Growing up with hemophilia

Health related quality of life and psychosocial functioning

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Chapter 11

Summary and general discussion
Introduction

This thesis ‘Growing up with hemophilia: health related quality of life and psychosocial functioning’ focused on the development and evaluation of reliable and valid instruments (Part I; chapters 2, 3, 4 and 5), health related quality of life (HRQOL) and psychosocial outcomes (Part II; chapters 6, 7, 8 and 9) and psychosocial care (Part III; chapter 10).

This final chapter of this thesis summarizes the main findings; it considers the limitations and challenges of the studies. Furthermore, clinical implications and future perspectives are discussed and finally, conclusions and key messages are highlighted. An overview of the main results of the studies are presented in Table 1.

Main findings

Part I: development and evaluation of instruments

The first study in this thesis, Chapter 2, addresses various important challenges when measuring HRQOL in children, such as generic versus disease-specific questionnaires, age-specific questionnaires with a narrow versus a wide age range, self-report versus proxy-report, and paper-pencil versus online questionnaires. Although not comprehensive, this overview provides the most relevant topics to keep in mind when considering the implementation of HRQOL measures in daily clinical practice or starting a research program measuring HRQOL in children.

The aim of Chapter 3, a systematic review, was to obtain a comprehensive overview of the measurement properties of HRQOL questionnaires in hemophilia across geographic and age boundaries, by systematically assessing the methodological quality of studies. In total, 22 articles were assessed, including 8 questionnaires. The findings suggest that from the three questionnaires for children, the CHO-KLAT questionnaire is the most optimal disease-specific questionnaire to use at this moment. For adults, out of five questionnaires, the Haemophilia Well-Being Index and the HAEMO-QoL-A are the most optimal instruments. No new disease-specific HRQOL questionnaires in hemophilia are required. However, additional research using the existing
Chapter Aim Sample Measures/content Main findings/conclusions
2 To demonstrate the importance of measuring HRQOL in pediatrics and its challenges. HRQOL measures provide the unique opportunity to have insight into a number of different domains of the child's functioning. This chapter provides a global overview of the philosophy of and tools used in HRQOL research in children. Important challenges regarding the use of HRQOL instruments are reported: generic versus disease-specific questionnaires, age-specific questionnaires with a narrow versus a wide age range, self-report versus proxy-report, and paper-pencil versus online questionnaires. 1) Taking HRQOL into account in clinical practice is of utmost importance, but comes with challenges. 2) Paying attention to HRQOL makes it possible to monitor a child over time and provide interventions where appropriate.

3 To assess the methodological quality of studies on the psychometric properties of HRQOL instruments developed in patients with hemophilia, using the COSMIN checklist. The initial search yielded 1597 articles, of which 22 articles were included and assessed: full-text original research articles (e.g. not an abstract or review), published in English, and focused on the development or evaluation of measurement properties of a HRQOL questionnaire. The questionnaire had to be self- or parent proxy-reported, and specifically developed or evaluated in individuals with hemophilia (≥50% of the sample with hemophilia A/B). Three pediatric questionnaires: - CHO-KLAT - Haemo-Qol - Unnamed measure (‘Toddler questionnaire’) Five adult questionnaires: - Hemophilia-Qol - Haemophilia Well-Being Index - HAEMO-Qol-A - Haem-A-Qol - SF-36 1) The CHO-KLAT was the pediatric measure that showed the strongest measurement properties in high quality studies. 2) The Haemophilia Well-Being Index and HAEMO-Qol-A performed best among the adult measures. 3) There is no need for new disease-specific HRQOL questionnaires for hemophilia. 4) Additional research is necessary to document the measurement properties of the currently available questionnaires, specifically focusing on the structural validity, measurement error and responsiveness.

4 To assess the reliability and validity of the HCPT (board game), aiming to assess coping and perception in boys with hemophilia. N=32 boys with hemophilia (8-12 years). - Socio-demographic questionnaire - The Hemophilia Coping and Perception Test (HCPT) - Coping with a Disease (CODI) - Questionnaire Op Koers for Children (QOK-c) - State-Trait Anxiety Inventory for Children (STAI-C) - Evaluation questionnaire 1) The HCPT coping scale assesses the more practical competencies of coping, such as self-management, rather than the psychological construct of coping. 2) The HCPT can be used by nurses or psychologists as a tool to get insight into the knowledge, self-management and perception of boys with hemophilia and to provide tailored psycho-education. 3) Boys and parents had a positive attitude towards the HCPT.

