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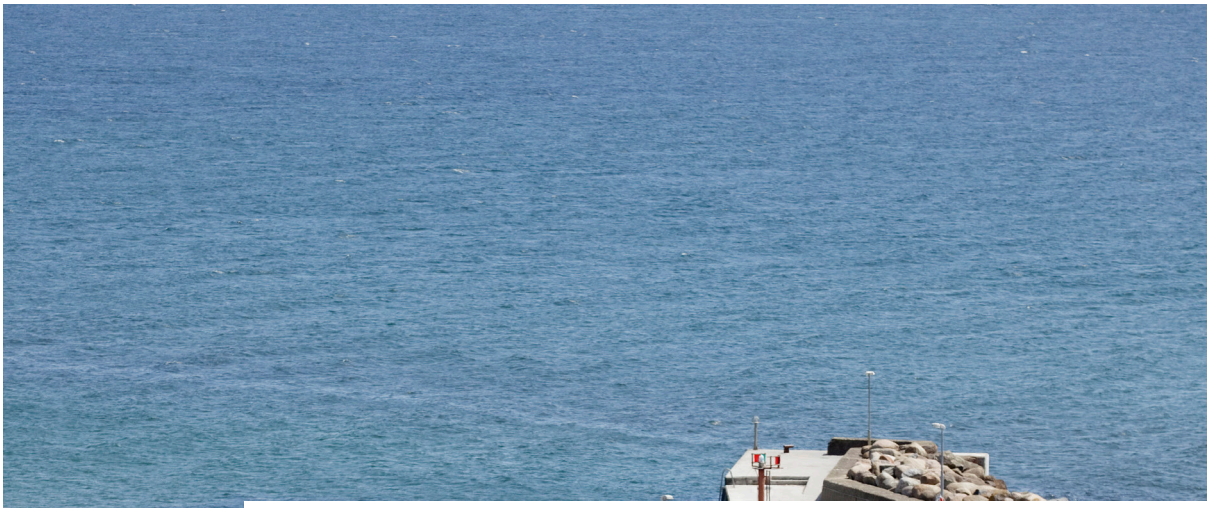

Register-based studies to assess long-term outcomes in haemophilia

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DEPARTMENT OF TRANSLATIONAL MEDICINE | LUND UNIVERSITY 2017

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LUND
UNIVERSITY

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Register-based studies to assess long-term outcomes in haemophilia

Introduction

Haemophilia is a X-linked bleeding disorder affecting mostly males. Women are mainly carriers of haemophilia, however, they can expereince high bleeding tendency and assocaited symptoms as with males. In the absence of the appropriate treatment, bleedings, especially into the joints, result in adverse outcomes. The general aim of this thesis was to promote the use of register-based data to investigate long-term outcomes among persons with haemophilia. In addition, we investigated some long-term ouctomes among persons with haemophilia and carriers of haemophilia using the available registers.

Methods

We conducted a scoping study and several large-scale register-based studies to evaluate outcome assessment practice and joint and survival outcomes in haemophilia, respectively. We used data from the Malmö single centre register (n=167), National Patient Register (mild haemophilia=315 and carriers of haemophilia=561) and the KAPPA register (severe haemophilia=173) as sources of inclusion of participants and data on their outcomes. Cross-sectional and longitudinal designs were used to maximize the use of available data. We investigated joint disease, haemophilia joint health score, joint surgery and survival of the study participants.

Results and conclusion

The assessment of the literature revealed a paucity of productive registers and inconsistency in their outcome reporting. Carriers and persons with mild haemophilia are at higher risk of joint disease and surgery compared to the general population. The index joints are more at risk of surgery in both groups especially among the older age groups. The KAPPA study showed remarkable health utility and joint status among younger persons with severe haemophilia on prophylaxis started by age 3. In the Malmö register study, persons with severe haemophilia born 1980 owards did not have surgery. This thesis suggests that carriers of haemophilia and persons with mild haemophilia are at high risk of joint disease and should be monitored at haemophilia treatment centres for their outcomes. Registers, when harmonized in terms of structure and outcome asessement, are valuable resources for generation of epidemiological evidence.

Key words: registers, haemophilia, carriers of haemophia, long-term outcomes, joint surgery, survival, longitudinal studies

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I know that I know nothing

Socrates

To my family for all their support and tolerance during my intensive studies

Content

List of figures

Abbreviations

BC	Birth cohort
BMI	Body mass index
CCC	Comprehensive care cantre
CF	Clotting factor
CI	Confidence interval
Coef.	Coefficient
EAHAD	European Associtation of Haematology and Alied Disorders
FC	Factor concentrate
HIV	Human immunodeficiency syndrome
HJHS	Haemophilia joint health score
HRQL	Health related quality of life
HTC	Haemophilia teratment centre
ICE	Iterative chained equations
IQR	Inter-quartile range
IRR	Incidence rate ratio
ISTH	International society of thrombosis and haemosthasis
ITI	Immune tolerance induction
MRI	Magnetic resonance imaging
NBHW	National Board of Health and Welfare of Sweden
NPR	National patient register
OLS	Ordeinary least square
PRO	Patient-reported outcomes
PWH	Persons with haemophilia
PWMH	Persons with mild haemophilia
ROM	Range of motion
SHR	Sub-hazard ratio
TF	Tissue factor
UDC	Universla data collection
WFH	World Federation of Haemophilia

Papers

I. Osooli M, Berntorp E. Registry-based outcome assessment in haemophilia: a scoping study to explore the available evidence. *J Intern Med*, 2016. 279(6): p. 502-14.

II. Osooli M, Steen Carlsson K, Baghaei B, Holmström M, Rauchensteiner S, Holme PA, Hvitfeldt L, Jan Astermark J, and Berntorp E. The association between health utility and joint status among people with severe haemophilia A: findings from the KAPPA register. *Haemophilia.* 2017.

III. Osooli M, Lovdahl S, Steen Carlsson S, Knobe K, Baghaei F, Holmstrom M, Astermark J, and Berntorp E. Comparative burden of arthropathy in mild haemophilia: a register-based study in Sweden. *Haemophilia*, 2017. 23(2): p. e79-e86.

IV. Osooli M, Donfield S, Steen Carlsson K, Astermark J, Berntorp E. Joint disease among carriers of haemophilia. (submitted in *Blood*)

V. Osooli M, Steen Carlsson K, Astermark J, Berntorp E. Surgery and survival in birth cohorts with severe haemophilia and differences in access to replacement treatment: the Malmö experience (submitted in *Haemophilia*)

Introduction

Haemostasis

Haemostasis is the response of the body to control bleeding. Several elements function in a stepwise process to form a clot that will stop bleeding. These elements include: enzymes (circles), inhibitors (hatched circles), zymogens (boxes), and complexes (ovals). There are two haemostasis pathways: the primary extrinsic pathway and the intrinsic pathway (Figure 1). There is not any known bleeding etiology for intrinsic pathway. The main haemostatic pathways is therefore the extrinsic one. When a blood vessel is damaged, the tissue factor gets exposed to the circulating factor VIIa and this results in the activation of the extrinsic pathway. From this stage the haemostasis elements get activated one by one to form the fibrin clot. Factor VIII and factor IX are essential elements in this pathway without which the haemostasis process will not go further than where their function is needed.

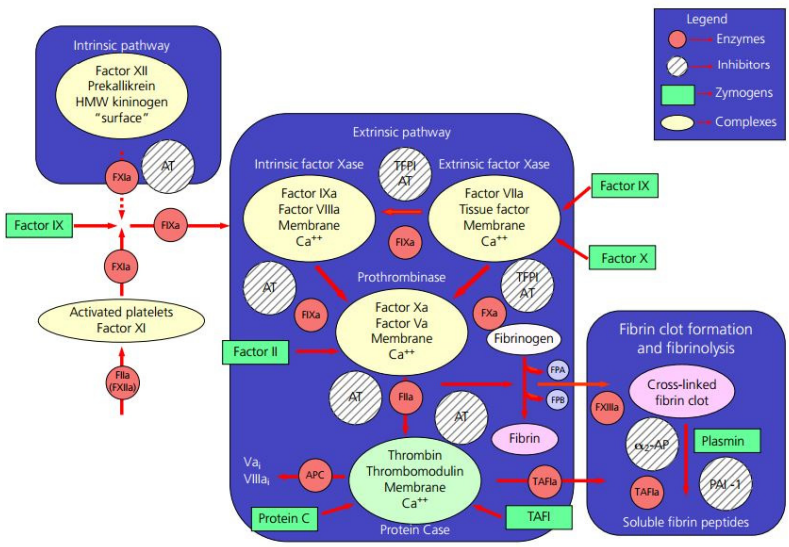

Figure 1. Overview of haemostasis. There are two coagulation pathways: the primary extrinsic pathway (on the right) and the intrinsic pathway (also known as the accessory pathway, on the left). The components of these multistep processes are illustrated as follows: enzymes (circles), inhibitors (hatched circles), zymogens (boxes), or complexes (ovals). Figure was reproduced (with permission of John Wiley and Sons Ltd) from Textbook of Haemophilia, 3rd ed. [1])

All the needed elements used in haemostasis are available in sufficient amount and functional status in a healthy human body. The insufficiency or malfunction of any of these elements can result in impaired haemostasis and prolonged bleeding.

