. Missing values were imputed and the available and imputed data were used in the analyses.

Table 1 Validity of combinations of failure on one or two milestones at each age visit based on the imputed data (n=253 controls, n=253 cases)

Age in months	Milestone	Number of children		Outcomes on milestones	Sensitivity % (95%CI)	Specificity % (95%CI)
		cases n	controls n			
24	A	226	244	A-	72 (67-78)	88 (84-92)
	B	204	220	B-	38 (32-44)	94 (91-97)
	A and B	203	219	A- or B-	78 (73-83)	85 (81-90)
				A- and B-	32 (26-38)	97 (95-99)
36	C	200	226	C-	49 (43-56)	100 (99-100)
	D	203	238	D-	56 (50-62)	97 (95-99)
	C and D	194	220	C- or D-	64 (58-70)	97 (94-99)
				C- and D-	41 (35-47)	100 (98-100)
45	E	88	130	E-	52 (45-58)	98 (96-100)
	F	101	122	F-	56 (50-63)	97 (95-99)
	E and F	76	115	E- or F-	64 (58-70)	95 (92-98)
				E- and F-	44 (38-50)	99 (99-100)

A = *Says two-word "sentences"*
B = *Points at six parts of a doll's body*
C = *Says "sentences" of three or more words*
D = *Speech is understood by acquaintances*
E = *Talks spontaneously about events at home/playground*
F = *Asks questions about "who", "what", "where" and "how"*

A- = failure on milestone A

Table 1 also shows the predictive validity per age visit using combinations of the two milestones. The outcomes showed specificities ranging from 85% to 100% and sensitivities ranging from 32% to 78%. High sensitivity rates were always combined with specificity rates below 90%.

The predictive validity of the combinations of all six milestones was calculated (Table S1). At the age of 36 months the milestone *speech is understood by acquaintances* did not contribute much to the detection of more children with SLI, but decreased the specificity rate and this milestone was therefore excluded from the tool. The final version of the concise tool consisted of the following combination: two milestones at the age of 24 months, *says two-word sentences* and *points at six parts of a doll's body*, one milestone at the age of 36 months, *says sentences of three or more words* and two at the age of 45 months, namely *talks spontaneously about events at home or in the playground* and *asks questions about who, what, where and how*. This combination, which had the optimal predictive value, with a sensitivity of 71% and a specificity of 96%, is shown in Figure 1.

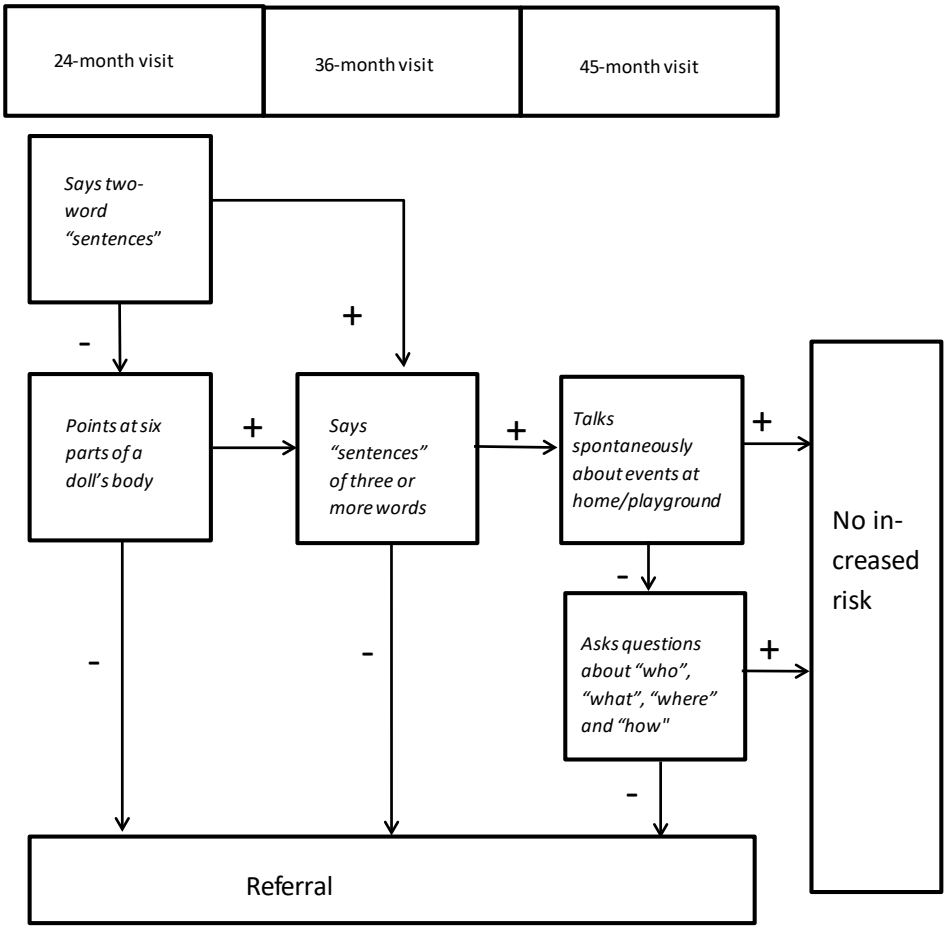

Figure 1 Flow chart with optimal combination using five milestones referred to as concise tool

Discussion

The main finding of our study was that a combination of language milestones may provide a useful instrument that can be used in well-child care and paediatrics to detect children with a high risk of SLI. Our latest study showed that the concise tool was quick and easy to administer and helpful in facilitating the early identification of children with SLI. However, this tool will need to be validated in a new study in the community.

As described in our previous study (13), important factors when choosing satisfactory values for sensitivity and specificity of a screening instrument include the prevalence and severity of the disease, the consequences of not detecting the disease, the importance of early detection and avoiding needless parental concern. Furthermore, we do not currently have irrefutable evidence of the benefits of early treatment (11). When we had

to choose between high values of specificity or sensitivity we preferred a low percentage of false-positives (high specificity) rather than the chance of missing a child with SLI (lower sensitivity). Accordingly, we concluded that optimal predictive values for a suitable instrument for screening for SLI were a specificity of at least 90% while a sensitivity of at least 70% was acceptable.

A review on screening for speech and language delay published in 2005 reported on the accuracy of screening instruments (11) and it stated that sensitivity and specificity rates of at least 70% were considered acceptable. Screening instruments used by parents had sensitivity rates ranging from 50% to 94% and specificity rates ranging from 45% to 96%. For screening instruments used by trained examiners the sensitivity rates were 17% to 100% and specificity rates were 46% to 100% (22). The gold standard used in these studies was another language test carried out at the same time or, in exceptional cases, a language test one year later. In our study, we used the diagnosis of SLI at school age, that is after the age of four years, as the gold standard. This means that slow starters were excluded from the study population. Therefore, we consider our gold standard to be superior to the gold standards in the studies mentioned by Wallace et al (22).

In the Netherlands there is a well-organised well-child care system, where 95% of all children are seen at regular age-points, making it easy to implement this screening tool. With the present system, many children with SLI are not detected or are detected later than desired (23). Implementation of this concise tool in the Netherlands would improve this. Our study shows that using a combination of two milestones at 24, 36 or 45 months of age will detect some children with SLI at a young age. Based on the outcomes shown in Table 1 we can conclude that children who fail on both milestones at a specific age have a very high risk for having SLI. When this is the case, we recommend that the professional takes a medical history, performs a physical examination and gains the opinion of the parents before a child is referred for further diagnostic investigations. Children who fail on only one of the two milestones at a specific age should be followed up, because they have an increased risk for having SLI. This way the specificity rate of the test will remain high and the sensitivity rate will increase.

Several of the milestones used in this study are also used as language milestones by the National Institute on Deafness and Other Communication Disorders. These include *knows a few parts of the body* and *can point to them when asked* and *puts two words together, such as more cookie or no juice,* at the age of 24 months of age (24). The American Family Physician Website considers it a red flag when the child *does not use unique two word phrases, including noun-verb combinations* at the age of 30 months (25). Milestones in the Dutch language were used in our study and the healthcare system in the Netherlands is different to that in many countries. However, we believe that the combinations of our concise tool can be useful in other countries, as it uses language milestones used by the National Institute or as red flags by other investigators. Further investigations in other countries with different healthcare systems and different languages will be necessary before our concise tool can be implemented there.

A limitation of the study was the number of missing values for two milestones at the age of 45 months. This was caused by a change in Government policy for economic reasons during the period of data registration. This meant that the child was no longer seen by a physician but by a well-child care nurse at 45 months. The nurses were not trained to administer the Dutch developmental instrument and this meant that it was not used by them. Because of this, the percentage of missing values in the language milestones at 45 months was 56-57%, which is much higher than usual. Missing data at this age are therefore not likely to be related to the outcome and can be considered as missing at random. Multiple imputation was applied to take the missing structure of the data into account.

We expect that when this concise tool is used that some children with other developmental problems will be included in the false-positive children. Even though they will not be diagnosed as having SLI, referral for investigation may be useful for many of these children.

Since 2014 several experts have recommended that the term SLI should no longer be used for children with language disorders that are not associated with a known biomedical aetiology (26). The expression developmental language disorder (DLD) is now recommended instead of SLI (27). DLD has a broader reach than SLI and the criteria for meeting the definition of DLD have become less stringent than for the definition of SLI. A new development is that low intellectual capacity or no significant difference between verbal and non-verbal abilities are no longer exclusion criteria. The cases in our study were not assessed with these new criteria, as we used the criteria that schools for children with severe speech and language difficulties in the Netherlands used for their selection procedure. Therefore, our cases were more strictly selected and did not fit with the new criteria of DLD. For this reason, we used the old name SLI. We assume that our concise tool will also be able to detect many children diagnosed with DLD, even though DLD includes children with a broader range of problems than SLI. However, this should be tested in a new study.

A strength of our study was the prospective design. Data on language milestones were registered before the diagnosis of SLI was made. This means that recall bias can be excluded. Furthermore, the language milestones were collected in a uniform manner by trained professionals. Another strength was that all cases were thoroughly investigated and diagnosed. As the diagnosis of SLI was made after the age of four years, this meant that the impairment was likely to have been persistent and we considered it unlikely that slow starters were included in our case group. In the Netherlands the majority of children attend well-child care services and practically all children in our study region with SLI would have been referred to the two special needs schools.