Table 1. Main findings of this thesis: development and evaluation of instruments.
Table 1. Main findings of this thesis: development and evaluation of instruments. (Continued)

5 To validate and collect normative data for a generic HRQOL instrument for young adults.
- N=649 young adults from the general population (18-30 years).
- Socio-demographic questionnaire
- PedsQL_YA Generic Core Scale Young Adult version (PedsQL_YA)

1) The Dutch version of the PedsQL_YA Generic Core Scales demonstrates overall adequate psychometric properties.
2) With the obtained norm data, the PedsQL_YA can be utilized as a tool to evaluate HRQOL in young adults.

6 To assess the generic and disease-specific HRQOL of children with bleeding disorders.
- N=146 children with bleeding disorders (0-18 years)
- Socio-demographic questionnaire
- TAPQOL (0-5 years; n=43)
- PedsQL (6-18 years; n=103)
- Haemo-QoL (4-18 years; n=48)

1) Boys 0-12 years do not report lower HRQOL than healthy peers.
2) Boys 13-18 years report higher total HRQOL and emotional functioning than healthy peers.
3) Girls (13-18 years) report lower total HRQOL, school functioning and psychosocial health than healthy peers.
4) Boys with severe hemophilia report worse family functioning than boys with non-severe hemophilia.

7 To capture the perspectives of adolescents and young adults (YA) with congenital bleeding disorders on their condition and identify which themes are relevant in their daily life, based on qualitative data.
- N=12 YA with bleeding disorders (16-30 years)
- Socio-demographic questionnaire
- 3 Focus groups

1) YA with bleeding disorders still experience obstacles in daily life.
2) Major themes were: relationship with parents, capabilities in sports, capabilities in outings and traveling, self-management, illness perception and acceptance, and capabilities in education and employment.
3) The findings provide additional insights into YAs experiences, especially regarding the transition period to adulthood.

8 To assess the health related quality of life, developmental milestones and self-esteem in Dutch young adults with bleeding disorders, compared to a group of peers.
- N=95 YA (18-30 years) with bleeding disorders
- Socio-demographic questionnaire
- Course of Life Questionnaire (CoLQ)
- Rosenberg Self-Esteem Scale (RSES)

1) YA men with bleeding disorders report an impaired total HRQOL, physical functioning, school/work functioning and lower self-esteem in comparison to their healthy peers.
2) YA women do not report differences on any of the outcomes in comparison to their peers.
3) Systematic monitoring of HRQOL in daily clinical practice is needed.

9 To describe the psychosocial impact of hemophilia on mothers.
- N=30 mothers of boys with hemophilia (8-12 years)
- Socio-demographic questionnaire
- Hospital Anxiety and Depression Scale (HADS)
- Distress Thermometer for Parents (DT-P)
- Haemo-QoL, (8-12 years)

1) Mothers of boys with hemophilia do not report aberrant levels of anxiety and depression in comparison to mothers of healthy children.
2) 21% of mothers reported clinical levels of distress (on distress thermometer).
3) This underlines the importance of monitoring maternal psychosocial functioning and distress systematically in daily clinical practice.
### Table 1. Main findings of this thesis: development and evaluation of instruments. (Continued)

<table>
<thead>
<tr>
<th>Main findings/objectives</th>
<th>Main findings/conclusions</th>
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<tr>
<td><strong>Chapter Aim</strong></td>
<td>To provide a description of psychosocial care provided by the multidisciplinary team of the Hemophilia Comprehensive Care Centre (HCCC) at the Emma Children's Hospital in Amsterdam, the Netherlands.</td>
</tr>
<tr>
<td><strong>Sample</strong></td>
<td>Psychosocial care provided by the multidisciplinary team, for all children under treatment at the HCCC and their parents.</td>
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<tr>
<td><strong>Measures/content</strong></td>
<td>Core elements of the psychosocial care are: monitoring and screening of HRQOL (e.g. in daily clinical practice via <a href="http://www.hetklikt.nu">www.hetklikt.nu</a>), psychoeducation (hemophilia camp, hemophilia school, disease specific activities, meetings for girls, parent meetings, practical and educational visits and activities for adolescents and young adults; Educational Facility and school visits), psychosocial interventions (the On Track group intervention and the Hemophilia Coping and Perception Test), and individual care (psychological counselling and referrals).</td>
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<tr>
<td><strong>Table 1. Main findings of this thesis: development and evaluation of instruments. (Continued)</strong></td>
<td>1) By introducing an overview of psychosocial support offered and by sharing this knowledge, psychosocial care can become more structured and consistent between HCCCs around the world. Potentially, processes and outcomes of care can be improved.</td>
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| **Chapter 4** | Describes the reliability, validity and evaluation of the Hemophilia Coping and Perception Test (HCPT), which is a board game that has been developed by the Hemophilia Comprehensive Care Center (HCCC) of the Emma Children's Hospital/AMC in 2009/2010. The HCPT consists of two scales (coping and perception), and can be played with children under supervision of a nurse or psychologist to get insight into coping and perception. The coping scale showed satisfactory reliability and low construct validity. Based on the insights gained during this study, we hypothesize that the HCPT coping scale assesses the more practical competencies of coping, such as self-management, rather than the psychological construct of coping. The perception scale showed adequate validity and low reliability, which may be caused by the items tackling diverging aspects of this concept (e.g. anxiety, feeling different). Regarding the evaluation, boys appreciated talking about experiences and difficulties regarding their
disease in a playful way. The HCPT is a tool to get insight into the knowledge, self-management and perception of boys with hemophilia and to provide tailored psycho-education.