Haemophilia

Haemophilia is a congenital bleeding disorder affecting mainly males. It is also known as the royal disease because Queen Victoria of the UK was a carrier of haemophilia and passed the gene to her daughters (carriers) and her son Leopold (haemophilia) (Figure 2) [1]. Persons with haemophilia (PWH) lack sufficient amounts of or functional CF VIII or IX in their blood resulting in an increased bleeding tendency. CF VIII and IX deficiencies are known as haemophilia A (HA) and haemophilia B (HB), respectively. HA is more common and occurs 1:5,000 live male births. However, HB occurs 1:1,500-25,000 male births. Globally there is a large gap in haemophilia incidence/prevalence statistics which mainly arises from diagnosis coverage differences, improvement in treatment, and mortality due to viral infections rather than the real incidence (occurrence) of haemophilia itself [2]. While in most cases haemophilia is inherited, about 30 % of haemophilia is the result of a new mutation in a person without prior family history.

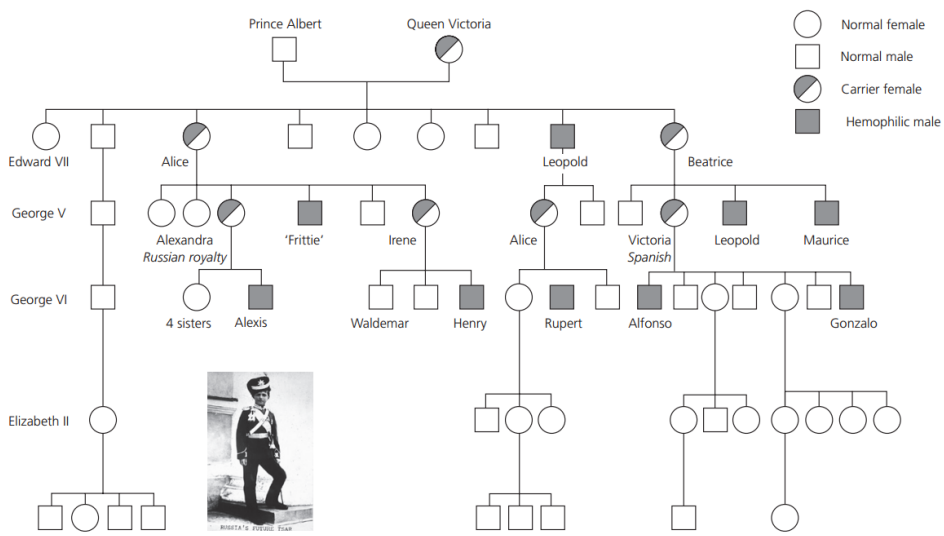

Figure 2. The family tree of Queen Victoria. Reproduced (with permission of John Wiley and Sons Ltd) from Textbook of haemophilia. 3rd ed. [1]

Severity of haemophilia

Depending on their CF level at diagnosis, PWH may have mild, moderate or severe phenotype (Table 1). Those with the severe phenotype may bleed spontaneously and into their joints starting in the early years of life. They have the highest bleeding tendency and are highly depending on replacement therapy to live a normal life. Before replacement therapy become available, PWH of severe phenotype could hardly survive to their third decade of life. Persons with moderate haemophilia usually bleed due to trauma but could also experience spontaneous bleeding. Finally, those with mild phenotype mostly bleed due to trauma. They are usually diagnosed as a result of family investigation or prolonged bleeding following trauma or surgery.

Table 1. Bleeding phenotype and recommended treatment in relation to severity of haemophilia

Severity	Clotting factor level	Bleeding phenotype	Most common treatment
Mild	>0.05-0.40 kIU L^{-1}	Mainly due to taruma	Episodic
Moderate	0.01-0.05 kIU L^{-1}	Mostly trauma related and sometimes spontaneous	Episoid or prophylaxis (depending on the resources)
Severe	< 0.01 kIU L^{-1}	Spoentaneous and trauma related	Prophylaxis

It should be noted that, the current categorization of haemophilia severity is somehow a simplification and routes back to several decades ago when the treatment was not affordable and available to majority of PWH. Molecular severity may not reflect on the clinical severity meaning that people with similar CF level may have different bleeding tendencies [3]. In addition, the CF levels may rise over age resulting in changes in the severity of haemophilia [4]. Rise of CF level reduces the need for treatment and has implications for tailoring treatment among adults.

Diagnosis

Haemophilia is usually diagnosed through bleeding symptoms or family investigation. Big bruises, bleeding into muscles and joints, spontaneous bleeding and or prolonged bleeding are among the most common bleeding symptoms resulting in haemophilia diagnosis. New-borns from families with positive history of haemophilia and those whose mothers are known carriers of haemophilia get screened for haemophilia [5].

Different bleeding disorders share some symptoms, even so, they require different treatment. An accurate diagnosis is essential and the first step in providing

appropriate treatment and care for haemophilia. An accurate haemophilia diagnosis can only be obtained through combining information from clinical symptoms with the results from comprehensive laboratories tests [5]. Such laboratories must meet quality assurance requirements, have sufficient knowledge and expertise in coagulation and be equipped with correct equipment.

Main screening coagulation tests for haemophilia diagnosis include: prothrombin time (PT), and activated partial thromboplastin time (APTT). Factor assays are essential for determining the haemophilia diagnosis. The one-stage factor assays are most common type; however, haemophilia treatment centres (HTCs) should have the chromogenic assays or two-stage tests available for confirming diagnoses in certain cases [6]. Special considerations should be taken into account in performing laboratory tests for diagnosis of haemophilia diagnostic as described in the treatment guideline published by World Federation of Haemophilia (WFH) [5].

Treatment

Over the past few decades, PWH have benefitted from substantial progress in developing effective treatment products and strategies. Current haemophilia treatment consists of infusion of the missing CF known as replacement therapy. There are two main methods of replacement therapy: on-demand (episodic) and prophylaxis. Prophylaxis (primary) is defined as infusing the missing CF at least on time per week for more than 40 weeks per year to prevent bleeding [7]. Infusing the CF after occurrence of bleeding is known as episodic treatment. The superiority of prophylaxis over episodic treatment has been well established [8, 9].

Treatment regimens

The main aim of replacement therapy is to increase the trough level of CF and to prevent bleeding, particularly spontaneous. To achieve this goal, Professor Nilsson developed prophylaxis to keep the blood CF level above 1% and to convert severe into moderate haemophilia [10]. Traditionally the severity was used to assess need for treatment. However, PWH of the same severity may have different bleeding tendency and their treatment can be individualized [7, 11].

There are three main prophylactic regimens in terms of dose and frequency: the low-dose or Canadian tailored [12] (starts with 50 IU/kg once per week and can increased up to 30 IU/kg on alternate days) [13], the intermediate or Dutch regimen (15-25 IU kg^{-1} per infusion) and high-dose or the Swedish prophylaxis (25-40 IU kg^{-1} per infusion) [14]. The outcomes of these regimens have been investigated in several publications [12, 14-16].

The economic resources and availability of insurance and governmental support remains as one of the main determinants in choosing a special regimen. Some other

important aspects of prophylaxis are the time at its initiation and duration. Figure 3. presents different prophylaxis and their impacts on outcomes among PWH.