Conclusion

We concluded that our concise tool, which was based on combinations of language milestones at specific ages, could be helpful in detecting children with SLI. The tool was quick and easy to administer. A major advantage was that it could enable the majority of children with SLI to be identified before the age of four years and before starting primary school. This makes it possible for adequate educational support to be in place when these children start school, thus giving them the best possible start in their education.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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Supplementary files

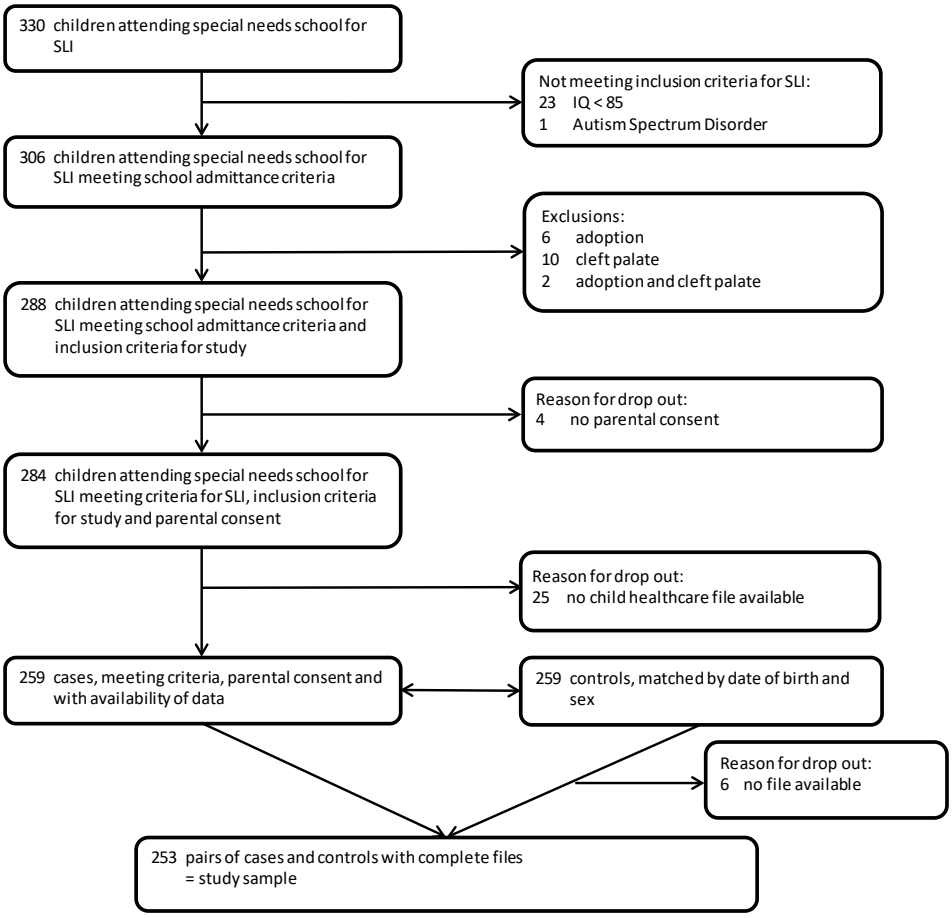

Figure 1 sup Study population

Table 1 sup Validity of combinations of all milestones at all age visits based on the imputed data (n= 253 controls, n= 253 cases)

Milestones	Sensitivity % (95%CI)	Specificity % (95%CI)
(A- and B-) or C- or E-	73 (67-78)	95 (92-97)
(A- and B-) or D- or E-	74 (69-80)	92 (89-96)
(A- and B-) or (C- or D-) or E-	78 (72-83)	92 (89-96)
(A- and B-) or (C- and D-) or E-	69 (63-75)	95 (92-97)
(A- and B-) or C- or F-	77 (72-83)	94 (91-97)
(A- and B-) or D- or F-	79 (74-84)	92 (88-95)
(A- and B-) or (C- or D-) or F-	81 (77-86)	92 (88-95)
(A- and B-) or (C- and D-) or F-	75 (70-80)	94 (92-97)
(A- and B-) or C- or (E- and F-)	71 (66-77)	96 (94-99)
(A- and B-) or D- or (E- and F-)	73 (68-79)	94 (91-97)
(A- and B-) or (C- or D-) or (E- and F-)	77 (72-82)	94 (91-97)
(A- and B-) or (C- and D-) or (E- and F-)	67 (62-73)	97 (94-99)

A- = failure on milestone A

Chapter 4

Among perinatal factors, only the Apgar score is associated with specific language impairment

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Among perinatal factors, only the Apgar score is associated with specific language impairment.

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Abstract

Aim: The purpose of this study was to assess the relation of perinatal risk factors with later development of specific language impairment (SLI).

Methods: In a case-control study, 179 children attending special needs schools for SLI were matched with children attending mainstream schools. Both groups consisted of 134 males and 45 females (age range 4–13y; mean age 9y, SD 2y 4mo). Data on duration of pregnancy, birthweight, delivery complications, birth characteristics, and Apgar scores were collected from the Preventive Child Health Care files of the Municipal Health Service.

Results: The gestational age of the children with SLI (mean 39.6wks, SD 0.9days) and for the comparison group (mean 39.4wks, SD 0.9days) and the birthweight of children with SLI (mean 3330.4g; SD 41.4g) and for the comparison group (mean 3388.1g; SD 39.8g) were not statistically different; neither were other pregnancy and birth characteristics, with the exception of the Apgar scores (effect of group for Apgar score after 1min p=0.045; after 5min p=0.001). The difference in Apgar scores was larger for females than for males (effect of group × sex for Apgar score after 1min p=0.049; after 5min p=0.043).

Interpretation: The relation between Apgar scores and SLI together with the influence of sex may be meaningful for predicting modelling and for understanding the causal pathway for SLI.

Specific language impairment (SLI) is an isolated developmental disorder.[1–3] By definition, this means that SLI is unrelated to other disorders like hearing loss, low intelligence, a contact disorder, or acquired brain damage.[3] The reported prevalence of this disorder varies widely in a range of 2 to 12% owing to differences in definition and methods of investigation. Very little is known about the aetiology of SLI and multicausality is probable. In studying twins, Bishop found obvious clues for a familial component, but there is also evidence for other factors such as perinatal hazards being involved.[4] In a systematic evidence review for the US Preventive Services Task Force, it was concluded that the most consistently reported risk factors for SLI include a family history of speech and language delay, male sex, and perinatal factors.[5]

From follow-up studies of preterm children,[6,7] it is known that these children have a high risk of multiple developmental disorders such as neurodevelopmental disorders and intellectual disabilities. De Kleine et al.[6] have shown that very preterm (<32wk and/or <1500g) children have more combined developmental disorders, whereas isolated language disorders are seldom found.[8] Most language problems are part of more complex developmental disorders. However, it is conceivable that less complicated perinatal problems might cause a single developmental disorder such as SLI. Nevertheless, literature on this subject is scarce and shows contradictory results. Gestational age, very low birthweight, complications during delivery, delayed first antenatal care, and an Apgar score less than 6 at 5 minutes have been studied as potential perinatal risk factors for SLI.[1,4,9–17] In some of these studies one or more of these factors were identified as having an association with language delay or SLI, whereas in other studies such associations were not found. The contradictions are probably caused by differences in definition or age when language delay or SLI was diagnosed, insufficient study group size, or recall bias by using questionnaires for perinatal hazards long after birth and after the diagnosis SLI was already established.

We had the opportunity to perform a case–control study in which we used data collected shortly after birth, so recall bias could be avoided. The diagnosis of SLI was in this study independently established through a government-controlled procedure for attending special needs schools for SLI at the age of 4 years or older.

The aim of our study was to assess the relations between the duration of pregnancy, birthweight, complications during delivery, and the Apgar scores after 1 and 5 minutes with later diagnosed SLI.

Methods

Population and design

The study was designed as a case–control study. Figure 1 shows information on the study population. The group with SLI was recruited in 2008 from 203 students in a special needs

school, who were born between 1994 and 2003, having an age range of 4 to 13 years. These children met the following strict criteria for special needs education formulated by the Dutch Department of Education:[18] a score of more than 1½ SD below normal for two or more tests on auditory processing, speech production problems, grammatical problems, and/or lexical–semantic problems; in addition, the disorder should not be caused by limited cognitive skills or hearing impairment. Children were diagnosed with SLI by a multidisciplinary team of specialists with an audiologist, a psychologist, a didactic specialist, and a speech therapist. Subsequently, their report was examined by an independent, government-controlled committee.

Exclusion criteria for the SLI group were missing or lack of perinatal data (*n*=20) or adoption (*n*=4), leaving 179 children to be included. Files were missing (*n*=4) or incomplete (*n*=16) mostly because of moving from another region. The comparison group was a random sample from the same region consisting of 179 children attending mainstream schools, representing those with normal cognitive abilities. They were matched with the included children of the affected group by date of birth and sex.

Children with SLI and the comparison group were recruited from schools situated in the service area of the Municipal Health Service of Nijmegen. Informed consent for anonymous use of filed data was given by the parents at their first contact with the Preventive Child Health Department of the Municipal Health Service. The Central Committee on Research Involving Human Subjects did not consider that their approval was needed.

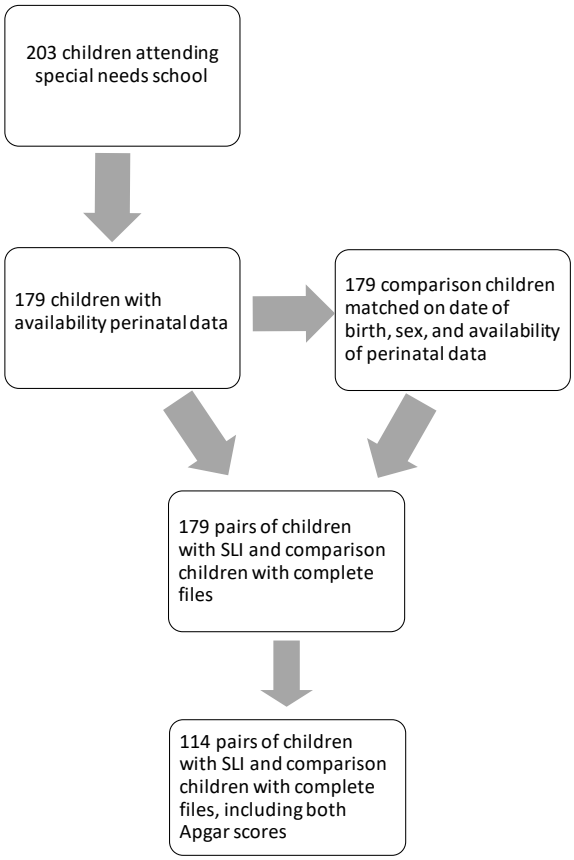

Figure 1 Flow chart of inclusion in the study.

SLI, specific language impairment

Data collection

From both groups the Preventive Child Health Department care files were obtained and the data concerning pregnancy and birth were studied. These data included duration of pregnancy, birthweight, complications during delivery, and the Apgar scores at 1 and 5 minutes after birth. Data on complications during delivery consisted of duration of the delivery and the expulsive phase of labour, whether spontaneous delivery occurred, and whether meconium-stained amniotic fluid was discharged. These data were prospectively acquired shortly after birth at the first visit from the Preventive Child Health Department. Kloosterman curves, as assessed in 1970, were used to determine whether the children were dysmature, normal, or heavy in weight for the duration of the pregnancy. Data on all the children in the study and comparison groups were analysed.

Statistical analyses

Data from children with SLI and the comparison group were analysed as pairs. The percentage of pairs with missing values per variable varied considerably between 0% (duration of pregnancy and birthweight) and 36% (Apgar score after 1min). To solve the problem of missing data, multivariate imputation by chained equations in R was performed.[19] Five imputed data sets were created, in line with Rubin, who stated that 5 to 10 imputed datasets are enough to achieve high efficiency.[20]

Continuous variables were inspected for normality, and skewed variables (i.e. both Apgar scores) were log-transformed. Differences between the two groups were examined with a McNemar test (for categorical variables) and dependent *t*-tests for continuous variables. As a measure of effect size, Cohen's *d* was computed.[21] A *d* value of 0.20, 0.50, and 0.80 was considered as small, medium, and large respectively.[21] To control for sex, a repeated-measures analysis was performed, with the group variable as within factor and sex as the between factor. Analyses used SPSS, version 20.0 (SPSS Inc, Chicago, IL, USA). The mean of the five imputed datasets was used as the final point estimate per group. Furthermore, if possible, the results of pooled tests were reported. For all tests, a two-tailed significance level of α=0.05 was used.

Results

Our sample consisted of 179 pairs of children with SLI and a non-affected comparison group, 134 (75%) pairs of males, and 45 (25%) pairs of females. The mean age of all children was 9 years (SD 2y 4mo). There were no differences in socio-economic status between the children with SLI and the comparison group as determined by analysis of postal area codes.

Also, for duration of pregnancy, birthweight, percentage of preterm births, dysmaturity, and delivery characteristics, we found no differences between the affected and comparison groups (Tables I and II). However, the Apgar score 5 minutes after birth showed a significant difference between children with and without SLI (Table III). The estimated effect size (Cohen's *d*) indicated that the difference was small (Table III). Table IV shows the results of repeated-measures analysis using group (children with SLI or comparisons) as within factor and sex as between factor. After controlling for sex, a significant difference between children with and without SLI was found for both Apgar scores. In addition, an interaction effect was found between group and sex. This effect implies that for females the difference in Apgar scores between the SLI and comparison groups is significantly larger than for males. The estimated effect sizes (Cohen's *d*) were small for males and medium for females (see Table III).