With the increase of research on young adults with a chronic health condition, and for use in clinical practice, norm data for this age group have become indispensable. Chapter 5 provides Dutch norm data and psychometric properties of the Pediatric Quality of Life Inventory Young Adult Generic Core Scales (PedsQL_YA) in 649 Dutch young adults (both men and women) aged 18–30 years. The Dutch version of the PedsQL_YA demonstrates overall adequate psychometric properties. With the obtained norm data, the PedsQL_YA can be utilized as a tool to evaluate HRQOL in young adults with chronic health conditions, such as hemophilia.

Part II: HRQOL and psychosocial outcomes
In the second part of the thesis, HRQOL and psychosocial outcomes of patients (in different age groups) and of mothers are described. In Chapter 6, the generic and disease-specific HRQOL of patients (0-18 years) under treatment at the HCCC was assessed. In total, 146 children participated and results show that boys and girls with bleeding disorders (0-12 years) do not experience lower HRQOL than their peers. Contrary to our assumption, boys of 13-18 years report higher HRQOL than their chronically ill and healthy peers on total HRQOL and emotional functioning. On the other hand, girls (13-18 years) experience lower HRQOL than their healthy peers on total HRQOL, school functioning and psychosocial health. Boys with severe hemophilia report lower HRQOL than their peers with non-severe hemophilia on family functioning. The results suggest that the overall HRQOL of boys with hemophilia is comparable to peers. However, it is important to systematically monitor HRQOL, of girls especially, because possible influencing psychosocial factors can change over time.

Chapter 7 captures the perspectives of adolescents and young adults (YA; 16-30 years) with bleeding disorders on their condition and identifies which themes are relevant in their daily life, based on qualitative data from
focus groups. In total, 3 focus groups were conducted, including 12 YA. Despite growing up in a developed country with adequate treatment, YA with bleeding disorders still experience obstacles in daily life. Several major themes were identified: relationship with parents, capabilities in sports, capabilities in outings and traveling, self-management, illness perception and -acceptance, and capabilities in education and employment. Moreover, two paradoxes were identified; with having the responsibility over their treatment, YA may feel that the consequences, such as joint damage or pain, are in their own hands. This responsibility creates a complex situation; when adherent to treatment, life can be lived to the fullest and YA feel ‘normal’. On the other hand, patients often do deviate and are not adherent, and confrontation with the consequences is immediate. The second paradox identified was that YA are often being told to be grateful for living in a country and era where treatment is available, unlike many developing countries and previous generations, while they are still suffering from pain, arthropathy and limitations. This may result in feeling like they ought not to complain. These findings provide additional insights into YA’s experiences, especially regarding the transition period to adulthood.