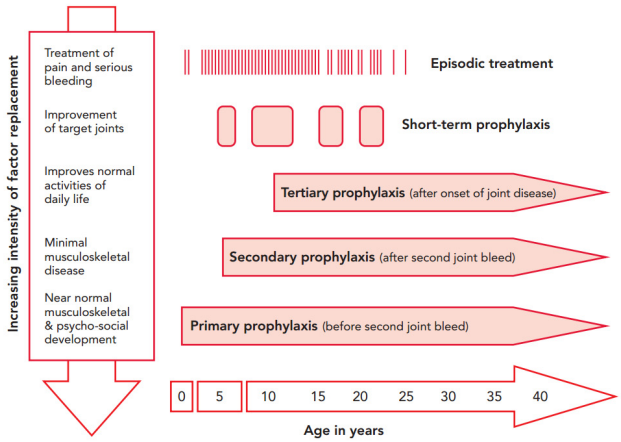

Figure 3. Strategies for clotting factor replacement therapy at different ages and impact on outcomes. Figure reproduced (with permission of John Wiley and Sons Ltd) from Textbook of haemophilia. 3rd ed. [1]

Outcomes

Bleeding as the main manifestation of haemophilia results in numerous negative consequences depending on its location, extent and management. Consequences of bleeding include but not limited to: joint pain and destruction (arthropathy), mobility reduction, anaemia, loss of work or school, psychosocial issues, and poor health related quality of life (HRQL). In addition, treatment of haemophilia may be associated with development of CF inhibitor [17], blood-born viral infections and infections related to the site of injection [18]. In the following text some of the most common and important haemophilia outcomes are reviewed.

Bleeding

Bleeding as the main characteristic of haemophilia can occur in any part of the body; however, it most commonly occurs in muscles, joints and soft tissue. Majority of bleedings are minor, however, massive bleedings (due to trauma or surgery for example) or intracranial bleedings can be life threatening if not treated immediately and sufficiently. Annual bleeding and joint bleeding are among the most commonly reported and important outcomes in haemophilia [19].

Musculoskeletal health

Bleeding into the joints, if not treated early and appropriately, can cause irreversible damage into the joint structure. Untreated bleeding causes joint damage and increases the likelihood of further bleedings into the same joint, known as the target joint [20]. A target joint experiences more frequent bleedings and enhanced destruction. In the past, crippling was a characteristic of people with severe haemophilia, however today, PWH on early started continuous prophylaxis (mostly from high resource settings) have maintained relatively healthy joints by fourth decade of life. Restricting physical activity to prevent bleeding among PWH can lead to poor bone development and osteoporosis [21, 22].

There are several methods to assess the joint status and early occurrence of arthropathy. Imaging techniques including x-ray, magnetic resonance imaging (MRI) and ultrasound can detect joint structural changes but have some benefits and limits. While MRI is a very sensitive tool, it is costly and less feasible especially for children. X-ray is easy to implement, but not sensitive enough. However, ultrasound has proved to be a reasonably sensitive, relatively easy, and less costly to evaluate joints.

Apart from imaging techniques, there are few functional assessment methods to evaluate joint health. Pettersson score and Gilbert score became first available and used. During rennet years, haemophilia joint health score which is an adaptation of Gilbert score has received more attention and being used for its high sensitivity. Haemophilia joint health score (HJHS) has been validated for children on prophylaxis [23]. Another instrument for joint assessment is haemophilia activity list (HAL). HAL measures the impact of haemophilia on self-perceived functional abilities among adults [24].

Inhibitor

Around 25-30% and 3-13% of persons with severe and mild-moderate haemophilia A develop inhibitor, respectively [25]. Those with haemophilia B have a lower risk of inhibitor development compared to haemophilia A. The inhibitor risk is higher in the first 50 exposure days [26]. There are currently two main approaches in managing inhibitor: immune tolerance induction (ITI) and use of bypassing CF products which are both very costly. While in about two thirds of cases inhibitor may disappear without any intervention [27], the rest of the cases may benefit from ITI to eradicate their inhibitor [28]. PWH with positive inhibitor, experience more bleedings, complicated treatment, higher number of days absent from school/work, and consequently reduced HRQL [29].

Viral diseases

In the past, epidemics of Human Immunodeficiency syndrome Virus (HIV, 1981) and Hepatitis C Viral (HCV, 1988) have affected many PWH. Among the Dutch cohort with severe haemophilia, 26% of deaths were related to HIV [30]. After exclusion of viral disease related deaths, life expectancy was increased from around 60 years to 72 years. In the UK, death rate among PWH who were negative for HIV was around 8 per 1000 (1985-1992) compared to 81 per 1000 among those who were HIV seropositive (1991-1992) [31].

Patient reported outcomes (PRO)

Over the past three decades, the importance of perspective of patients on their health status and efficiency of treatment has attracted clinicians' and health decision makers' attention. Such information can be achieved through specific outcome measures known as PRO [32]. Numerous instruments have been developed and used for different subgroups of PWH. PRO assessment instruments used in haemophilia include both generic instruments such as SF-36 and EQ5D and also specific or targeted instruments such as Haem-QoL-A, Haem-A-QoL, Haemo-QoL and CHO-KLAT [33].

Psychosocial health

Living with haemophilia or having a family member with this condition can be hard to cope with in the absence of professional support [34, 35]. At different stages of life, PWH and their families face challenging situations including: comorbidities, intensive burden of treatment, and limitations in lifestyle due to their high bleeding tendency. Psychosocial problems can affect HRQL of PWH and need to be addressed in an efficient manner [36].

Outcome monitoring

Routine follow-up and monitoring is crucial to ensure the efficiency of replacement therapy and to maintain high HRQL for PWH. Joint bleeding, musculoskeletal health (x-ray and HJHS), and CF inhibitor are most commonly monitored [19]. However, the assessment of psychosocial outcomes, physical activity, social participation and HRQL have received less attention until recent years.

The interval for follow up and optimal outcome measures are still debated and are quite dependent on the available resources. For PWH of moderate to severe phenotype, annual follow-ups are recommended. However for those with mild haemophilia, less frequent visits, such as every third year could be planned. In cases where a person has complications, shorter follow-ups may be required.

The consensus is still missing on which instruments to use for monitoring outcomes among PWH. While some efforts have been made to address this issue [37-41], the variety of instruments available and the divided opinion on their benefits and limitations remains a challenge. Using different instruments makes it difficult to sum up the results of various studies and to compare them with each other.

Benefits of regular monitoring and documentation of the evaluated outcomes in haemophilia for use in clinical practice and research has been shown over past few decades. However, many HTCs do not have sufficient infrastructure and resources for regular documentation of outcomes.

Comprehensive haemophilia care

Bleeding is the main characteristic of haemophilia. It can result in several negative conditions including but not limited to: joint damage, pain, psychosocial issues and infections. Investigation and monitoring of bleeding and its consequences requires a team with relevant specialties and a multidisciplinary approach, which is known as comprehensive care. The concept of comprehensive care centre (CCC) has been initiated based on the WFH recommendations of diagnosis and care for persons with bleeding disorders.

In 2008, the European Association for Haemophilia and Allied Disorders (EAHAD) suggested the establishment of CCC as one of the principles of haemophilia care [42]. The healthcare team in a CCC consists of several of following experts: nurse, haematologist, orthopaedist, physical therapist, psychologist, social worker, dentist, laboratory technicians and other needed staff. A full list of all the principles is presented in Table 2.

Table 2. European princliples of haemophilia care [42]

1	**A Central Haemophilia organisation with supporting local groups**
2	**National Haemophilia Patient Registries**
3	**Comprehensive Care Centres and Haemophilia Treatment Centres**
4	**Partnership in the Delivery of Haemophilia Care**
5	**Safe and Effective Concentrates at Optimum Treatment Levels**
6	**Home Treatment and Delivery**
7	**Prophylaxis (Preventative) Treatment**
8	**Specialist Services and Emergency Care**
9	**Management of Inhibitors**
10	**Education and Research**

Carriers of haemophilia

Carriers of haemophilia (carriers) are women with an impaired factor VIII/IX gene. Most of carriers have a CF level within normal range; however, few carriers might have CF level equivalent to those with mild, moderate or severe haemophilia. Most of carriers are detected through family investigation for PWH and the rest are detected due to a prolonged bleeding or via their coagulation tests taken for medical/surgical procedures. Carriers who deliver a son with haemophilia may experience extreme psychosocial problems including suicidal thoughts following learning about the diagnosis and learning about their carrier status [43].

Episodic treatment with desmopressin is the treatment of choice for most of carriers. However, carriers with very low CF levels should be treated similar to males with haemophilia. The same diagnostic categorization of PWH applies to carriers. This means that symptomatic carriers or those with low CF levels should be regularly followed up and treated at HTCs [44].

Over the past few decades, some research has suggested that some carriers may have a relatively high bleeding tendency. Mauser Bunschoten *et al*. [45] performed a survey in the Netherlands and compared bleeding symptoms among 135 carriers of haemophilia A and B with the 60 women without a relative with haemophilia. They concluded that carriers had a higher bleeding tendency than healthy comparisons.