Table I: Pregnancy characteristics for the specific language impairment (SLI) and comparison groups (*n*=179)

Characteristic	SLI group	Comparison group	*p*	Cohen's *d*
Gestation, mean (SD) wks	39.6 (0.9)	39.4 (0.9)	0.34[a]	0.10
Birthweight, mean (SD) g	3330.4 (41.4)	3388.1 (39.8)	0.30[a]	−0.10
Preterm birth, %	7.8	8.4	1.00–1.00[b]	
Dysmaturity, %	2.8	1.7	0.73–0.73[b]	

Note. Values are displayed as means (standard error) or percentages, averaged over the five imputed data sets. Cohen's *d*, standardized mean difference between the groups (for continuous variables only). [a]Pooled results are given of the dependent *t*-tests for the five imputed data sets. [b]The range of the *p* values is given for the McNemar tests for the five imputed data sets.

Table II: Delivery characteristics for the specific language impairment (SLI) and comparison groups (*n*=179)

Characteristic	SLI group	Comparison group	*p*	Cohen's *d*
Duration of labour, mean (SD), h	10.1 (0.8)	10.0 (0.9)	0.90[a]	0.01
Expulsion, mean (SD), min	29.9 (3.2)	29.0 (2.3)	0.83[a]	0.03
Non-spontaneous birth, %	38.8	36.1	0.53–0.67[b]	
Meconium staining, %	20.6	20.9	0.44–1.00[b]	

Note. Values are displayed as means (standard error) or percentages, averaged over the five imputed data sets. Cohen's *d*, standardized mean difference between the groups (for continuous variables only). [a]Pooled results are given of the dependent *t*-tests for the five imputed data sets. [b]The range of the *p* values is given of the McNemar tests for the five imputed data sets.

Table III: Apgar scores 1 and 5 minutes after birth for specific language impairment (SLI) and comparison groups (*n*=179) and for males and females

	SLI group	Comparison group	*p*	Cohen's *d*
After 1min				
Total (*n*=179)	8.2 (0.2)	8.6 (0.1)	0.17[a]	−0.20
Males (*n*=134)	8.4 (0.2)	8.5 (0.1)		−0.06
Females (*n*=45)	8.2 (0.4)	8.6 (0.1)		−0.55
After 5min				
Total (*n*=179)	9.3 (0.1)	9.6 (0.1)	0.01[a]	−0.24
Males (*n*=134)	9.4 (0.1)	9.5 (0.1)		−0.12
Females (*n*=45)	9.3 (0.2)	9.6 (0.1)		−0.57

Note. Means (standard errors) are shown, averaged over the five imputed data sets (for the non-transformed scores). Cohen's *d*, standardized mean difference between the SLI and comparison groups. The *t*-tests were performed for the total group only. The results adjusted for sex are given in Table IV. [a]Pooled results are given of the dependent *t*-tests for the five imputed data sets, using the log-transformed scores.

Table IV: Results of repeated-measures analysis using group as within factor and sex as between factor

Apgar score	Within factor: group (SLI vs comparisons)		Between factor: group × sex	
	F (df1, df2)	*p*	*F* (df1, df2)	*p*
After 1min	6.02 (1, 177)	0.045	5.08 (1, 177)	0.049
After 5min	12.91 (1, 177)	0.001	4.91 (1, 177)	0.043

Pooled results of the *F*-tests are given for the five imputed data sets, using the log-transformed scores.

Discussion

In the present study we found no relation between the duration of the pregnancy, preterm birth, dysmaturity, birthweight, and complications during delivery and later development of SLI. However, children with SLI tended to have a lower Apgar scores 5 minutes after birth. In addition, the difference in Apgar scores between both groups was larger for females than for males.

The distribution of females (25%) and males (75%) in our study is somewhat different from other community cohorts.[1,2,5] In most studies males are in the majority, but not as high as in ours. We have no explanation for this result.

Our findings that gestational age has no influence on SLI is in line with most other studies, although published data are scarce. Stanton-Chapman et al.[1] performed a population study of perinatal risk factors in children with SLI identified at school. The study group existed of approximately 250 000 children, of whom almost 6000 (2.4%) had SLI. No relation with gestational age less than 37 weeks was established. Bishop[4] performed a study with homo- and heterozygote twins with and without SLI. Eighty-four twins, one or both with SLI, were compared with 36 twins with no history of speech–language difficulties. She found no relation with gestational age in her small study group. In the study by Luoma et al.,[12] 55 children born preterm at no more than 32 weeks' gestational age were examined at the age of 5 years for speech and language skills and compared with children born at term. Although they found significant differences in several language measures between both groups of children, SLI was not more frequent in the preterm group. Also, in the Victoria Study of Reilly et al.,[15] no significant relation was found between preterm birth and low language status or SLI at the age of 4 years in approximately 1500 children. In contrast, in an Australian study of nearly 5000 children of 4 to 5 years old, a relation was found between preterm birth and later attendance at speech–language pathology services.[10]

We found no difference in birthweight between children with SLI and the comparison group. Our results are in line with the findings of some studies.[9,10,15,17] However, others[1,14] did find low birthweight as a risk factor for language developmental problems. Tomblin et al.[16] interviewed parents of 177 children with SLI and 925 comparison children and did not find this relation for children with a low birthweight (<2500g). Also Aram et al.,[9] who studied 249 children with very low birthweight (<1500g) and 363 comparison children with a normal birthweight, did not. They also found no relation between a very low birthweight and speech and language disorders, after excluding the children with major neurological abnormalities. In the large population study of Stanton-Chapman et al.,[1] very low birthweight and medium low birthweight (1500–2499g) were established as risk factors for SLI, whereas gestational age was not an influence. Recently Prathanee et al.[14] have published a study of 3125 Thai children of whom 12% were identified with an early language delay at 2 years old. They found birthweight as a risk factor for early language delay. It should be noted that language delay at the age of 2 years is not predictive of

later SLI.[22] In the study by Keegstra et al.[11] a relation between low birthweight and parental concern about the language skills of the child was recorded. They investigated 240 children between 2 and 5 years of age, of whom 35% had adequate language development. This group was compared with the group of children with a subnormal score at the language tests. Neither group differed in birthweight. Also, in the study of Marschik et al.,[17] there was no relation between birthweight and delayed word production at the age of 18 months. Here also delayed word production at the age of 18 months did not imply SLI later on.

In our study there was no apparent difference between both groups in percentages of dysmaturity. As far as we know, dysmaturity has never been described in the literature in relation to SLI.

We found no difference between our groups for duration of delivery or the expulsive phase of labour, nor for the percentage of spontaneous delivery or meconium staining. None of the studies analysing complications during delivery and speech and language disorders found an association between these complications and SLI.[1,16]

We found low Apgar scores to be a risk factor for later SLI. The difference in Apgar scores was larger for females than for males. Study results on Apgar scores in relation to SLI are variable. Bishop[4] found no relation with the Apgar scores, but Stanton-Chapman et al.[1] did. It is interesting that Marschik et al.[17] describe an association between toddlers with a small word production at the age of 18 months and a low Apgar score 5 minutes after birth. Although this study was not about children with SLI and had only 15 toddlers and 15 comparison children, the results are in line with our findings. We found no study on the influence of sex on Apgar scores and having SLI.

Based on the results of the present study, we conclude that the relation between perinatal factors and subsequent SLI is restricted, which is in line with most studies.[1,4,9–12,14–17] Only the Apgar scores seem to be related to the later development of SLI in children, especially in females.

The Apgar score can be regarded as a measure of health status shortly after birth.[23] It is conceivable that lower Apgar scores are an expression of reduced health status. Recently, an association of cerebral palsy with an Apgar score 5 minutes after birth has been shown.[24] This relation was most obvious in children with a normal birthweight. The results of this study[24] and our findings suggest that this reduced vitality has an association with later developmental disorders, independent of birthweight and duration of pregnancy. Presumably vitality and therefore the Apgar score can be seen as indicators of brain immaturity or impairment. SLI is a disorder that is more frequent in males. Females are presumably less 'vulnerable' to this disorder unless there is an additional problem like a lower Apgar score. Future research may reveal if the Apgar score can be useful as a prediction model for SLI and/or other developmental disorders, with other known risk factors for these conditions.

One of the strengths of our study is that most data were collected shortly after birth, so recall bias was avoided. Another strength was that the comparison group was a

random sample from the same region as the children with SLI. In addition, the diagnosis of SLI was established by an independent committee on the basis of strict criteria for special needs education at the age of 4 years or older. Our study also had some limitations. Not all Apgar scores were available. However, we have no reason to assume that there is a relation between not registering the Apgar score and later development of SLI. In addition, the criteria we used for dysmaturity were the Kloosterman curves[25] for establishing whether a child was born dysmaturely. These curves originate from 80 000 deliveries in two Amsterdam clinics between 1931 and 1967, so may be somewhat out of date.[26] Because these criteria were used for both groups it is not likely that they influenced the results. We do not have data for the profiles of the children with SLI, so we cannot describe specifics about the SLI profiles of the individuals with a low Apgar score. This will be an item for further research. We found that for females the difference in Apgar scores was larger than for males. The fact that the number of females, especially females with low Apgar scores, was small may have influenced this result. Further studies on this subject are necessary.

Conclusion

Based on the results of the present study, we conclude that the relation between perinatal factors and subsequent SLI is restricted. Only the Apgar scores appear to be related to the later development of SLI in children. For females, the difference in Apgar scores was even larger. Further investigation of the relation of the Apgar score with isolated developmental disorders and the difference in sex can give us greater understanding of the causal pathway of these disorders. These results may also be useful in developing prediction tools for early detection of SLI.

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Chapter 5

Specific language impairment is associated with maternal and family factors

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Specific language impairment is associated with maternal and family factors.

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Abstract

Background This study aimed to identify risk factors associated with specific language impairment (SLI).

Methods In a nested case-control design, 253 children attending special needs schools for severe speech and language difficulties in the Netherlands, were matched for sex and date of birth with 253 children attending mainstream education. Data on perinatal, maternal and family issues were retrieved from well-child care files registered shortly after birth.

Results Children with SLI had younger mothers than children in the control group (mean 30y 9mo versus mean 31y 9mo) (p=0.02). Children with SLI were less frequently breastfed directly after birth (55% versus 71%) (p=0.0007) and were less frequently firstborns (33.3% versus 46.2%) (p=0.002). No statistically significant differences were found for any of the other risk factors.

Conclusions A relationship was found between SLI and maternal age, being breastfed and place in the birth order. Perinatal risk factors do not seem to be strongly associated with SLI.

Introduction

Language development may be impaired by disorders such as hearing loss, low intelligence, a contact disorder, inadequate language input, congenital defects or acquired brain damage. When no cause is found it is regarded as a primary language disorder or specific language impairment (SLI). SLI is probably the most prevalent developmental disorder in childhood with a prevalence of 7 % (Tomblin *et al*. 1997).

Understanding risk factors associated with SLI could provide more insight into the aetiology of isolated developmental disorders such as SLI. However, literature on this issue is sparse and contradictory.

A recent systematic review mentioned the following risk factors for speech and language delay: male sex, family history, low parental education and various perinatal risk factors (Wallace *et al*. 2015).

This study investigated the association between SLI and prenatal, perinatal and postnatal risk factors and maternal factors, such as hypertension, use of medication, smoking and alcohol or drugs use during pregnancy, the child being breastfed and family circumstances, such as parental age and place in birth order.