Chapter 8 builds on the findings of Chapter 7, by administering several validated questionnaires to 95 YA (18-30 years) with bleeding disorders, related to the themes identified. This study assesses HRQOL, developmental milestones and self-esteem in Dutch YA with bleeding disorders compared to a group of (healthy) peers. The results show impaired total HRQOL, physical functioning and school/work functioning young adult men with bleeding disorders. Significant lower self-esteem was found in YA men with bleeding disorders in comparison to peers. YA men with bleeding disorder achieved significantly more psychosexual developmental milestones than peers, but show a delay in ‘paid jobs, during middle and/or high school’. For YA women with bleeding disorders, no differences were found on any of the outcomes in comparison to their peers. These findings emphasize the need for systematic monitoring of HRQOL, especially with regard to school/work functioning, in daily clinical practice.
Discussion

Next, Chapter 9 addresses the psychosocial impact of hemophilia on mothers. Mothers of 32 boys with hemophilia (ages 8-12 years) do not report aberrant levels of anxiety and depression in comparison to mothers of healthy children. However, still 21% of mothers report clinical distress, which underlines the importance of also monitoring maternal psychosocial functioning and distress systematically.

Part III: psychosocial care

In Chapter 10, a description of the psychosocial care provided by the multidisciplinary team of the HCCC at the Emma Children’s Hospital in Amsterdam, the Netherlands, is given. The focus of the psychosocial care provided by the multidisciplinary team is on preventing psychosocial problems and medical related stress, and supporting and equipping the child with hemophilia and its parents with as many skills as possible to lead an independent life with a high HRQOL. Core elements of the psychosocial care are therefore monitoring and screening of HRQOL (e.g. in daily clinical practice via KLIK), psycho-education (hemophilia camp, hemophilia school, disease specific activities, meetings for girls, parent meetings), practical help (Emma at Work, an employment agency for adolescents and young adults; Educational Facility and school visits), psychosocial interventions (the On Track group intervention and the Hemophilia Coping and Perception Test), and individual care (psychological counselling and referrals). By providing this overview of psychosocial support offered and by sharing this knowledge, psychosocial care can become more structured and consistent between HCCCs around the world. Potentially, processes and outcomes of care can be improved.

Limitations

The studies described in this thesis have some overall limitations to take into account.

Adequate measurement properties

In pediatrics, the abundance of different instruments, user fees and limited
use in international research and clinical settings, makes it difficult to obtain enough empirical data about specific instruments’ measurement properties [1]. As a result, performing (methodological) research with such instruments is extremely complicated.

A guideline to assess the methodological quality of instruments, is the standardized COSMIN checklist, which we used in chapter 3. However, it has some limitations, such as high standards that often cannot be met in research in rare diseases such as hemophilia, or not being able to distinguish between low reporting and low methodological quality of studies. However, COSMIN has been developed in an international Delphi study and has widely been used internationally. It can be considered a strong starting point for a methodological assessment of outcomes [2, 3]; we are not aware of a more standardized applicable system for the rating of the quality of measurement properties.

Most measures available for patients with hemophilia have shown to have good group-level measurement properties (chapters 3 and 5). However, most are not sufficiently strong to be able to make individual clinical decisions and most information on interpretability is lacking. When looking at the concrete steps to develop usable instruments, some of those steps have been missed in hindsight. For example, responsiveness was not addressed in our study in Chapter 5. Therefore, we have no information on how well the PedsQ_YA is able to detect change over time in HRQOL of YA in the Netherlands.

**Sample size and representativeness of patients**

Small sample sizes often led to poor or fair rating for the quality of the study in the systematic review (chapter 3). Unfortunately this is often the reality with disease-specific questionnaires in rare diseases, making the development of instruments with adequate measurement properties difficult. In the case of chapter 4, the cause of a small sample in the HCPT study was due to the narrow age range of the HCPT (8-12 years old) and the response rate being rather low.

Even though nearly 700 participants from the general Dutch population were included in the PedsQL_YA study (chapter 5), sample sizes were still
relatively small for some subgroup analyses. More importantly, the assessment of the health condition status was based on self-report rather than on physician-report, which is an important limitation in collecting normative data. Also, it is possible that more severely ill young adults did not participate because they were not able to sit behind the computer and complete questionnaires due to the severity of their health condition or not wanting to burden themselves with participation. Therefore, it is possible that our sample contains a slightly different type of chronic condition than encountered in clinical practice, which is a common issue when collecting norm data. Another concern with regard to representativeness of our samples, is that most participants were born in the Netherlands, were mostly highly educated and ethnic minorities were underrepresented. Moreover, we did not have information regarding non-respondents and their medical information, and therefore examining selection-bias was not possible in chapters 7, 8 and 9.

A reference group for the Distress Thermometer for Parents (DT-P) was not available in chapter 9. Thus, we could not compare our DT-P results to the general population. However, recently, normative data has been collected for the DT-P, and it would therefore be interesting to study a larger sample of both mothers and fathers, and compare their levels of distress to the general population [4].