Several years later, Plug *et al.* also from the Netherlands conducted a postal survey and compared bleeding symptoms among carriers of haemophilia and women who were not carriers but from families with haemophilia [46]. Based on their findings, carriers had a greater risk of bleeding following tooth extraction, tonsillectomy or

adenotomy and some medical/surgical operations. Some more recent studies have reported increased risk of haemarthrosis [47] and reduced joint range of motion (ROM) [48] as well as the structural joint changes [49] among carriers of haemophilia. Carriers also may experience lower HRQL than women free from bleeding disorders due to pain and impaired physical health [50]. Literature remains scarce on long term outcomes among carriers of haemophilia, especially the joint status.

Research in haemophilia

Research in haemophilia has evolved substantially over the past few decades. Changes include the subject area, sources of information as well as the research methods. Before 2000, most research on haemophilia was laboratory assessments, clinical trials, cross sectional and only few longitudinal studies. During the past two decades, the study designs have become more sophisticated, and assessment techniques have been improved considerably. Meanwhile, patients' preferences have been researched more frequently as a haemophilia outcome.

On the other hand, the rarity of haemophilia has challenged research in terms of finding sufficient number of eligible PWH for various research projects. In addition, in many cases data were needed on history of treatment and outcomes which occurred several years before the study was conducted. Then, some centres started to set up and use registers as source of PWH for research. The expansion of haemophilia registers and their application in research became one of the critical advancements for such a rare disease.

Healthcare registers

Based on Merriam-Webster dictionary a register [51] is "a written record containing regular entries of items or details" or "a device (as in a computer) for storing small amounts of data; especially: one in which data can be both stored and operated on". The term registry [52] on the other hand is "a place for registration" or "an official record book" or "an entry in a registry". The literature tends to use the terms registry and register interchangeably.

For many years, healthcare professionals have collected, stored and used healthcare data for administrative, planning and research purposes. The term register in healthcare refers to a routine data collection system to collect and store data on healthcare conditions of people. Brooke E.M. in a World Health Organization (WHO) publication has defined a register as "a file of documents containing uniform

information about individual persons, collected in a systematic and comprehensive way in order to serve a predetermined purpose" [53]. In this definition there is no mention of a computerized database. However, today almost all registers are computerized and some are internet-based. Electronic databases enable efficient storage, management, retrieval and analysis of data.

Healthcare registers can be used for different purposes including: identification of individuals (with a certain condition such as an infectious disease), surveillance, epidemiological investigations, "planning, operation and evaluation of services", evaluation of treatment, research, and education [53]. There are more than 100 quality healthcare registers in Sweden, that systematically collect data on different issues including HRQL, life style, disease specific data and other health conditions [54]. These registers have minimal sets of variables and high quality data, which can be used for research. Over the past few years, the value of participation of patients in development, maintenance and utilization of healthcare registers has gained attention [55].

Registers have some pros and cons when used for research purposes (Figure 4). They are limited by loss of follow up and change in data quality and definition changes over time. However they are practical resources that can save a lot of time and resources needed for data collection. They also are optimal for long term outcome assessment and for hypothesis generation.

Haemophilia registers

WFH encourages all member countries to have their own national haemophilia (or bleeding disorders) register to efficiently manage their resources, improve well-being and lives of PWH, to save money through improving purchasing processes, and to efficiently deliver high quality care [56]. The rarity of haemophilia and its chronic nature and wide range of outcomes makes it a perfect choice for register-based research. While conducting clinical trials is cumbersome, complicated and sometimes unethical (due to proven benefits of prophylaxis over episodic treatment). Registers can be used as a supplementary source of evidence. Several large haemophilia registers have been created with various goals and have contributed substantially with research and clinical development in haemophilia over the past few decades.

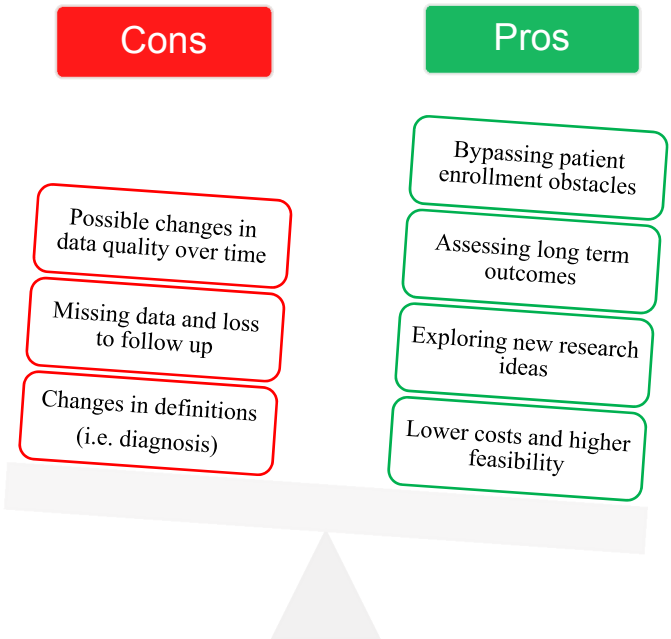

Figure 4. Advantages and disadvantages of using registries for haemophilia research. Figure retrieved (with permission of John Wiley and Sons Ltd) from Osooli M. and Berntop E. **[57]**.

Haemophilia is a life-long condition. PWH or carriers of haemophilia, may experience various symptoms dependent on their bleeding tendency and treatment. Evidence on long-term outcomes especially on joint status among these populations is still scarce. Registers provide an opportunity to investigate those outcomes at relatively low cost and with longer time perspectives.

General aim

The aim of this thesis was to provide new evidence on long-term outcomes among persons with haemophilia and carriers of haemophilia utilizing registers.

Specific objectives

Paper I

The aim of this study was to map the haemophilia registers with peer reviewed publications. We also extracted, classified and reported their evaluated treatment outcomes and the extent of their inclusion in the retrieved registers to learn from about common practice of register-based outcome assessment in haemophilia.

Paper II

The aim of this work was to estimate health utilities and to evaluate their potential correlates including demographics and clinical characteristics and type of treatment using register data among persons with severe haemophilia and current negative inhibitor from three Denmark, Norway and Sweden. Prophylaxis has been available from early years of life for PWH since 1980s in Sweden followed by Denmark (after a few years) and (about 20 years later) in Norway.

Paper III & IV

In papers III and IV, we investigated whether persons with mild haemophilia and carriers of haemophilia have higher incidence of joint disease (arthropathy) and related surgeries and hospitalizations compared to general population in Sweden.

Paper V

The aim of the current study is to examine the impact of access to prophylaxis on postponing joint surgery among persons with severe haemophilia treated in the Malmö centre. In addition, we used published international as well as historical Swedish data to describe survival gains in the Malmö cohort in relation to access to treatment during past few decades.

Materials and methods

Paper I

This was a scoping review. Scoping studies are most useful for developing specific research questions. In addition, they are helpful in retrieving, organizing and reporting findings in a broad area. Using a broad search strategy, we searched PubMed and Web of Science databases and also Google Scholar. We used following keywords domains to obtain peer reviewed papers published between January 1990 and January 2015 based on haemophilia registers:

1. Haemophilia A, Haemophilia B, Factor VIII, Factor IX
2. Treatment
3. Treatment Outcome

Our definition for a register was any computerized database for follow-up of patients that serves as a platform for both clinical practice and research. There was no eligibility criterion for the number of patients included in a register in order to qualify for this study. Whenever there was more than one publication on a topic from the same register we included the paper with most recent and complete data.

A single reviewer conducted the paper screening and enrolment in a stepwise process. In a stepwise method, we screened titles, abstracts and then full texts to include eligible papers. We excluded articles belonging to non-observational and animal studies, those from reviews and references without full text (such as meeting abstracts).

Paper II

This was a cross sectional study. Eligible participants had severe haemophilia A (CF<0.01 kIU L^{-1}), were ≥15 years of age, and did not currently have an inhibitor to factor VIII. Participants were from centres in Denmark, Norway and Sweden that were included in the KAPPA register. This report was confined to the Scandinavian centres as the enrolment and data collection were most complete for those sites.