Methods

Design

A nested case-control study was performed (Diepeveen *et al*. 2013). Cases were children meeting the criteria for SLI attending special schools for children with severe speech and language difficulties. Controls were normally developing children from mainstream schools in the same region. Cases and controls were matched pairwise for date of birth (± two days) and sex.

Study population

Children attending special schools for children with severe speech and language difficulties have to meet strict criteria formulated by the Dutch government (Table 1). These criteria correspond with the internationally used criteria for SLI.

Exclusion criteria for cases and controls were adoption, cleft palate and non-availability of the well-child record. The Dutch Central Committee on Research Involving Human Subjects advised that parents' approval was not needed because anonymity of the filed data was guaranteed. Although not obligatory, parents of the cases were asked for consent.

Table 1 Entrance criteria for special needs school for children with severe speech and language difficulties:

Concerning language	a score of a score of more than 1.5 standard deviation (SD) below the mean on two or more validated language tests on: * auditory processing, * speech production problems, * grammatical problems and * lexical-semantic problems
Concerning co-morbidity	the disorder should not be due to hearing impairment or contact disorder
Concerning intelligence	cognitive skills in the normal range, as established with a validated test

Formulated by Dutch government (wetten.nl - Regeling - Wet op de expertisecentra - BWBR0003549,) (wetten.nl - Regeling - Besluit leerlinggebonden financiering - BWBR0014753)

Measures

In the Netherlands almost 95% of parents make use of the extensive well-child healthcare system (CBS - Ouders geven consultatiebureau gemiddeld een ruime 7 - Webmagazine). About 10 days after birth data concerning pregnancy, birth and maternal and family circumstances are noted. The records of both cases and controls were obtained. Data, including perinatal factors such as gestational age, birthweight, complications during delivery and Apgar scores, as well as parental age and place in the birth order, were collected from these records. Pre- and postnatal risk factors such as medication, smoking or alcohol or drugs use during pregnancy and breastfeeding directly after birth were also included.

Statistical analyses

Data from cases and controls were analysed as pairs. Differences between groups were examined with a McNemar test for categorical variables and a paired *t*-tests for continuous variables. For skewed variables such as the Apgar scores logtransformed values were used.

Results

The study population consisted of 330 children, aged 4 - 11 years, attending two schools for children with severe speech and language difficulties. Of these, 306 met the strict admission criteria. Eighteen were excluded because of cleft lip and/or palate and/or adoption. Parents of four case children declined consent, leaving 284 cases in our study population. Sufficiently documented well-child care records of 259 were found. Matching controls were sought and 253 sufficiently documented well-child care records of control children were found, giving a total study sample of 506 children (Figure 1). The mean age of both groups was eight years and three months (SD= 1 year and 10 months) and 77% were boys.

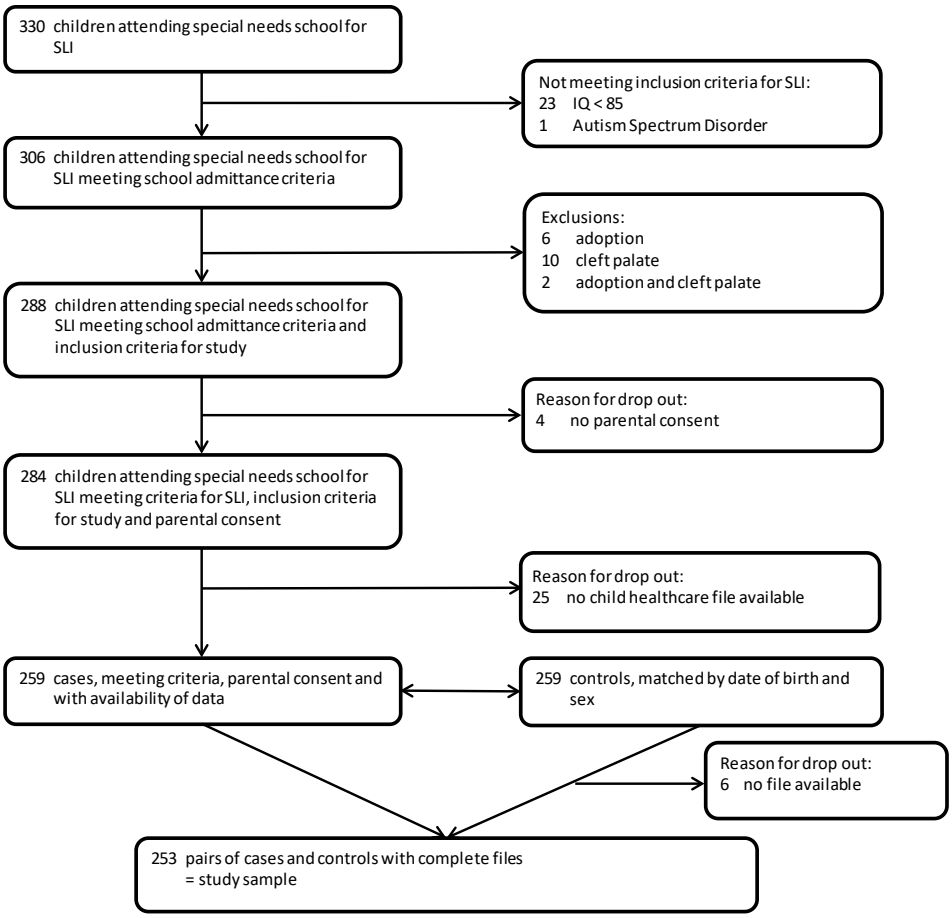

Figure 1 Study population

Assuming a proportion of 50% and a correlation coefficient between the characteristics of the matched cases and controls of 0.2, this sample of 506 subjects achieves 80% power to detect an odds ratio of 1.76 versus the alternative of equal odds using a Chi-square test with a 0.05 significance level. The odds ratio increases to 2.28 when we assume a proportion of 10%.

No statistically significant difference between the children with and without SLI was found for pregnancy characteristics such as duration of gestation, preterm birth, birthweight, small for gestational age or delivery related characteristics such as duration of labour, duration of expulsion, non-spontaneous birth, meconium staining or Apgar scores (Table 2).

Table 2 Results of comparisons between group of children with Specific language Impairment (SLI) and control group

	SLI group Mean (SD) or %	Control group Mean (SD) or %	*p*-value
Pregnancy characteristics			
Gestation, wks	39.7 (1.80)	39.4 (1.99)	0.19
Birthweight, g	3440 (579)	3426 (633)	0.79
Preterm birth, %	8	9	0.64
Small for gestational age, %	11	13	0.49
Delivery Characteristic			
Duration of labour, h	6.22 (7.01)	6.88 (8.53)	0.35
Expulsion, min	21.3 (31.4)	21.5 (26.0)	0.92
Non-spontaneous birth, %	22	27	0.29
Meconium staining, %	20	14	0.18
Apgar scores			
Apgar score 1 min	8.60 (1.09)	8.72 (1.01)	0.26/ 0.20[a]
Apgar score 5 min	9.50 (0.96)	9.63 (0.64)	0.09/ 0.22[a]
[a] using logtransformed scores			
Family characteristics			
Age father, y; mo	33;10 (5;8)	34;7 (5;3)	0.17
Age mother, y; mo	30;9 (5;4)	31;9 (4;3)	0.02
Being firstborn, %	33	46	0.002
Family history			
Diabetics, %	20	18	0.6
Intellectual disability, %	6	3	0.11
Epilepsy, %	10	6	0.06
Hearing defects, %	14	9	0.11
Congenital defects, %	14	12	0.53
Other pregnancy characteristics: illnesses, medication, smoking and breastfeeding			
Hypertension during pregnancy, %	13	14	0.88
Special medication during pregnancy, %	24	21	0.39
Smoking during pregnancy, %	13	9	0.19
Alcohol during pregnancy, %	1	1	1.0
Drugs during pregnancy, %	1	0	0.16
Start breastfeeding directly after birth, %	55	71	0.0007

Analysis of family characteristics showed that mothers of SLI children were younger (30 years and 9 months versus 31 years and 9 months, p=0.02, Cohen's d 0.21), but the age difference between fathers was smaller and not statistically significant (33 years and 10 months versus 34 years and 7 months). Thirty-three percent of children with SLI were firstborns versus 46% of control children (OR 0.58) (Table 2). A family history of diabetes, intellectual disability, epilepsy, hearing defects or congenital defects was present more frequently in the children with SLI, but this was not statistically significant (Table 2).

In the study population hypertension, use of special medication, smoking and use of alcohol or drugs during pregnancy were more frequent in the SLI group, but not statistically significant. Shortly after birth 55% of the children with SLI were breastfed which is statistically significantly less than the control children (71%) (OR 0.51) (Table 2).

Discussion

Mothers of children with SLI were younger at delivery, although the effect size was small. The association between maternal age and SLI has been described earlier *(*Reilly *et al*. 2010; Sutcliffe *et al*. 2012). However, others report no such association (Harrison & McLeod 2010; Prathanee *et al*. 2007; Reilly *et al*. 2010; Stanton-Chapman *et al*. 2002 Whitehouse *et al*. 2014). An explanation for how older maternal age could protect the child from SLI could be that older mothers are more confident and responsive to their children, resulting in better language stimulation.

Children with SLI were less frequently firstborns. The combination of children with SLI tending to have younger mothers and also being firstborns less often is remarkable. The relationship between the place in the birth order and SLI has also been reported by others *(*Prathanee *et al.* 2007*;* Reilly *et al*. 2010; Stanton-Chapman *et al*. 2002). Children with older siblings have been reported as having lower levels of language comprehension at 18 and 36 months of age (Zambrana *et al*. 2012). Being the firstborn child seems to stimulate language development and be protective against SLI.

A clear difference between the groups was found for breastfeeding directly after birth. This has previously been reported (Tomblin *et al*. 1997; Vestergaard *et al*. 2007), but some disagree (Prathanee *et al*. 2009). Possible explanations why breastfeeding can be protective for SLI are: less ear infections in early life, more face to face communication between mother and child, or it may be due to nutritional advantages of breast milk for neurodevelopment.

Surprisingly the control group generally had less favourable pregnancy and birth outcomes than children with SLI. However the differences were not statistically significant. The finding that perinatal risk factors are not associated with SLI is in line with several other studies. Previously we found no relationship between perinatal factors and SLI, with the exception of the Apgar score (Diepeveen *et al*. 2013). Whitehouse (Whitehouse *et al.* 2014) also concluded that there was no clear relationship between prenatal, perinatal and neonatal complications and SLI.

Unfortunately we were unable to collect data on the Social Economic Status (SES). This may have influenced some outcomes. It is possible the differences between both groups are all related to the same risk factor, namely the family SES.

Another limitation of this study is that we were not able to detect very small effect sizes with a sample of 506 subjects. When we corrected for multiple testing with the

Bonferroni correction, there was no significant association between SLI and maternal age. All other associations remained significant.

One of the main advantages of our design is that we could avoid recall bias by using data registered shortly after birth, which was long before SLI was established. Another strong point is that all cases have been thoroughly diagnosed.

We conclude that younger maternal age, the child not being the firstborn and not being breastfed directly after birth are associated with having SLI. No association was found between pre-, peri- and postnatal risk factors and SLI.

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Chapter 6

Children with specific language impairment are more likely to reach motor milestones late

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Children with specific language impairment are more likely to reach motor milestones late.

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Abstract

Background

Delayed language development without an obvious cause is considered an isolated developmental disorder and is called specific language impairment (SLI). SLI is probably the most prevalent developmental disorder in childhood with a generally cited prevalence of 7 %. This study aimed to investigate whether SLI is always an isolated disorder or if children with SLI also have delayed motor development.

Methods

We used data of an earlier study with a prospective nested case-control design in which developmental data were collected from child healthcare files. Cases were children (4-11 years) with diagnosed SLI. They were matched by sex and date of birth with control children attending mainstream education. Data of both groups on seven gross and six fine motor milestones which had been registered in the Dutch Developmental Instrument between the ages of 15- 36 months were retrieved from child healthcare files.