Clinical implications and future perspectives

Burden on patients and adequate measurement properties

When asking patients to report on their functioning, the burden should be as little as possible. To satisfy previously noted limitations (e.g. small sample sizes, inadequate measurement properties), patients would ideally only have to complete one single set of questionnaires, while this information is used for multiple purposes: research as well as clinical care. A method to decrease the burden for patients is with the use of computer adaptive testing (CAT). With CAT, items from an item bank (a set of questions that all measure the same construct) can be administered more efficiently compared to short questionnaires with fixed items [5]. The patient-reported outcomes measurements information system
(PROMIS) is an initiative developed in the USA, aiming to develop self-reported item banks using CAT and item response theory (IRT) that are applicable across a wide variety of chronic disorders. By using PROMIS item banks in the future, patients or parents may only need to answer 4–8 items per item bank, because with CAT only relevant questions are presented. This new system has shown to have higher validity, reliability, and better responsiveness than the existing PROMs [6-9]. It is expected that PROMIS will be implemented worldwide and will rapidly replace existing PROMs [5, 10-12]. PROMIS measures have already been used in several pediatric populations, such as sickle cell disease and asthma [13-15]. As emphasized by Recht et al. (2016), there is a need for personalization patient-reported outcomes in hemophilia. This could be an enormous improvement in psychometric assessment of HRQOL in hemophilia [15]. With the most appropriate items of existing questionnaires put together in a CAT, the most optimal HRQOL instrument can be developed for patients with hemophilia. Therefore, our next project is to develop a hemophilia-specific item bank, to facilitate the use in different international studies and to decrease the burden for patients.

Another option to minimize respondent burden and improve information on measurement properties, is by using core outcome sets of instruments across studies [16]. Core sets represent the minimum that should be measured and reported in all clinical trials of a specific condition [17]. It is expected that when core outcomes are always collected and reported, the results of trials can be compared, contrasted and combined [17]. For example, the systematic review performed in chapter 3, can provide a basis for what HRQOL questionnaires to choose in a core outcome set for hemophilia. It is obviously beneficial to use corresponding strategies for HRQOL assessment in rare diseases such as hemophilia.

(Inter)national collaboration

With the previously mentioned issues of small sample sizes and lack of information on measurement properties (e.g. cross-cultural validity) in mind, expanding collaboration across centers and borders could overcome some
of these issues. Concrete steps in the development of internationally usable instruments involve item development, translation, psychometric testing (e.g., examination of reliability, validity, and responsiveness), and collection of norm data (obtaining reference data for the questionnaire from large (non)clinical populations). Guidelines on how to conduct these steps have been published [18, 19]. As stated in 2005 already, there is a need of (inter)national collaboration in clinical research on hemophilia [20]. Very few of the research questions can be tackled by studies done in single, albeit large, hemophilia centers. Sufficient sample size is essential for research in a rare disease such as hemophilia and this goal can only be achieved through collaborative multicenter studies. Moreover, it is necessary to maintain a high interest and expertise in the field of hemophilia, with advances in treatment happening so quickly [20]. An excellent example of national collaboration is the ‘Hemophilia in the Netherlands’ (HiN) study; since 1972, a series of 5 national surveys have been performed [21, 22], and the sixth edition is planned for 2017.

**New developments in hemophilia**

Some very interesting advances in hemophilia treatment that are currently going on, behold the long acting factor replacement products. Several studies have shown that recombinant factor VIII and factor IX have prolonged half-life, and also demonstrated safety, bleeding control and prevention in patients with hemophilia A and B [23-25]. This means that, instead of infusing two or three times a week, patients now have the possibility to infuse once every two weeks. It is expected that this will influence HRQOL positively [23], since the treatment burden for patients will be lower. But on the other hand, new issues will arise such as staying adherent to (infrequent) treatment, insecurity related to remaining factor levels present in the blood or self-management issues regarding the decision on what day to infuse. Such issues can also influence HRQOL, which means a new area of discovery in hemophilia research and -care will be revealed. In any case, all HCCCs should pay close attention to patients shifting to new treatment products, systematic monitoring of HRQOL and adequate guidance in this process is warranted. With the use of the KLIK
system at the HCCC in Amsterdam, we will have the possibility to follow the
HRQOL and psychosocial functioning of children and young adults shifting to
new treatment products over time and compare their HRQOL to before the
new products were used.