Health utility -our primary outcome- was measured using the EQ-5D-3L. We estimated preference-based utilities and utilized the UK tariff to rank the health states on a scale between 1 (full health) and 0 (death). The independent variables included: age, treatment history, concomitant disease, inhibitor history, education

level, and body mass index (BMI). We used the HJHS for the assessment of joints. Treatment was defined as episodic treatment if participants only infused factor VIII upon the onset of bleeding. We defined prophylaxis as receipt of at least one infusion per week for more than 40 weeks in a year. Those on prophylaxis were categorized into two groups: prophylaxis started by age of three (early prophylaxis) and prophylaxis started after three years of age (late prophylaxis). Definition of positive or resolved inhibitor status was at the discretion of the investigators.

We presented HJHS and EQ-5D (utilities) based on age and treatment categories using box-plots. To assess demographic and clinical correlates of health utilities among participants we performed ordinary least squares (OLS) regression analysis with robust standard errors. Using iterative chained equations (ICEs) imputation missing values in EQ-5D, HJHS, BMI, inhibitor history, concomitant disease, and education were imputed. Participation in this study was voluntary and all participants signed an informed consent prior to enrolment. The Regional Ethical Review Board of Lund University (dnr.: 2012/118) reviewed and approved the KAPPA register protocol. This approval was valid for Sweden and Denmark. We obtained an additional approval from The Regional Committees for Medical and Health Research Ethics for the Oslo centre (ref nr.: 2014/453).

Paper III and IV

We used national patient register (NPR) of Sweden to include participants with mild haemophilia (paper III) and carriers of haemophilia (paper IV) and also to obtain data on their joint disease, surgery and hospitalizations. Eligible participants were born between 1941 and 2008. A sex and birthdate-matched sample of persons without bleeding disorders was randomly selected from the general population as comparison group in each study. Participants were permanent residents of Sweden and lived in the country for some period between 1984 and 2008.

The National Board of Health and Welfare of Sweden (NBHW) selected the comparison group from the Swedish population register. The follow–up period began at the participants' date of birth, but earliest January 1984 for the mild haemophilia project (paper III) and 1987 for the carrier project (paper IV). Follow-up continued until participants emigrated, died or until the end of study period (December 2008).

We selected a number of joint diagnoses and surgeries based on their clinical relevance (Appendix 1). Joint outcomes were categorized into index (knee, elbow and ankle) and non-index (all other included joints). The following outcome variables were defined to evaluate joint disease (arthropathy): number of hospital admissions due to selected diagnoses/surgeries, having a joint diagnosis or surgery

and the age at first joint diagnosis or surgery. In paper III, we divided the study sample based on year of birth into two birth cohorts (BC). Participants from the BC1 and BC2 were born between 1941-1983 and 1984-2008, respectively. The reason for this categorization was to separate those for whom we did not have follow-up from birth (BC2) from the remainder of the sample (BC1). During follow-up, the age of participants in BC1 ranged from 26-68 and in BC2 1-25 years. In paper IV, we derived age specific survival estimates instead of dividing the sample according to birth cohort.

In both papers III and IV, we reported observed and relative frequencies for categorical variables and median and inter quartile range (IQR) for quantitative variables. We also used Kaplan–Meier curves to plot the age at first joint disease diagnosis (arthropathy) and surgery.

In paper III, using negative binomial regression we estimated the incidence rate ratios (IRR) of hospital admissions (count variable) primarily for arthropathy diagnoses or surgeries. We performed competing risk Cox regression to estimate sub-hazard ratios (SHR) of arthropathy diagnosis and surgery. We adjusted for birthdate and the number of hospital admissions primarily for non-musculoskeletal diagnoses/surgeries in both negative binomial regression and Cox regression models.

In paper IV, we used Mantel-Cox regression to estimate incidence rate ratios (IRR) of joint disease and related surgeries among carriers of haemophilia. Both overall and age-specific estimates were reported.

In both papers, for quantitative estimates the 95% confidence intervals (CI) were reported considering a P-value (P) <.05 as statistically significant. Both studies were parts of a larger project and had ethical approval from Lund University, Sweden (reg. number: 706/2008).

Paper V

In this longitudinal study we included PWH of severe form who have been treated at the Malmö centre since 1980 to assess the impact of access to better treatment (prophylaxis) on mortality and joint health in this cohort. To investigate joint outcomes we defined and compared three birth cohorts who had different treatment options (episodic and prophylaxis with various intensities) during early years of life.

To analyse the survival among persons with severe haemophilia, however, we used data available in the publications by Larsson *et al.* [58] and Darby *et al.* [59]. We also compared the survival among persons with severe haemophilia in the Malmö centre with of the general male population in Sweden using publicly available data from Statistics of Sweden for years 1951-1955 [60] and year 2009 [61]. We used

Kaplan-Meier estimates to plot the age at first and second surgery and also the survival among participants and the comparison groups. The study had ethical approval from Lund University.

Results

Paper I

Registry-based outcome assessment in haemophilia: a scoping study to explore the available evidence

An initial 2,352 references were screened in a step-wise process. Out of the 822 selected titles, 295 abstracts were eligible. In the final stage 26 original articles were included in the study. We identified eleven registers that yielded in the included publications. The oldest register was established in 1969 in the UK, and the largest registry, with 15,527 patients, was the UDC database from the USA. Most of the registers were located in Europe, where in all of them prophylaxis has been available for many years.

HIV and CF inhibitor were the most reported comorbidities (Table 4). Though inconsistently reported, data on mortality and cause of death were available from five registers. Despite the importance of joint outcomes in haemophilia, data on joint outcomes including ROM, HJHS, Gilbert score and joint surgery was still scarce (Table 5). Data on characteristics of bleeding including location, frequency and cause were available through 4 registers. Measures including time to resolution, effectiveness of treatment and re-bleeding were introduced to evaluate treatment efficiency in some registers. The PedNet register introduced the extent of bleeding as an outcome measure.

Three and two registers have reported on hospitalizations and days lost from work/school due to haemophilia, respectively. The factor consumption was reported in 6 registers. Other outcomes such as the number of patient visits for care per year, impact of haemophilia on patients' social and family life and body mass index were each reported by one register.

Table 4
Comorbidities and mortality reported by haemophilia registries

Registry	Inhibitors	Adverse events	HIV/ viral hepatitis	Cause of death	Survival/ mortality	Other comorbidities [a]
Canadian Haemophilia Registry	✓	-	✓	✓	✓	✓
Emilia-Romagna Regional Registry	✓	✓	✓	-	-	-
Haemophilia database of the Van Creveld clinic	✓	-	-	-	-	-
Haemophilia registry of the Centre for Thrombosis and Haemostasis, Malmö	✓	-	✓	✓	✓	-
HemoRec Registry	✓	✓	✓	-	-	-
Italian Registry of Haemophilia and Allied Disorders	✓	-	✓	-	-	-
PedNet Haemophilia Registry	✓	-	-	-	-	-
Registry of Italian Regional Haemophilia Centre of Pescara	✓	-	✓	-	-	-
Swiss Haemophilia Registry	-	-	-	✓	✓	-
UK Haemophilia Registry	✓	-	✓	✓	✓	✓
Universal Data Collection database	✓	-	✓	✓	✓	-
Total number registers reported the outcome	10	2	8	5	5	2

Table 5 Joint outcomes reported by haemophilia registries

Registry	Joint bleeding	Target joint	Arthropathy	Range of motion	Gilbert score	HJHS	Joint surgery
Emilia-Romagna Regional Registry	✓	-	✓	-	-	-	-
Haemophilia database of the Van Creveld clinic	✓	-	✓	-	✓	-	-
Haemophilia registry of the Centre for Thrombosis and Haemostasis, Malmö	✓	✓	-	✓	-	✓	✓
HemoRec Registry	✓	✓	-	-	-	-	-
Universal Data Collection database	-	✓	-	✓	-	-	-
Total number of registers reported the outcome	4	3	2	2	1	1	1

HJHS, Haemophilia Joint Health Score.

Paper II

The association between health utility and joint status among people with severe haemophilia A: findings from the KAPPA register

The study included 173 participants with severe haemophilia and no current inhibitor. The sample consisted of about 49% of all persons with severe haemophilia being treated in the participating HTCs. The inclusion rate ranged from 30-71% across participating centres. Overall, 12 (6.9%) of participants were on episodic treatment and the rest were on prophylaxis at enrolment. Participants on episodic treatment (median age: 53 years) and prophylaxis started by age three years (median age: 26 years) were the oldest and youngest groups. Overall, 13 (7.5%) and 32 (18.5%) participants were positive for HIV and HCV, respectively.