McNemar tests were performed to test for differences in reaching motor milestones at the age norm between the case and control group.

Results

Data from 253 children in each group were available. A significant difference was found between both groups in the proportion failing to reach three of the seven investigated gross motor milestones at the age norm ($p < 0.05$). The proportion of children not reaching the motor milestone at the age norm was significantly higher for five of the six fine motor milestones in children with SLI compared with control children ($p < 0.05$).

Conclusions

More children with SLI are late in reaching motor milestones than children without SLI. This means that it is debatable whether SLI can be regarded as a "specific" impairment which is not associated with other developmental problems. A broad developmental assessment is therefore indicated when diagnosing SLI.

Introduction

A language developmental disorder or delay can be caused by deficits such as hearing loss, low intelligence, a contact disorder or neurological damage. When there is no obvious cause for language delay, this is called a primary developmental language disorder (DLD) or specific language impairment (SLI; Leonard, 2014). SLI is the most prevalent developmental disorder in childhood (Bishop, 2010) with a prevalence of approximately 7% being most frequently cited (Tomblin *et al*. 1997).

By its very definition SLI is an isolated developmental disorder, because only language development is affected. However several studies and reviews have shown that children with SLI also frequently have motor deficits (Bishop, 2002; Finlay & McPhillips, 2013; Flapper & Schoemaker, 2013; Hill, 2001; Leonard, 2014; Rechetnikov & Maitra, 2009; Sanjeevan *et al*. 2015; Webster, Majnemer, Platt, & Shevell, 2005). One of the final statements in the recent Delphi Consensus Study on identifying Language Impairment was "Language impairment often co-occurs with problems in motor skills…."(Bishop, *et al.* 2016). However most of the studies evaluated motor skills in children already diagnosed with SLI, which raises the possibility of bias.

The aim of this study was to investigate whether the motor development of children diagnosed with SLI was delayed compared to a control group of normally developing children. Our study had the advantage that we could use data on motor skills registered before the diagnosis of SLI was established. Hereby we could avoid bias which could be caused if parents and professionals were aware of the presence of a developmental problem.

Methods

Design

In an earlier study, data were collected to investigate the predictive value of language milestones for having SLI (Diepeveen *et al.* 2016). That earlier study compared children with SLI (cases) with children attending mainstream education (controls) in a prospective nested-case control design in achieving language milestones earlier in life.

In this present study the same study population was used to compare the group of children with SLI to the control group using data concerning gross and fine motor milestones at various visits to the well-child healthcare facility between the ages of 15 and 36 months. This meant that the data had been registered long before the diagnosis of SLI was known.

Study population

Cases were children, aged 4 - 11 years old, attending the two special needs schools for children with severe speech and language difficulties in a region in the eastern part of the Netherlands. Before admission to these schools, children have to meet the entrance criteria formulated by law (wetten.nl, 2017). In order to be admitted, the children have to score more than 1.5 standard deviation (SD) below the norm on two or more tests on at least two of four language aspects. The four aspects are *auditory processing, speech production, grammatical abilities* and *lexical-semantic abilities.* The language tests have to meet test criteria formulated by a special committee ("TTQkaart mei", 2016). In addition, the disorder should not be due to hearing impairment or limited cognitive skills, as established with a validated test. It must also be clear that the language disorder is not dominated by an autism spectrum disorder. These criteria correspond with the internationally generally used criteria for SLI (Leonard, 2014). Children were diagnosed by a multidisciplinary team of specialists including an audiologist, a psychologist, a didactic specialist and a speech therapist. Subsequently, their report was examined by an independent, government-controlled committee.

Controls were children from the same region, but attending mainstream education. Each case was matched with a control child with the same sex and date of birth (maximum 2 days younger or older).

Sometimes a child could be admitted to a special needs school for children with severe speech and language difficulties, despite the fact that the criteria were not fully met, for example if a more appropriate special needs school was too far away from the child's home. Therefore, we examined the records of all cases to check whether they met the inclusion criteria. Exclusion criteria for cases and controls were adoption, cleft palate and non-availability of the well-child record.

Ethical and legal aspects

The Dutch Central Committee on Research Involving Human Subjects assessed the research project and concluded that parents' approval was not needed because anonymity of the filed data was guaranteed. Although not legally mandatory, parental consent was asked for the cases.

Measures

There is an extensive system of well-child healthcare with a participation rate of almost 95% in the Netherlands (CBS, 2017). All children are invited for 11 visits to well-child care facilities from birth to the age of 4 years. At each visit developmental data are collected in a uniform manner using the Dutch Developmental Instrument, which is also known in Dutch as the Van Wiechenschema (Laurent de Angulo *et al.* 2008). This instrument is used to monitor child development. The Dutch Developmental Instrument is a modification of the Gesell test. It

consists of 75 milestones covering five developmental fields: communication, gross and fine motor activity, adaptive and social behaviour.

All milestones are assessed at an age when the chance of passing is at least 90% (the age norm). The Dutch Developmental Instrument is considered to have adequate measurement properties (Jacobusse, van Buuren & Verkerk, 2006). Child health professionals are trained to administer and register each separate milestone according to a uniform protocol. The results are registered in the personal file of the child in the well-child care system. For this study we used data on motor milestones from the files of case and control children recorded during their well-child care visits from birth to the age of 4 years. In our previous study we established that in this study population the mean ages of cases and controls at the time of the visits were not significantly different for most well-child care visits (Diepeveen *et al.* 2016).

Statistical analyses

Data from the well-child care records of matched cases and controls were analysed as pairs. The differences between the groups on reaching the motor milestones were analysed with the McNemar test using SPSS. *P*-values (two-sided) < 0.05 were considered statistically significant.

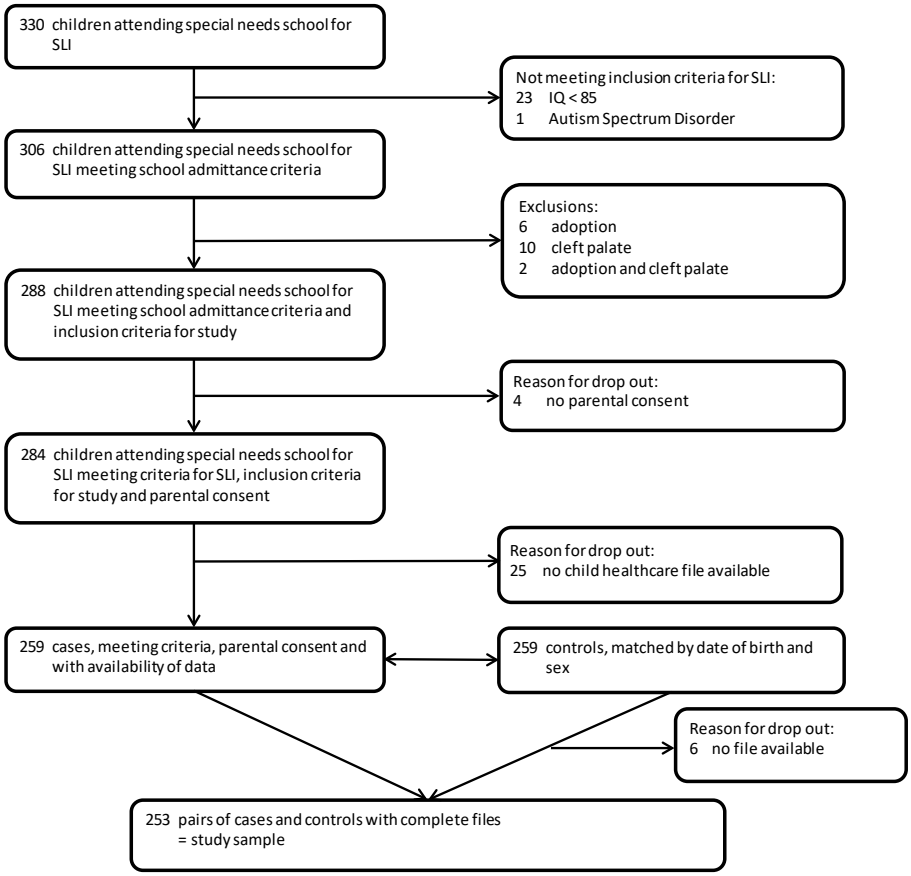
Explanation of terminology used

It has recently been recommended by several experts that the term SLI should no longer be used for children with language disorders not associated with a known biomedical etiology (Ebbels, 2014).The term "Developmental Language Disorder" is now recommended instead of SLI (Bishop *et al*, 2017). The term DLD has a broader reach than SLI and the criteria for meeting the definition DLD have become less stringent than for the definition of SLI. A new development was that low intellectual capacities or no significant difference between verbal and non-verbal abilities are no longer exclusion criteria. Our data were collected before the publication of these new views. The cases in our study were more strictly selected than would be the case using the new criteria. We used the criteria that schools for children with severe speech and language difficulties in the Netherlands used for their selection procedure. As the cases in our study were not diagnosed using the criteria for DLD we used the old term SLI. We assume that the outcomes of our study are not significantly influenced by this difference. However, a new study is needed to investigate whether our outcomes could also be applied to children diagnosed with DLD.

Results

Three hundred thirty children, aged 4-11 years attended the two special schools for children with severe speech and language difficulties in the studied regions. Of these, 42 did not meet our inclusion criteria, due to not meeting the inclusion criteria for SLI (i.e. 23 with IQ below 85, 1 with Autism Spectrum Disorder), due to adoption (6), due to cleft palate (10), or due to a combination of adoption and cleft palate (2). Twenty-five children were excluded because of missing well-child care records and four were excluded because parents did not give consent for participation (Figure 1). The records of six matching controls were missing, leaving 253 cases and 253 controls available for analysis. The mean age of both groups was 8 years and 3 months, with a standard deviation of 1 year and 10 months, and 77% were boys. In our previous study on risk factors associated with SLI we found no significant differences for pregnancy and delivery characteristics between the two groups in this study population (Diepeveen, van Dommelen, Oudesluys-Murphy, & Verkerk, 2017).

Figure 1 study population



The proportion of children not reaching the motor milestone at the age norm was significantly higher for three of the seven gross motor milestones in the group of children with SLI compared with the control group (Table 1). A significant difference was found between both groups in the proportion failing to reach five of the six investigated fine motor milestones at the age norm (Table 1). Compared to the control group more children with SLI were late in reaching the following milestones: *Walks along, Walks alone, Throws ball without falling down, Walks well alone, Rides (tri) cycle, Puts cube in and out of a box, Builds tower of 2 cubes, Builds tower of 3 cubes, Imitates building a truck*, *Places 3 shapes in shape-box* and *Imitates drawing vertical line*.

Table 1 Proportion of children NOT reaching the motor milestone at the age norm

Age norm	Motor milestones	Pairs (cases/controls) *N*	Cases with SLI % fail	Controls % fail	*p* value*
	Gross motor milestones				
15 months	Crawls, abdomen off the floor	222 (235/237)	4.5	6.3	0.541
	Walks along	215 (227/241)	7.4	3.7	0.134
18 months	Walks alone	158 (188/205)	15.2	5.1	0.006
	Throws ball without falling down	64 (111/143)	29.7	6.3	0.001
24 months	Squats or bends to pick up things	165 (193/216)	0.6	1.8	0.625
	Walks well alone	189 (204/230)	2.1	0.5	0.375
36 months	Rides (tri) cycle	156 (178/217)	25.6	13.5	0.013
	Fine motor milestones				
15 months	Puts cube in and out of a box	194 (216/230)	1.6	0	0.250
18 months	Builds tower of 2 cubes	63 (106/125)	27.0	9.5	0.019
24 months	Builds tower of 3 cubes	152 (182/210)	11.2	3.3	0.012
36 months	Imitates building a truck	127 (170/190)	39.4	11.0	0.000
	Places 3 shapes in shape-box	191 (204/236)	8.9	3.1	0.035
	Imitates drawing vertical line	137 (179/192)	19.7	10.9	0.082

*Mc Nemar test

Discussion

In this study more children with SLI did not reach motor milestones at the age norm than children from the control group. The difference seemed to be more pronounced for the fine motor than for the gross motor milestones.