**HRQOL and longitudinal data**

As we have seen in this thesis, the HRQOL of boys growing up with hemophilia
in the Netherlands is good. This may raise eyebrows and doubts with
regard to the necessity of monitoring HRQOL and providing a broad range
of psychosocial care for this population. However, as we described in the
introduction of this thesis, several factors are of influence on HRQOL, such
as psychosocial stressors (e.g. restrictions, treatment) and stress processing.
Psychosocial stressors, but also child- and family factors, change continuously
[26]. For this reason, although this population of boys with hemophilia fares
well, it is important to keep monitoring HRQOL and psychosocial problems in
clinical practice. Moreover, the finding that girls with bleeding disorders (13-
18 years) report lower HRQOL supports this as well. It is hypothesized that
girls are confronted with issues regarding their bleeding disorder as teenagers
(e.g. when they start menstruating, which can lead to very heavy bleeding),
while boys start to face consequences and issues when they are older (e.g.
physical impairments). From another perspective, it is also possible that these
boys are doing so well because of the psychosocial care they are receiving
from the HCCC (e.g. psycho-education, peer support). For that reason, it will
be interesting to follow this population over time.

Longitudinal data were not incorporated in this thesis. Longitudinal
analysis provides insight into the causality of outcomes over time. With this
information, children and adolescents can be identified who are more likely
to develop problems in daily life (e.g. low self-esteem), as well as having more
insight into the causality of problems. A method to collect this longitudinal
data is with the data collected in the KLIK portal, which has been described in
chapters 6 and 10 [27, 28]. KLIK has become standard care in five Dutch HCCCs:
Amsterdam, Rotterdam, Leiden, Groningen and Nijmegen. In the future, while
Discussion

increasing sample size, data from all these HCCCs should be analyzed in a collaborative study.

In addition, KLIK has recently been implemented (since January 2017) in the daily care for YA (18-30 years) with bleeding disorders in Amsterdam. This provides the opportunity to monitor children with bleeding disorders over time (from 0-30 years with the PedsQL questionnaire) while they grow up into YA. The studies in this thesis have incorporated two broad, but separate, groups of patients: children and young adults. This hinders the within-group comparison in children and YA at this point. In the future however, with the use of KLIK, we will be able to make statements about the course of HRQOL and psychosocial functioning over time in patients with bleeding disorders. Not only does this give insight in their functioning during the transitional phase, but the adult healthcare provider already has information on how the patient was functioning before transition. Moreover, this implementation also adds opportunities to our previously identified needs for (inter)national collaboration; KLIK can be implemented for young adults in other HCCCs in the Netherlands as well.

Furthermore, as we have seen in chapter 3, the CHO-KLAT [29] has shown to be the most optimal measurement in children at this point. However, the Haemo-QoL questionnaire has been incorporated in KLIK since 2014. Consequently, it would be interesting to add the CHO-KLAT to the KLIK system, perhaps instead of the Haemo-QoL [30], and study the lacking measurement properties.

Work and education

YA with bleeding disorders struggle with the impact of their condition on daily life. This finding is disturbing when realizing the adequate HRQOL boys (0-18 years) with bleeding disorders reported during childhood (as shown in chapter 6). In contrast to their younger counterparts, YA show impaired HRQOL (as shown in chapter 8). For all children, transition into adulthood is challenging. But the transition for YA with bleeding disorders is more challenging than for healthy peers, perhaps even more than expected. Although this is in line with previous research in patients with chronic health conditions [31], this could be
a starting point for increased psychosocial care for young adults with bleeding disorders. Apparently, transition is associated with a decrease in HRQOL in YA with bleeding disorders, indicating the necessity of awareness of this issue in both pediatric and adult healthcare providers. From our results, we can deduce that autonomy development is a complex process. Chapter 7, for example, shows that YA struggle with many issues regarding gaining independence; relationship with parents, being able to travel, finding a suitable job. Chapter 8 adds to these findings by demonstrating a lower HRQOL related to school/work functioning in YA men, as well as lower rates of paid employment. The previously mentioned nationwide HiN study also demonstrated that patients with severe hemophilia participated less in full-time work in 2001 compared with the general population, despite having comparable educational levels [32]. Although it can be assumed that those numbers have improved over the years, a possible explanation for this difference may be that hemophilia patients more often follow fulltime education over a longer period of time. This seems likely, as a higher level of education is needed for ‘white collar’ jobs, which are often suitable jobs for hemophilia patients, since the risk of bleeding due to physical activities at work is low [32]. It will be interesting to compare these findings in the sequel of the HiN study.