EQ-5D dimensions

About 2.0%, 4.0% and 8.0% of those on prophylaxis (started by age three years), prophylaxis (started after three years) and episodic treatment had extreme pain respectively. Only one participant had extreme problem in performing usual activities. Mobility and pain were the most affected EQ-5D dimensions, especially among those on late started prophylaxis or episodic treatment.

Distribution of HJHS and utilities

Median HJHS were lowest among those under 30 years (on prophylaxis) and among participants 30-44 years who were on prophylaxis started by age of 3 years (Figure 5). HJHS were higher among older participants. Among those 60 years or older, median HJHS were similar between participants on prophylaxis and those episodic. For the entire sample, the median utility was 0.796 (IQR: 0.725, 1.0). The utility was highest among those on early prophylaxis (median: 1.0) and lowest in the episodic treatment group (median: 0.718).

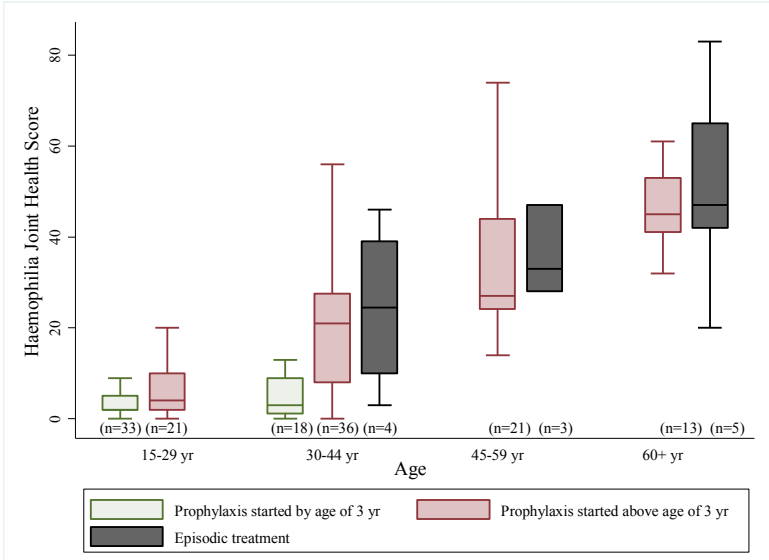

Figure 5. Haemophilia Joint Health Score presented by age and treatment history.

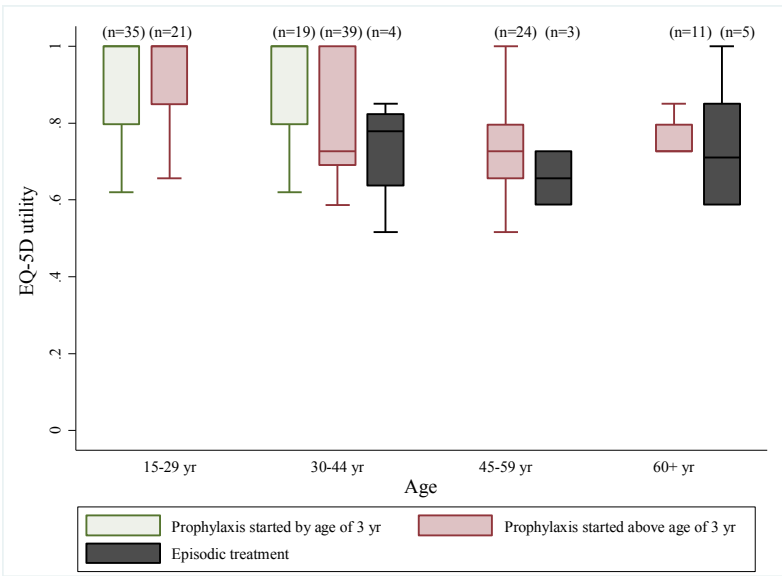

Figure 6. Preference-based EQ-5D utilities presented by age and treatment history.

Correlates of health utilities

After adjusting for age, treatment and other clinical and socioeconomic factors, increase of HJHS was associated with reduced utility (Table 6). In the imputed-based model, those with HJHS 16-25, 26-35 and ≥35 had 18% (Coef.: -0.18, CI 95%: -0.30, -0.06), 21% (Coef.: -0.21, CI 95%: -0.36, -0.06) and 37% (Coef.: -0.37, CI 95%: -0.52, -0.23) decreased utility, respectively, compared to the reference category (HJHS: 0). BMI, treatment history, inhibitor history, concomitant disease and education level were associated with utility at statistically significant levels after controlling for age, HJHS and country of residence.

Table 6. Assessing correlates of EQ-5D utilities using ordinary least square (OLS) regression a**nalysis**

	Complete data, Coef. (95% CI[1]) (n=134)	**Imputed data, Coef. (95% CI) (n=161)**
Age (ref: 15-29 year)		
30-44 year	0.04 (-0.06, 0.15)	0.02 (-0.06, 0.11)
45-59 year	0.06 (-0.07, 0.19)	0.07 (-0.06, 0.19)
≥ 60 year	0.17* (0.02, 0.32)	0.14 (-0.02, 0.30)
Haemophilia Joint Health Score (ref: 0)		
1-5	-0.06 (-0.13, 0.02)	-0.01 (-0.11, 0.08)
6-15	-0.10 (-0.21, 0.01)	-0.08 (-0.20, 0.04)
16-25	-0.17** (-0.28, -0.06)	-0.18** (-0.30, -0.06)
26-35	-0.24** (-0.40, -0.09)	-0.21** (-0.36, -0.06)
>35	-0.40*** (-0.51, -0.28)	-0.37*** (-0.52, -0.23)
Treatment history (ref: Primary started ≤ 3 year)		
Prophylaxis started > 3 year	0.03 (-0.04, 0.10)	0.02 (-0.05, 0.09)
Episodic treatment	-0.02 (-0.14, 0.10)	-0.02 (-0.15, 0.11)
Inhibitor history (ref : Negative)		
Resolved inhibitor	0.06 (-0.03, 0.16)	0.03 (-0.05, 0.12)
Concomitant disease (ref: No)		
Yes	-0.08 (-0.17,0.01)	-0.04 (-0.12, 0.04)
Education level (ref: Academic level)		
Non-academic education	0.01 (-0.06, 0.08)	-0.02 (-0.05, 0.10)
Body Mass Index (ref: 18.5 – 24.99)		
< 18.5	-0.12 (-0.37, 0.13)	-0.02 (-0.24, 0.21)
25-29.99	-0.02 (-0.09, 0.05)	-0.01 (-0.07, 0.06)
≥30	0.06 (-0.02, 0.15)	0.06 (-0.03, 0.14)

(In both models we adjusted for the country of residence. - * *P* <0.05, ** *P* <0.01, *** *P* <0.001). [1] Confidence Interval

Paper III

Comparative burden of arthropathy in mild haemophilia: a register-based study in Sweden

This study included 315 persons with mild haemophilia (PWMH) and 1,529 age and birthdate matched individuals free from bleeding disorders from the general population (as comparison group) from Sweden. Among PWMH, 239 (75.9%) and 76 (24.1%) had haemophilia A and B, respectively. The study collected 36,798 person years of follow-up including 6,366 and 30,432 person-years from PWMH and the comparison group, respectively. Overall, around 36% of participants were followed from birth (≥1984). PWMH were more likely to get hospitalized for arthropathy. PWMH from BC1 had about a two-fold (IRR: 1.6; 95% CI: 1.0, 2.4) and those from BC2 a nine-fold (IRR: 9.4; 95% CI: 3.3, 27.2) increased incidence rate of admissions for arthropathy diagnosis or surgery.

Age at first arthropathy diagnosis and surgery

PWMH received an arthropathy diagnosis earlier than those from the comparison group (Figure 7). By the age of 60 years half of PWMH have received one of the arthropathy related diagnoses as compared to around 11% from the comparison group. The difference in age at first arthropathy diagnosis was statistically significant different between the two groups (*P*=.002).

The age at first arthropathy among the study participants has been presented in Figure 8. Surgery was relatively uncommon by the age of 50 years. Above this age surgery started to increase among both groups but with a higher rate among PWMH. By the age of 60, 13.9% and 4% of PWMH and comparisons had their first surgery, respectively. The difference did not reach statistical significance (*P*=.103).