Studies with data on reaching isolated motor milestones in groups of children with and without SLI are scarce. Most studies with data on the time of reaching individual motor milestones of groups of children with and without SLI compare groups on

outcomes of an individual motor task or of complete motor tests. Sometimes a parental questionnaire on motor development is used.

In Trauner, Wulfeck, Tallal, and Hesselink's (2000) study on neurological findings of children with developmental language impairment, it was found that the group of children with language impairment were slightly, but statistically significantly, older when reaching the motor milestone *walked unassisted* compared with a group of normally developing children matched for age. In Trauner et al.'s study the data were collected using parental questionnaires and the groups were not matched for sex. The criteria for language impairment used by Trauner et al. resembled those for SLI. In our study more children with SLI were late in reaching the motor milestone *Walks alone* compared with children from the control group, which is in line with the result of the study of Trauner et al. (Trauner *et al*. 2000).

Among the population of children attending a special needs school for children with severe speech and language difficulties in the Netherlands, Flapper and Schoemaker (2013) reported that 32% had developmental coordination disorder according to the internationally used four criteria for this diagnosis. Finlay and McPhillps (2013) studied a group of children with SLI, a language-matched comparison group and normally developing children (all three groups consisted of around 35 children each). The results showed that children diagnosed with SLI showed significantly lower results on motor tests than both other groups.

A recent review on motor abilities of children with SLI (Sanjeevan *et al*. 2015) reported that there was enough evidence to conclude that children with SLI also have difficulties in gross and fine motor skills, both simple and complex. However, they reported that tasks on motoric timing and communicative gesturing were relatively unimpaired in children with SLI. Richtsmeier and Goffman (2015) also reported that children with SLI had similar results to typically developing peers when learning a speech motor task (i.e. nonword repetition). However, Vuolo, Goffman, and Zelaznik (2017) found that children with SLI had no problem when tested on a unimanual timing task, however they had significantly more problems with a bimanual timing test. This suggests that children with SLI experience only difficulties when tasks on motoric timing are more demanding. In our study there were no tasks where timing was an essential part.

Trauner et al.(Trauner *et al*. 2000) found abnormalities on neurological examination in 70% of children with SLI, compared to 22% of the controls with normal development. They also reported that, of the children who had a brain magnetic imaging scan (MRI), more children with SLI had abnormal findings than the control children.

In line with the findings of Trauner, we suggest that SLI is a neuro-developmental deficit which affects not only the brain areas related to language skills, but is a more widespread nervous system dysfunction. We therefore suggest that SLI is a complex neurodevelopmental disorder with multiple profiles of deficits in various developmental areas, with the impairment of language development being the most pronounced. Presumably each child diagnosed with SLI has his or her own range of strong and weak

developmental characteristics. This underlines the importance of a broader assessment of the child's development when a developmental language delay is found.

A strength of our study is that the observers were blinded for the diagnosis because all data were registered before the diagnosis of SLI was known. The registration of data was done by trained well-child professionals in a uniform manner. Furthermore the cases have undergone extensive diagnostic investigations.

A limitation of our study is the relatively low number of observations on several motor milestones. Most values were lost because we created pairs. This means that when values of one individual of a pair is missing, information on the complete pair is missed. However, more values were missing in the cases group than in the control group. This may perhaps be caused by the following two reasons. There is some anecdotal evidence that professionals are somewhat reluctant to register a negative score when they are in doubt. If this explanation is the case, then our results are possibly underestimated. Or, in other words, cases would have even more problems with motor development than we estimated. Another explanation may be that when a professional suspects a child may have a language problem this takes up extra time, not leaving sufficient time to completely register the motor milestones in some cases. If this latter explanation would be the case, then we expect that this would not have influenced our effect estimates.

We conclude that more children with SLI are late in reaching gross and particularly fine motor milestones, than children without SLI. This suggests that it may be debatable whether SLI can be regarded as a "specific" impairment which is not associated with other developmental problems. A broader developmental assessment then only language development is indicated when diagnosing SLI.

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Chapter 7

General discussion

On November 20^{the} 1989 the United Nations approved the convention of the rights of the child. In article 6 it states: *Governments must do all they can to ensure that children survive and develop to their full potential* (1). As specific language impairment (SLI) has a great impact on the development of the child and limits its potential as an adult this means that early identification of children with language problems should be considered a major task for public health services. The studies described in this thesis provide an evidenced-based recommendation for the Dutch healthcare system on how to detect children with SLI at an early age.

At the time of starting this study in 2012 we found that in our study population the mean age of entry of children with SLI to the designated special needs schools for children with SLI was 5 years and 6 months (25% were 6 years and 5 months or older). We also found that the mean age at which these children started speech and language therapy was 3 years and 7 months, and 25% were 4 years and 3 months or older. In view of the findings reported in Chapters 2 and 3 it may be presumed that on the grounds of data which had already been collected from these children at the well-child healthcare visits it could have been possible for many of them to have been diagnosed and already receiving appropriate guidance at an earlier age.

Several possibilities exist for detecting children with SLI. The outcomes of the studies presented in this thesis will be discussed in connection with this and taking the situation in the Netherlands into account.

The two available options for identifying children with SLI, as described in chapter 1, are:

- Screening, with the option of using risk factors
- Developmental surveillance/monitoring

Screening

The advantage of screening is that it can be used as a quick and easy to apply method to distinguish between children who may need extra care and children who do not. The main issue with screening is that a standardized protocol is necessary. Language milestones reached at a fixed age norm (= age visit) could be suitable for screening for developmental language problems.

In the study described in Chapter 2 we investigated whether language milestones could be used as a screening test to detect children with a high risk for severe SLI. The outcome was that from the age of 24 months failure to meet an individual language milestone was predictive for SLI. However, due to the low sensitivity, this failure on an individual language milestone was proved not suitable for screening purposes. The predictive values of combinations of milestones are presented in Chapter 3. This showed that combinations of milestones at a single age visit also have high specificities, but sensitivities were generally low. A concise tool with acceptable predictive properties for

detecting children with SLI was constructed, using a combination of language milestones at several age visits. This concise tool could easily be implemented in the Dutch well-child healthcare system because it uses data which at present are collected and registered in the regular files. The concise tool as described in Chapter 3 is quick and easy to administer and is acceptable to children and parents. The concise tool, with its established acceptable predictive properties, is an improvement on the current policy. Implementation of the concise tool in the Dutch well-child healthcare system does not need more time, equipment, personnel or training than the current Dutch Developmental Instrument (=DDI) method. It could increase the efficiency of detecting children with a high risk for having SLI at a young age and may therefore be more cost-effective than the present system.

However, a disadvantage of the concise tool is that its sensitivity is not optimal, implying that some children with SLI will still be missed. Also, as the children who were studied as cases had severe SLI, it means that the calculated predictive properties are for detecting children with severe SLI. However detecting such children should be a priority. The specificity of the concise tool is very high, but not perfect. This means that some children who do not pass the test do not have (severe) SLI. Some of these children could have a less severe form of SLI or another developmental disorder. This implies that the false positive test result can still be valuable. Since signs which could point to SLI are not always very specific, failure on the test is not always an indication of the presence of SLI, but could be an indication of another developmental disorder. So, when a child fails on the concise tool further assessment is needed. This may reveal a disorder, but not necessarily SLI.

Screening using risk factors (targeted screening)

Screening using risk factors or targeted screening is frequently used for many disorders. Law et al. (2000) discussed using targeted screening for speech and language delay, selecting a subgroup with higher risk levels for screening, as one of the alternatives to universal screening (2). In their review, Berkman et al. (2015) reported that in the outcomes of multivariate analyses of cohort populations the risk factors generally associated with speech and language delays or disorders were as follows: being male, a family history of speech and language concerns, lower levels of parental educational achievement and perinatal risk factors (3). The perinatal risk factors, determined in at least one study, were maternal binge drinking, prematurity, low birth weight and younger maternal age. This does not completely agree with our findings described in Chapters 4 and 5 of this thesis. We found no relationship with perinatal factors, apart from an indication that the Apgar score, especially in girls might have an association with SLI (Chapter 4). In Chapter 5 we established risk factors associated with SLI as: younger maternal age, not being breastfed directly after birth and not being the firstborn in the

family. However, socio economic status (SES) could be a confounder in this and may reduce the effect size of these risk factors. Using these risk factors for targeted screening would not improve the yield as they have very low sensitivity and specificity rates for predicting SLI.

Using parental questionnaires as a step in a targeted screening program for language problems is not advisable. There is a strong chance that parents of children with SLI will have language and/or reading difficulties themselves, as SLI is found more often in families where parents also have language problems. This could influence the outcomes of questionnaires and make them unreliable.

Screening using risk factors or targeted screening is therefore not a viable option to detect children with SLI.

Developmental surveillance/ monitoring

The AAP recommended developmental surveillance as the preferable method to identify children with developmental disorders (4). Developmental surveillance is an ongoing process which can be accomplished by monitoring attainment of developmental milestones, eliciting parental concerns and informally observing age appropriate tasks. The shortcomings of such a surveillance method are the subjective judgments of the observers and the fact that detection is usually later (5-7). Developmental surveillance is a time-consuming method for professionals and parents and the predictive properties are unknown (7).

A possible third option could be:

Combined approach, combining screening and developmental surveillance

The outcomes of our studies provide an alternative option for detecting children with SLI. This is developmental screening using the concise tool in combination with developmental surveillance. The concise tool developed in our study, described in Chapter 3, provides an instrument suitable for developmental screening. The developed concise tool has acceptable predictive properties, however it also has some disadvantages as described earlier. To compensate for its shortcomings the tool could be combined with developmental surveillance. The developmental surveillance is already in use in the Dutch well-child healthcare system. This means that children who are not identified with the concise tool can be detected later on. The same applies to the detection of children with a less severe form of SLI. Furthermore, the broad insight into the development of the

child, gained by ongoing developmental surveillance, will enable the professional to choose the most suitable facility for further diagnostic investigations when a child fails on the concise tool. The data on achievements in other developmental areas will provide additional information to the professional and help to decide whether the failure on the concise tool should be regarded as a language problem or whether other developmental disorders are more probable. As we have shown in Chapter 6, SLI may now be regarded as a developmental disorder which is not restricted to only language skills. A broad assessment by an experienced assessor is required when a child fails the concise tool.

In conclusion we can state that the best option for detecting children with SLI at an early age in the Netherlands is a combined approach, i.e. implementation of the concise tool alongside the long-running program of developmental surveillance in the well-child healthcare system. This recommendation requires very little extra effort, because the data for the concise tool are already collected during the usual well-child health visits in the present program. No extra instrument or training is necessary. However, it is important that the age visits at 24, 36 and 45 months of age are used to assess the language milestones of the DDI. Using this combined approach will increase the number of children with SLI who are detected before the age of starting elementary school. This makes it possible for appropriate educational support to be in place when these children start school, thus giving them the best possible start in education.

One of the goals of this thesis was to gain insight into the characteristics of children with SLI which could provide a better understanding of the etiology of this developmental disorder. In the pilot study described in Chapter 4 we concluded that no association could be established between perinatal risk factors and SLI except for a relationship with the Apgar score. However, this finding could not be reproduced in the major study (Chapter 5), where no association was found between perinatal risk factors and SLI. The only factors which were found to have a weak association with SLI were maternal age, being breastfed directly after birth and place in the birth order. Therefore, these studies have not provided extra insight into the etiology of SLI.

An interesting finding was that more children with SLI were also late with motor development, compared to normally developing children (Chapter 6). This suggests that it may be debatable whether SLI can be regarded as a "specific" impairment which is not associated with other developmental problems. The earlier theory that isolated developmental disorders, such as SLI, could exist is difficult to explain and is not supported by our study.