Transition in healthcare
Another factor that adds to the difficulties during the transition phase is the large difference between pediatric and adult healthcare. The multidisciplinary care for children with bleeding disorders is extensive (as is demonstrated in chapter 10), and YA are expected to be independent and fully responsible for their own treatment when they are 18 years old. However, research has demonstrated that the mean age of YA for complete self-management and responsibility is not reached until the age of 22 [33]. With this information in mind, the gap between pediatric and adult healthcare is currently too large. Despite the availability of protocols for transition, more effort should be put into the improvement of healthcare during transition [34-36]. A first step that just has been taken is the monitoring of HRQOL with KLIK during the transitional
phase. A step further could be to use the questionnaires incorporated in KLIK as reports of symptoms and health status from home before, or instead, of visiting the outpatient clinic. This way, KLIK can be used as a tool to decide whether a patient needs an outpatient visit, and care can become more patient-centered. Moreover, the increase of cross-over outpatients clinics (with both the pediatric and adult healthcare providers present) could be beneficial. In the current situation, YA have one conjunct consultation before transition. It is advisable to start with such conjunct consultations earlier, during adolescence (around age 15) and continue until the age of 25 years. In this process, the role of the pediatric hematologist, in collaboration with parents and YA, should be diminished slowly, while the role of the adult hematologist and YA slowly increases. A pediatric nurse can also be involved to smoothen this process, being a familiar person for the YA with hemophilia. In addition, implementing a transition checklist for healthcare providers into daily clinical practice may be beneficial. Initiatives such as the Transition Readiness Questionnaire (TRAQ [37]) and the Dutch ‘On Your Own Feet Transfer Experiences Scale’ [31] could be useful to incorporate in KLIK for this challenging population.

**Screening parents and families at risk**

The results of chapter 9 underline the importance for healthcare providers to be aware of the fact that parents, mothers in this case, of boys with hemophilia are at risk for distress. In clinical practice, parents with high levels of distress should be identified by the multidisciplinary team. In the Emma Children’s Hospital/AMC, the Distress Thermometer for Parents (DT-P) is used in clinical practice as a screening tool for parental distress. However, it is still difficult to identify which parents need or want psychosocial support in advance. The identification of families at risk for psychosocial problems can be improved by screening early with the Psychosocial Assessment Tool (PAT). This is a screening instrument developed in the US, that assesses psychosocial risk in families [38]. In the PAT, psychosocial problems are assessed, as well as problems in beliefs regarding the illness, availability of social support, symptoms of traumatic stress, and other psychosocial stressors within the family [39]; domains that are
related to the risk- and protective factors described in the model by Wallander & Varni in the introduction of this thesis [26, 40]. The PAT has potential clinical utility in hemophilia practice and has been validated among multiple pediatric populations [39, 41, 42]. The PAT takes 10-15 minutes to complete, and could be included in the KLIK portal to be completed (once) before clinic visits to assess the risk for psychosocial problems, for example when patients are new to the HCCC. This screening could make the psychosocial support more targeted towards those families who need it the most, while preventing problems from deteriorating.

As mentioned earlier, the findings in chapter 9 encourage more research on psychosocial functioning of mothers of boys with hemophilia. In hemophilia, mothers have a unique position. Due to the X-linked nature of the condition, mothers are often carriers of the hemophilia gene, which means they have a father or brother who has hemophilia as well. However, the difference between the generation of the father growing up with hemophilia and a son growing up with hemophilia is immense. It has been shown that a family history of hemophilia is related to increased stress in mothers of children with hemophilia [43]. Our clinical experience points in the same direction; mothers of children with hemophilia are often stressed, worried and anxious. This could be related to the degree of enmeshed cohesion shown by mothers [43]. In addition, it suggests that prior knowledge of hemophilia does not necessarily improve coping: it is not the same when a brother or father has hemophilia compared to a son. Although levels of distress and anxiety may also depend on the stage the parents have attained in their management of hemophilia and how well they are managing the condition, this has never been truly captured in research before [44, 45]. Relating these outcomes to the psychosocial functioning of children would be interesting.