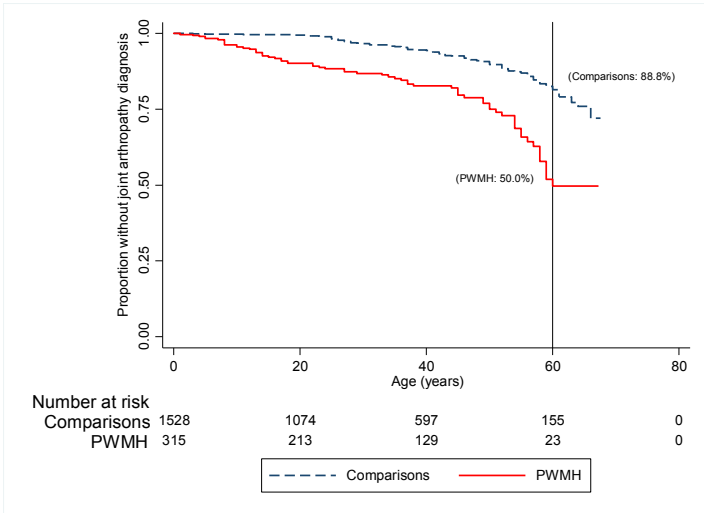

Figure 7. Kaplan-Meier curve for age at first arthropathy diagnosis among people with mild haemophilia (PWMH) and the comparison group born 1941-2008.

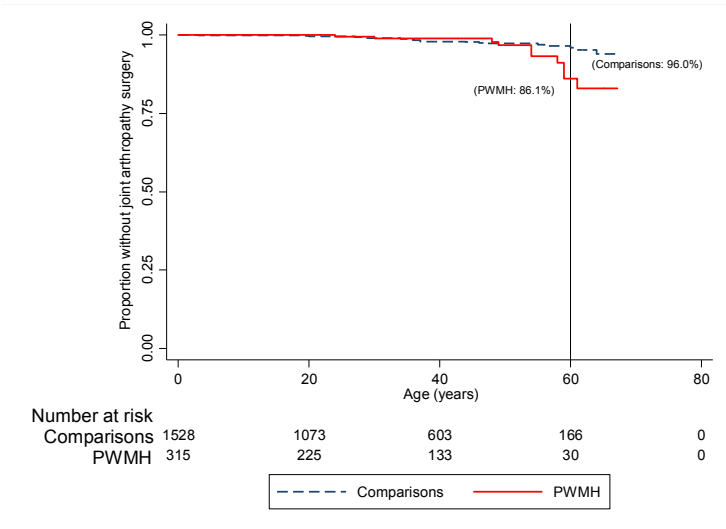

Figure 8. Kaplan-Meier curve for age at first arthropathy surgery among people with mild haemophilia (PWMH) and the comparison group born 1941-2008.

Comparative incidence of arthropathy diagnosis and surgery

After adjusting for the number of hospital admissions (non-musculoskeletal diagnoses), the hazard of arthropathy in both BC1 (SHR: 2.2; 95% CI: 1.6, 3.1) and BC2 (SHR: 15.6; 95% CI: 6.7, 36.5) was higher among PWMH (Table 7). Among participants aged over 25 years (BC1) PWMH had a nearly two-fold (SHR: 1.8; 95% CI: 1.0, 3.2) incidence rate of arthropathy of the index joint than comparisons. PWMH from BC1 (under 25 years age during observation period) had a two-fold (SHR: 2.0; 95% CI: 0.2, 23.8) hazard rate of arthropathy of the index joints. Only one of the participants under age of 25 years from the comparison group had a joint surgery. Risk of arthropathy surgery for the index joints was nearly six-fold (SHR: 5.5; 95% CI: 1.7, 17.8) among PWMH. For all joints surgery, PWMH had a two-fold hazard rate (SHR: 1.8; 95% CI: 0.9, 3.5).

Table 7. Sub-hazard ratio (SHR) estimates for arthropathy diagnosis and surgery in people with mild haemophilia (PWMH) in relation to comparison group stratified by birth cohort (BC)

	BC1*, SHR (95%CI) (PWMH = 205 & comparisons = 979)		**BC2†, SHR (95%CI) (PWMH = 110 & comparisons = 550)**	
	Crude	Adjusted‡	Crude	Adjusted‡
Arthropathy diagnosis				
Index joints §	1.9 (1.1, 1.4)	1.8 (1.0, 3.2)	2.5 (0.2, 29.3)	2.0 (0.2, 23.8)
All included diagnoses	2.4 (1.7, 3.4)	2.2 (1.6, 3.1)	18.2 (7.8, 42.4)	15.6 (6.7, 36.5)
Arthropathy surgery‖				
Index joints ¶	6.1 (1.9, 19.8)	5.6 (1.7, 17.8)	-	-
All included surgeries	1.9 (1.0, 3.8)	1.8 (0.9, 3.5)	-	-

* BC1 born 1941–1983
† BC2 born 1984–2008
‡ Adjusted based on the number of hospital admissions with a primary diagnosis of non-musculoskeletal diseases
§ Included joint arthropathy diagnoses: M17, M22, M23 and 717
‖ No one had arthropathy surgery in BC2.
¶ Included surgery codes: NCK, NGB, NGC, NHB, NHC, NHG, 842

Paper IV

Joint disease among carriers of haemophilia

Overall, 561 carriers and 2,684 comparisons were included in the analysis. Among carriers, 90 (16%) and 240 (33%) aged 40-46 and under 20 years at inclusion, respectively. During the observation period, 26 (4.6%) carriers and 84 (3.0%) comparisons were lost to follow-up due to death (IRR: 1.8; 95% CI: 0.9, 3.5). On the other hand, 230 (8.2%) comparisons and seven (1.2%) carriers emigrated from the country (IRR: 0.4; 95% CI: 0.2, 1.1) and could not be followed up through the end of study. This study accrued 11,537 and 54,687 person years of follow-up for carriers and comparisons, respectively.

The Kaplan-Meier estimate in Figure 9 presents age at first joint disease diagnosis among carriers and comparisons. Carriers got diagnosed with joint diagnosis at earlier ages than comparisons (P<0.001). By the age of 60 years, approximately 35% of carriers compared to 21% of non-carriers had a joint diagnosis.

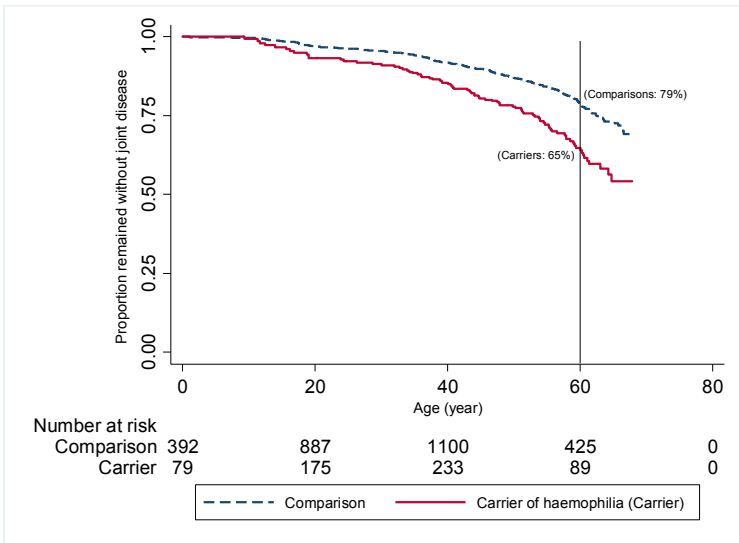

Figure 9. Kaplan-Meier curve for age at first joint diagnosis among carriers of haemophilia and the comparison group born 1941-2008.

Joint surgery was rare up to the age of 40 years among both carriers and women from comparison group. However, above the age of 40, carriers underwent joint surgery, earlier than non-carriers (P<0.01). By the age of 60, approximately 8% of carriers had undergone surgery as compared to 4% of comparison group.

Incidence of joint disease and surgery

Overall, carriers had 1.9-fold (95% CI: 1.3, 2.7) and 1.5-fold (95% CI: 1.1, 2.0) higher incidence of index joint and non-index joint diagnosis, respectively. Looking at age groups, highest difference was among those under age of 20 years (IRR: 3.0; 95% CI: 1.0, 8.7). Carriers aged 20-39 and 40 years or older, had 1.7-fold and 1.8-fold greater incidence of index joint diagnosis than non-carriers, respectively. Incidence of non-index joint disease did not differ between carriers and comparisons aged under 20 years (IRR: 1.1; 95% CI: 0.4, 3.0). Among those aged 20-39 and 40 years or older, carriers had higher incidence rate of non-index joint disease.