Conclusions

The main aim of the studies in this thesis was to find the best method to detect children with SLI at an early age within the framework of the well-child healthcare system in the Netherlands.

We have shown that, for the situation in the Netherlands, the best approach to identify children with SLI as early as possible is a combined approach using our concise tool of language milestones at age visits at 24, 35 and 45 months of age in combination with developmental surveillance already in place in the Dutch well-child healthcare system. At present the data used in the concise tool are part of the information collected at the visits to the well-child clinics and have been registered in the well-child files along with data on developmental monitoring. Therefore implementation of this method will need very little extra money, time or effort.

The outcomes of the studies regarding the characteristics of SLI showed that most perinatal risk factors were not associated with SLI. Only younger maternal age, not being breastfed directly after birth and not being the firstborn in the family were found to have a relationship with the child having SLI. However, the effect size of these risk factors could potentially be reduced when SES is taken into account.

An important finding of our study was that children with SLI were also late in reaching motor milestones. This suggests that SLI is not an isolated developmental disorder.

Directions for further study

The concise tool developed in this study is a promising innovation. The predictive properties of language milestones for SLI described in **Chapters 2 and 3** are specifically calculated for the Dutch language and Dutch healthcare system. Further studies are needed to investigate whether our outcomes are applicable in other languages, countries and healthcare systems.

Cases in our study population were children with such severe SLI that they were unable to attend mainstream education. Therefore our studies do not provide information on how useful our findings could be in detecting children with less severe forms of SLI who are still able to attend mainstream education. Additional studies could provide tools for identifying these children.

Further investigations are needed to provide more insight into the population of children who fail when the concise tool is used but who do not have SLI. It may be possible to calculate predicative properties for other developmental disorders, for instance autism spectrum disorder or ADHD, using a combination of milestones which are also registered in the DDI. These could include data on adaptive and personal/social behaviour. It could also be valuable to investigate whether early milestones in other developmental regions could also be predictive for SLI, such as milestones concerning executive functioning (8).

There is as yet limited evidence for benefits of early treatment for most developmental disorders and this is clearly the case for SLI. More studies are needed to investigate the effects of early detection of developmental disorders.

A limitation of our studies is that data on social economic status (SES) were lacking or were not very precise. In the pilot study we used postal area codes as a variable. While

this gives information on the SES of the population in the postal area it cannot be used as an accurate measure of SES of the individual child (9). Larger studies which include more exact information on SES could provide more information on factors influencing the etiology of SLI.

An important outcome of our study was that children with SLI reached motor milestones later than children who were developing normally. This supports the recent ideas that SLI may not be an isolated developmental disorder. This needs to be investigated further.

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Chapter 8

Summary
Nederlandse samenvatting

Summary

The subject of this thesis is developmental language disorder, which is a developmental disorder with no obvious cause, usually called specific language impairment (SLI). In Chapter 1 the background and impact of SLI are described. SLI is the most prevalent developmental disorder in childhood, found in 2-12% of children and has many negative consequences for the potential development and well-being of the individual. The American Academy of Pediatrics (AAP) recommends early identification of developmental disorders and this also applies to language developmental disorders such as SLI. Early diagnosis and treatment of SLI is generally considered to be beneficial for the child although there is as yet no hard evidence to support this. A possible benefit of early detection of SLI is that parents and co-educators are made aware of the child's problems and can adjust their expectations for the child. Furthermore early diagnoses can be followed by appropriate interventions. However at present there is limited evidence that earlier treatment leads to better outcomes.

A major problem with identifying children with SLI is that the natural history of language delay or disorder is unknown. Symptoms such as being late with talking or not talking at all at a certain age are not very specific for predicting a developmental language disorder. Some children are late starting to use verbal language to express themselves, but they catch up later. Other children start talking at a normal age, but later on it becomes obvious that their language development is inadequate and they are diagnosed as having SLI. The fact that symptoms of SLI resemble those of psychiatric disorders and learning problems makes it even more difficult to predict which child will have SLI.

The great majority of children with SLI are identified late or not at all, even in the Netherlands with its extensive and well-organized system of well-child healthcare. The goal of this thesis was to investigate the best way to detect children with specific language impairment (SLI) at a young age in the Netherlands. For this purpose studies were performed to investigate characteristics of children with SLI and compare these with normally developing children. Information on these characteristics could also provide more insight into the etiology of an isolated developmental disorder such as SLI.

The studies had a nested case-control design, where cases were children attending special needs schools for children with severe speech and language difficulties and controls were normally developing children attending mainstream education. The data of all children in the study population had been registered in the files of the Dutch well-child healthcare system in a uniform way by trained professionals long before the diagnosis of SLI was known. The fact that the children with SLI had been extensively investigated and the diagnosis had been confirmed meant that they may be regarded as meeting the internationally used criteria for SLI.

An overview of the predictive properties of 23 isolated language milestones for identifying children with SLI is given in Chapter 2. From the age of 18 months a significant difference was seen in reaching language milestones between children with SLI and

normally developing children. From the age of two years onwards failing to meet language milestones at the corresponding age norm is predictive of SLI, however the low sensitivity rate is a shortcoming, limiting its value as a screening test for SLI. However, failure on a language milestone at the age norm, especially after the age of two years, is a reason for concern.

The predictive properties improved when language milestones were combined. This is described in **Chapter 3**. Outcomes are given for combinations of milestones at 24, 36 and 45 months of age. The outcomes showed that combinations of two language milestones at 24, 36 or 45 months of age had high specificity rates, but lower sensitivity rates. Using a combination of five milestones at these three different ages made it possible to achieve a specificity of 96% (95% CI 94%-99%) and a sensitivity of 71% (95% CI 66%-77%). This means that many children with SLI can be identified before the age of four years using language milestones at 24, 36 and 45 months of age. This lead to the development of a concise tool, which is easy to use and can help professionals detect those children needing further investigations before the age of four years old and before starting elementary school.

The outcomes of the pilot study searching for perinatal risk factors for SLI are given in **Chapter 4**. This study showed that none of the perinatal risk factors studied had a significant relationship with having SLI. Only the Apgar score had a slight association with SLI and this was more pronounced in girls than in boys.

No relationship was found between perinatal risk factors and having SLI in the larger population in the major study with the same study design and using more variables (**Chapter 5**). The previous findings concerning the Apgar score could not be reproduced. However, children with SLI had younger mothers than children in the control group (mean 30y 9mo versus mean 31y 9mo) (p=0.02). Also, children with SLI were less frequently breastfed directly after birth (55% versus 71%) (p=0.0007) and were less frequently firstborns (33.3% versus 46.2%) (p=0.002), but effect sizes were small.

In **Chapter 6** the outcomes of the study comparing groups of children with and without SLI on reaching motor milestones at the age norm are reported. More children with SLI were late in reaching motor milestones compared with normally developing children. A significant difference was found between both groups in the proportion failing to reach three of the seven investigated gross motor milestones at the age norm ($p < 0.05$). The proportion of children not reaching the motor milestone at the age norm was significantly higher for five of the six fine motor milestones in children with SLI compared with control children ($p < 0.05$). This led to the conclusion that it is debatable whether SLI can be regarded as a "specific" impairment which is not accompanied by other developmental problems.

In the general discussion in **Chapter 7**, various methods for detecting children with SLI in the Netherlands based on the outcomes of the studies are discussed. The following possible methods were discussed 1) screening or screening in combination with use of

risk factors 2) developmental surveillance/monitoring and 3) a combined approach combining screening and developmental surveillance.

Screening using isolated language milestones or a combination of milestones at a certain age had high specificity rates for detecting children with SLI, but due to the lower sensitivity rates, could not be recommended for screening purposes. However, the constructed concise tool using combinations of language milestones at three different age visits had better predictive properties. Nevertheless, some children with SLI could be missed due to the lower sensitivity rate. Also, due the design of the study the predictive properties were calculated for detecting only those children with severe SLI. As a failure on the concise tool is not specific for developmental language problems, additional investigations are indicated.

Screening using risk factors is not a viable option for detecting children with SLI, mainly because of the limited effect size of these factors. Developmental surveillance is valuable but has significant problems such as being based on subjective judgment, being time consuming and needing experienced and well-trained professionals.

The third option, which is a combined approach, that is, screening using a screening tool in combination with developmental surveillance is, in our opinion, the best way to detect children with SLI within the Dutch well-child healthcare system. The concise tool developed in this study and described in **Chapter 3**, provides an instrument for developmental language screening. Due to its relatively poorer sensitivity and some other shortcomings, this instrument should be combined with the presently used system of developmental surveillance. Implementation of the concise tool is easy because the data used are already registered, meaning no extra time, training or equipment is needed.

The finding that more children with SLI were later in reaching motor milestones at the age norm than normally developing children raises a discussion about the generally used definition of SLI which was used until recently. From these findings it is clear that children who fit the definition and diagnosis of SLI have much broader developmental problems than only language development. This means that it is debatable whether SLI is an "isolated" developmental disorder.

Nederlandse samenvatting

Het onderwerp van dit proefschrift is taalontwikkelingsstoornissen zonder een duidelijke oorzaak, ofwel TOS. Hoofdstuk 1 beschrijft de achtergrond en impact van het hebben van TOS. TOS wordt gevonden bij 2-12% van alle kinderen en is daarmee de meest voorkomende ontwikkelingsstoornis op de kinderleeftijd. Het hebben van TOS heeft vele nadelige consequenties voor de ontplooiingskansen en het welzijn van een individu. De American Academy of Pediatrics (AAP) beveelt aan om kinderen met ontwikkelingsstoornissen zo jong mogelijk op te sporen, dit geldt ook voor taalontwikkelingsstoornissen. Vroege opsporing en behandeling van TOS wordt beschouwd als belangrijk voor het welzijn van het kind, hoewel er nog geen duidelijk bewijs is om dit te ondersteunen.

Een mogelijk voordeel van vroege opsporing van TOS is dat ouders en medeopvoeders bewust zijn van de problemen van het kind en hun verwachtingen kunnen aanpassen. Verder kan een tijdige diagnose gevolgd worden door aangepaste interventies, hoewel er op dit moment beperkt bewijs is dat eerdere behandeling betere resultaten geeft.

Een knelpunt bij de opsporing van kinderen met TOS is, dat het natuurlijk beloop van een taalachterstand onbekend is. Symptomen, zoals laat zijn met praten of nog niet praten op een bepaalde leeftijd, zijn weinig specifiek voor het voorspellen van het hebben van een TOS. Sommige kinderen zijn laat met het zich verbaal uiten, maar halen hun achterstand later in. Andere kinderen starten op tijd met praten, maar bij hen blijkt op latere leeftijd het niveau van hun taalvaardigheden onvoldoende te zijn en wordt alsnog de diagnose TOS gesteld. Het feit dat veel symptomen van TOS lijken op die van kinderpsychiatrische stoornissen en leerproblemen, compliceert het vroeg opsporen van kinderen met TOS nog meer.

Ook in de Nederlandse situatie, met een goedgeregelde preventieve gezondheidszorg voor de jeugd (JGZ), is duidelijk dat niet alle kinderen met TOS tijdig worden gesignaleerd of zelfs worden opgespoord. Het doel van de studies beschreven in dit proefschrift is om te onderzoeken wat de beste manier is om in Nederland kinderen met TOS op een zo jong mogelijke leeftijd op te sporen. Hiervoor werden onderzoeken verricht naar de kenmerken van kinderen met TOS. Onderzocht werd of er verschillen waren in vóórkomen van deze kenmerken bij kinderen met TOS, in vergelijking met kinderen met een normale ontwikkeling. Kennis van deze kenmerken kan tevens behulpzaam zijn bij het verkrijgen van meer inzicht in de ontstaanswijze van een geïsoleerde ontwikkelingsstoornis zoals TOS.