Furthermore, questionnaires currently used for parents are possibly not capturing the true experience, including feelings of guilt and continuous anxiety for life-threatening bleeds. By adding a qualitative aspect to future research, other problems can come into focus, which do not result from questionnaires. We learned from conducting focus groups, as described in chapter 7, that
some problems are not exposed easily and perhaps cannot be captured in questionnaires [46]. An interview or focus group approach could add value to identify what mothers of boys with hemophilia experience, but also to get insight into what ways we can support them, tailored to their needs. For example, although more research is needed in parents of children with hemophilia to develop the appropriate treatments for parents, parent support groups could be beneficial. The previously mentioned group course ‘On Track’ has just been developed online for parents of chronically ill children at the Emma Children’s Hospital/AMC, and its effectiveness is being studied at this point. In this online group course, problem solving therapy and stimulation of social support are an important base of the intervention.

In addition to an increased need for research in mothers, young girls who are carriers or who have lower factor levels in their blood deserve more attention. Within the range of hemophilia being a rare condition, being a girl with a bleeding disorder (or low levels of factor VIII/IX due to being a carrier) is even more rare. Nevertheless, problems are substantial, as is shown in chapter 6, where girls with bleeding disorders show lower HRQOL than their healthy peers. This should be kept in mind when developing new studies or interventions.

Cost-effectiveness
Psychosocial care is not standard everywhere, mostly due to lack of financial resources. Although the role of psychosocial care providers (such as health psychologists and social workers) is increasingly recognized, guidelines as to what minimum of psychosocial care should be offered, do not exist unfortunately [47-50]. It is recommended that such guidelines are established. For the future, it would be interesting to address the cost-effectiveness of the psychosocial care. Interventions can have other desirable outcomes, related to costs. For example, interventions that promote adaptation to the illness and that promote adherence to treatment could potentially reduce hospital days, use of clotting factor, visits to the clinic and prevent problems from deteriorating [51]. Another cost-beneficial example can be the use of online interventions
and networks, especially for adolescents. Modern communication technologies may offer health benefits through peer support and learning gained through online social networking [52].

Conclusions

In this thesis, three major elements in the research around growing up with hemophilia are presented: development and evaluation of instruments (Part I), HRQOL and psychosocial outcomes (Part II) and psychosocial care (Part III). This thesis is the first to describe what it is like to grow up with hemophilia, in terms of HRQOL and psychosocial functioning, for both patients and their mothers. The development and evaluation of several HRQOL and psychosocial instruments (Part I) showed us that this process is difficult, although measuring HRQOL with adequate instruments is indispensable, and should be an integral part of care. Additional research using the existing measures is necessary to support and document the lacking measurement properties of currently available questionnaires. The instruments developed and evaluated gave us the opportunity to assess psychosocial outcomes (Part II), showing that HRQOL in young boys with hemophilia, in contrast to their females counterparts, is not impaired, until young adulthood is reached. YA men are struggling with physical impairments, gaining autonomy, transfer to adult healthcare and school/work functioning. All these aspects have a great impact on YA, and appropriate support should be offered during this transitional phase, to YA but also to parents; the gap between the extensive multidisciplinary care in childhood in terms of psychosocial support (part III) and YA healthcare is too big. Continuity of multidisciplinary healthcare for children, adolescents, YA and parents is necessary to ensure adequate health related quality of life and psychosocial functioning, and improve that of vulnerable groups (such as girls and YA men).
Discussion

Key messages

Part I
• Measuring HRQOL in pediatric patients is challenging.
• For children with hemophilia, the CHO-KLAT is the most optimal questionnaire at this point. For adults, the Haemophilia Well-Being Index and HAEMO-QoL-A are most optimal.
• The HCPT is a useful tool to assess knowledge, self-management and perception in boys with hemophilia (8-12 years).
• The PedsQL_YA reliably measures HRQOL in young adults (18-30 years) and with the obtained norm data, the PedsQL_YA can be utilized to evaluate HRQOL in young adults with chronic health conditions, such as hemophilia.

Part II
• HRQOL of boys with hemophilia (0-18 years) is comparable to peers, girls with bleeding disorders (13-18) do report lower HRQOL than their peers.
• Despite growing up in a developed country with adequate treatment, young adults with bleeding disorders still experience obstacles in daily life.
• Young adult men with bleeding disorders have a lower HRQOL and self-esteem than their (healthy) peers and struggle with school/professional functioning. Young adults with bleeding disorders do not experience a delay in developmental milestones compared to their peers.
• One in five mothers of boys with hemophilia (8-12 years) reports clinical distress.

Part III
• The current psychosocial care, with different degrees of intensity, is extensive for children with bleeding disorders and their parents at the Emma Children’s Hospital/AMC.
References


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Discussion