De studies hadden een nested case-control ontwerp, waarbij de cases leerlingen waren van een Speciaal Onderwijs school voor kinderen met ernstige spraaktaalmoeilijkheden (SO cluster 2). De controle kinderen waren normaal ontwikkelende leerlingen van het regulier basisonderwijs. Van alle kinderen werden de kenmerken verzameld zoals geregistreerd in de JGZ dossiers. Deze kenmerken worden binnen de JGZ op uniforme wijze en door getrainde professionals genoteerd, nog voor een eventuele diagnose TOS bekend is. Het feit dat kinderen voor plaatsing op het speciaal onderwijs

uitgebreid onderzocht werden, waarbij de diagnose TOS werd bevestigd, betekende dat deze kinderen kunnen worden gezien als kinderen met een diagnose TOS conform de internationaal gebruikte criteria voor deze stoornis, namelijk Specific Language Impairment (SLI).

Een overzicht van de voorspellende eigenschappen van de 23 geïsoleerde taalmijlpalen voor het opsporen van kinderen met TOS is beschreven in hoofdstuk 2. Vanaf de leeftijd van 18 maanden is er een significant verschil in het behalen van een taalmijlpaal tussen kinderen met TOS en normaal ontwikkelende kinderen. Vanaf de leeftijd van twee jaar is het niet halen van een taalmijlpaal op de bijbehorende leeftijdsnorm voorspellend voor het hebben van SLI, hoewel de lage sensitiviteit een nadeel is voor gebruik als screeningstest. Het niet halen van een taalmijlpaal op de leeftijdsnorm is, vooral vanaf de leeftijd van twee jaar, een reden tot zorg.

De voorspellende eigenschappen van taalmijlpalen verbeteren als taalmijlpalen worden gecombineerd. Dit is beschreven in hoofdstuk 3. Voor deze combinaties werden de gegevens gebruikt van de taalmijlpalen op de leeftijden van 24, 36 en 45 maanden. De resultaten laten zien dat combinaties van twee mijlpalen op één leeftijdsmoment hoge specificiteit hebben voor het voorspellen van TOS, maar dat een hogere specificiteit meestal gecombineerd was met een lagere sensitiviteit. We construeerden een beknopt instrument gebruikmakend van vijf mijlpalen op de drie leeftijdsmomenten. Hiermee zijn acceptabele voorspellende eigenschappen bereikt, nl. een specificiteit van 96% (95% CI 94%-99%) en een sensitiviteit van 71% (95% CI 66%-77%). Dat betekent dat veel kinderen met TOS kunnen worden opgespoord voor de leeftijd van vier jaar met het gebruik van deze combinatie van taalmijlpalen op leeftijden 24, 36 en 45 maanden. Deze combinatie is daarmee een beknopt instrument om professionals te ondersteunen bij het opsporen van kinderen met een verdenking van TOS en die verder onderzoek nodig hebben voor de basisschoolleeftijd. Verder onderzoek en eventuele interventie kunnen daardoor starten voor de basisschoolleeftijd.

De uitkomsten van de pilotstudie naar perinatale risicofactoren zijn beschreven in hoofdstuk 4. Deze studie liet zien dat geen van alle onderzochte perinatale risicofactoren een significante relatie had met het hebben van TOS. Alleen bij de Apgar score werd een geringe associatie gevonden met het hebben van TOS, en deze was meer uitgesproken bij meisjes.

Ook bij de herhaling van het onderzoek met dezelfde studieopzet maar met een grotere studiepopulatie en meer variabelen, werd geen relatie gevonden tussen perinatale risicofactoren en het hebben van TOS (hoofdstuk 5). De eerder gevonden relatie met de Apgar score kon niet worden gereproduceerd. Wel hadden kinderen met TOS jongere moeders in vergelijking met controle kinderen (gemiddeld 30jaar 9maanden versus gemiddeld 31jaar 9maanden) (p=0.02). Ook kregen kinderen met TOS minder vaak borstvoeding direct na de geboorte (55% versus 71%) (p=0.0007) en waren ze minder

vaak de eerstgeborene (33.3% versus 46.2%) (p=0.002). De effect groottes waren echter klein.

In **hoofdstuk 6** zijn de resultaten beschreven van de studie naar verschillen tussen de groepen van kinderen met en zonder TOS ten aanzien van het behalen van motorische mijlpalen. Meer kinderen in de groep met TOS dan in de groep normaal ontwikkelende kinderen waren laat in het halen van motorische mijlpalen. Een significant verschil tussen beide groepen in het halen van motorische mijlpalen op de leeftijdsnorm werd gevonden voor drie van de zeven onderzochte mijlpalen op grof motorisch gebied ($p < 0.05$). Op het gebied van de fijne motoriek was het aantal kinderen dat een motorische mijlpaal niet haalde op de leeftijdsnorm in de groep kinderen met TOS significant hoger bij vijf van de zes onderzochte mijlpalen in vergelijking met de controlegroep kinderen ($p < 0.05$). Dit leidde tot de conclusie dat het twijfelachtig is of TOS gezien kan worden als een "geïsoleerde" ontwikkelingsstoornis, zonder bijkomende andere ontwikkelings-problematiek.

In **hoofdstuk 7** werden de verschillende methodes voor het opsporen van kinderen met TOS voor de Nederlandse situatie beschouwd aan de hand van de uitkomsten van de studies. De volgende mogelijkheden werden besproken: 1) screening of screening met gebruik van risicofactoren 2) monitoring van de ontwikkeling en 3) een gecombineerde aanpak, met een combinatie van screening en monitoring van de ontwikkeling.

Screening met gebruik van een enkele taalmijlpaal of een combinatie van taalmijlpalen op één leeftijdsmoment heeft een hoge specificiteit, echter vanwege de lagere sensitiviteit is het niet aan te bevelen om deze methode te gebruiken voor de opsporing van TOS. Het "beknopte instrument" gebruikmakend van een combinatie van vijf taalmijlpalen op drie verschillende leeftijdsmomenten heeft betere voorspellende eigenschappen. Echter vanwege een niet optimale sensitiviteit van dit instrument worden er dan nog steeds kinderen met TOS gemist. Door de gekozen studieopzet zijn de berekende voorspellende eigenschappen alleen van toepassing voor het opsporen van kinderen met ernstige TOS. Verder is uitvallen op dit "beknopte instrument" niet specifiek voor het hebben van taalontwikkelingsproblematiek en is aanvullende diagnostiek geïndiceerd. Screening met gebruikmaking van risicofactoren is geen bruikbare oplossing voor het opsporen van kinderen met TOS, vooral vanwege de beperkte effect groottes van deze factoren, zoals eerder beschreven. De optie van monitoring van de ontwikkeling heeft belangrijke nadelen zoals, de noodzaak van ervaren en goed getrainde professionals en een grote tijdsinvestering. Verder is er sprake van een subjectieve beoordeling. De derde optie, nl. de gecombineerde methode, waarbij screening wordt gecombineerd met monitoring van de ontwikkeling, lijkt de beste manier om kinderen met TOS vroegtijdig op te sporen binnen het Nederlandse systeem van jeugdgezondheidzorg (JGZ). Het "beknopte instrument ", zoals ontwikkelt in onze studie en beschreven in **hoofdstuk 3**, biedt een instrument voor screening van de taalontwikkeling. Echter vanwege de minder goede sensitiviteit en andere nadelen, moet deze test worden gecombineerd met de al in de Nederlandse JGZ gebruikte monitoring

van de ontwikkeling, zoals het “van Wiechenonderzoek”. Implementatie van het “beknopte instrument” in de huidige JGZ is eenvoudig, omdat de hiervoor benodigde data al worden vastgelegd. Dit betekent dat geen extra handeling, tijd, training of instrumentarium nodig zijn voor de invoering hiervan.

De bevinding dat meer kinderen met TOS laat waren met het bereiken van motorische mijlpalen in vergelijking met normaal ontwikkelende kinderen, maakt duidelijk dat kinderen die voldoen aan de definitie en waar de diagnose TOS gesteld is, een bredere ontwikkelingsproblematiek hebben dan alleen de taalontwikkeling. Dit betekent dat het discutabel is of TOS wel een “geïsoleerde” ontwikkelingsstoornis is.

Appendices

List of abbreviations
List of publications
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Abbreviations

AAP	American Academy of Pediatrics
ADHD	Attention deficit hyperactivity disorder
CATALISE	Criteria and Terminology Applied to Language Impairments: Synthesising the Evidence
DCD	Developmental Coordination Disorder
DDI	Dutch Developmental Instrument or “van Wiechen” instrument
DLD	Developmental Language Disorder
JGZ	Jeugdgezondheidszorg
LR+	Positive likelihood ratio
NIDCD	National Institute on Deafness and other Communication Disorders
OR	Odds ratio
PPV	Positive predictive value
SD	Standard deviation
SDQ	Strengths and Difficulties Questionnaire
SES	Social-economic status
SHC	Speech and Hearing Centers
SLI	Specific language impairment
TOS	Taalontwikkelingsstoornis
USPSTF	United States Preventive Services Task Force
WHO	World Health Organization
ZonMw	Nederlandse organisatie voor gezondheidsonderzoek en zorginnovatie

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Curriculum Vitae

Frederique Babette Diepeveen is geboren op 8 januari 1956 te ’s-Gravenhage. Na het middelbare onderwijs te hebben gevolgd in ’s-Gravenhage (2e Vrijzinnig Christelijk Lyceum) en Deventer (Alexander Hegius Scholengemeenschap) werd in 1974 het diploma VWO behaald. Vanaf 1974 studeerde ze geneeskunde aan de Rijksuniversiteit Groningen, waar ze in 1981 de artsenbul ontving.
Na ruim een jaar als ANIOS orthopedie in het St Barbaraziekenhuis Geleen te hebben gewerkt, was ze vanaf 1983 werkzaam als school/consultatiebureauarts bij Groene Kruis Limburg en GGD Westelijke Mijnstreek. Van 1985 tot 1987 werd de opleiding tot jeugdarts gevolgd bij het Nederlands Instituut voor Preventieve Gezondheidszorg (NIPG) te Leiden. Daarna volgde registratie als jeugdarts KNMG en arts Maatschappij en Gezondheid. Vervolgens is ze werkzaam geweest als jeugdarts in Capelle aan den IJssel, Rotterdam en gedurende ruim 12 jaar in Nijmegen. Als jeugdarts van de speciaal onderwijs school voor kinderen met ernstige spraaktaalmoeilijkheden in Nijmegen is ze betrokken geraakt bij de problematiek van kinderen met taalontwikkelingsstoornissen. Vanaf 2001 was ze ook werkzaam bij het spraaktaalteam van het kinderaudiologisch centrum van de afdeling KNO van het Radboud UMC. Ze is gedurende 10 jaar verbonden geweest aan dit multidisciplinaire team, de laatste 5 jaar als coördinator. Daar is ook een start gemaakt met het wetenschappelijk onderzoek, dat werd ondersteund met een ZonMw subsidie. Dit onderzoek is grotendeels uitgevoerd als gastmedewerker van TNO, afdeling Child Health.

Inmiddels is Babette, naast haar onderzoekswerkzaamheden, werkzaam als jeugdarts binnen de jeugd GGZ bij Pro Persona.

Babette is getrouwd en heeft samen met Daan van der Vliet 4 zonen.

Dankwoord

Dit proefschrift en het onderzoek, waarop het gebaseerd is, kwam tot stand met hulp van velen.

De vraag van een ouderpaar over de invloed van problemen bij de geboorte van hun zoon op het ontstaan van zijn ernstige spraaktaalmoeilijkheden vormde de eerste aanzet tot mijn onderzoek. Dit leidde tot een pilotstudie naar voorspellende factoren voor taalontwikkelingsstoornissen.

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Marlou de Kroon heeft me op pad geholpen met de eerste publicatie.

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