Table 8. Mantel-Cox based incidence rate ratio (IRR) of joint disease in carriers of hemophilia in relation to comparison group (comparisons) stratified by age group

Age (years)	Index joints, IRR (95% CI)	Non-index joints, IRR (95% CI)	All joints, IRR (95% CI)
0-19	3.0 (1.0, 8.7)	1.1 (0.4, 3.0)	1.8 (0.9, 3.6)
20-39	1.7 (0.8, 3.3)	1.6 (1.0, 2.7)	1.7 (1.1, 2.6)
≥40*	1.8 (1.1, 3.0)	1.5 (1.0, 2.3)	1.5 (1.0, 2.1)
Overall†	1.9 (1.3, 2.7)	1.5 (1.1, 2.0)	1.6 (1.2, 2.1)

* Maximum age was 68 years. † Pooled estimate across age groups adjusted for birthdate.

Over the observation period 18 carriers (3.2%) and 40 (1.5%) comparisons had a registered joint surgery. Surgery was rare among both carriers and comparisons up to the age of 40. Among those 40 years and older, carriers had 3.3-fold (95% CI: 1.4, 8.0) higher incidence of surgery in index joints than comparisons.

Hospitalizations due to joint disease and surgery

Assessment of hospitalizations showed that the overall burden of joint disease hospitalizations was greater among carriers than comparisons (Table 9). Under age 20 years, the in-patient and out-patient hospitalization did not differ between carriers and comparisons. However, among those 20 years and above rates of in-patient and out-patient hospitalizations were 1.6 to 1.7-fold greater among carriers. Overall, carriers had 1.6-fold (95% CI: 1.2, 2.1) higher incidence of hospitalization for all joint diagnoses and surgeries evaluated in this study.

Table 9. Mantel-Cox based incidence rate ratio (IRR) of hospitalization due to joint disease in carriers of hemophilia in relation to comparison group (comparisons) stratified by age group

Age (years)	Inpatient, IRR (95% CI)	Outpatient, IRR (95% CI)
0-19	1.1 (0.4, 3.3)	1.1 (0.5, 2.4)
20-39	2.3 (1.4, 3.7)	1.6 (1.1, 2.3)
≥ 40-68†	2.1 (1.4, 3.2)	1.7 (1.4, 2.1)
Overall*	2.1 (1.5, 2.8)	1.6 (1.4, 1.9)

* Pooled estimate across age groups adjusted for birthdate.

† Maximum age was 68 years.

Paper V

Surgery and survival in birth cohorts with severe haemophilia and differences in access to replacement treatment: the Malmö experience

Overall, 167 persons with severe haemophilia treated in the Malmö centre were included in this study. Data on joint surgery were retrieved for 106 participants. Over the observation period, the number of registered joints ranged 0-4 per participant. Age at first joint surgery was lower among those born prior to 1970 than the younger cohorts (Figure 10). Half of those born before 1970 had their first joint surgery by the age of 45. Among those born 1970-1979 nearly 25% had their first surgery by age 30. A second joint surgery was observed only among those born before 1970. No one from the cohort born 1980 and later have experienced a joint surgery.

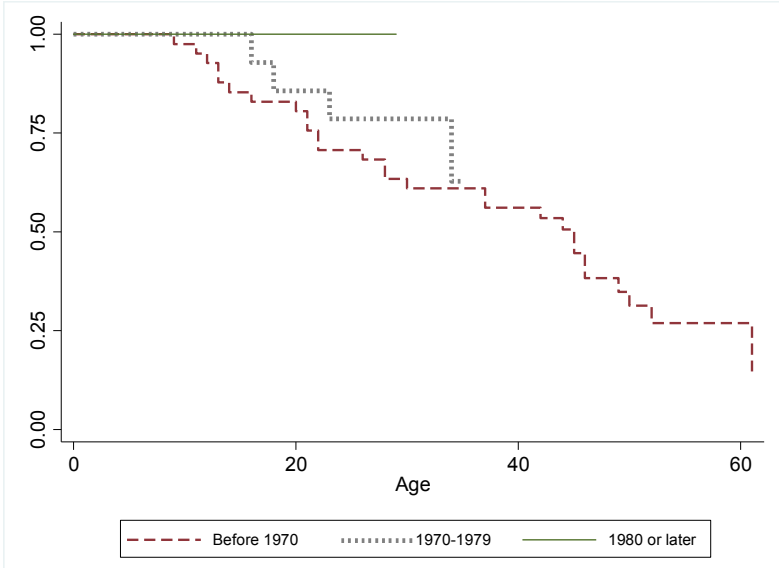

Figure 10. Kaplan-Meier curve for age at first joint surgery among persons with severe haemophilia and negative factor inhibitor treated in Malmö centre 1980-2009.

Figure 11 presents survival among persons with severe haemophilia from the Malmö centre, the UK cohort of severe haemophilia and negative HIV status, and the Swedish general population (estimate from year 2009). Excluding those with HIV, the survival of persons with severe haemophilia treated in Malmö is approaching that of the general population. Those living with HIV from the Malmö cohort had comparable survival to their comparators from the UK who were HIV negative.

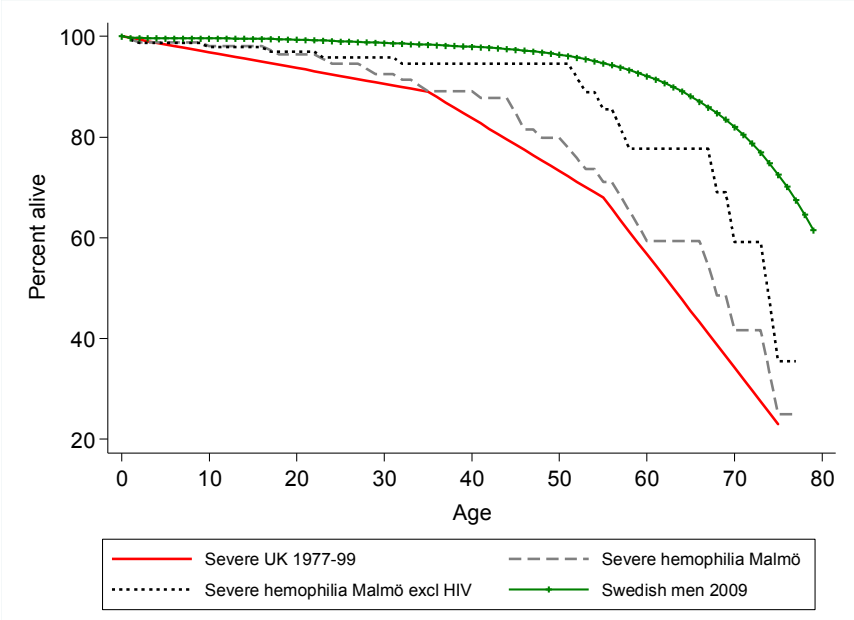

Figure 11. Comparison of survival among persons with severe haemophilia from the Malmö cohort (with and without HIV) with persons with severe haemophilia and negative HIV status from the UK and the Swedish general male population in 2009.

Discussion

Advances in haemophilia treatment have resulted in remarkable reductions in bleeding events and adverse musculoskeletal outcomes, and increases in HRQL and life expectancy for PWH. In this thesis, as the first step, we conducted a literature review of peer reviewed publications of register-based outcome assessment in haemophilia to map the available resources and their reported outcomes. Second, we used our available national register data and infra structure to respond to the general gap of knowledge on long term joint outcomes among carriers of haemophilia and persons with mild haemophilia. Third, we reported on HRQL and its correlates, most importantly joint status, among persons with severe haemophilia and negative CF inhibitor. We used data obtained in an international register (KAPPA). Finally, we used data from the Malmö single centre register to present survival and joint surgery outcomes in relation to access to treatment. In the following text, we will discuss the main findings of this thesis.

Burden of joint disease among persons with mild haemophilia (PWMH)

Similar to carriers of haemophilia, there is little known about long term outcomes of PWMH. They rarely visit HTCs and are difficult to reach for research purposes in many settings. Few studies have investigated haemarthrosis [62, 63] and/or joint disease (arthropathy) [64], and ROM changes [65] among PWMH. Those that have, however, had one or more of the following shortcomings: small or unrepresentative comparison groups, limited range of outcomes, lack of a reliable source or method of joint assessment, and short follow-up or cross sectional design. Therefore, in a longitudinal register-based study using the Swedish NPR we compared burden of joint disease between a large national cohort of PWMH and individuals without bleeding disorders from the general population in Sweden.

Our study confirmed previous observations with respect to a higher burden of joint problems among PWMH. Joint disease began to increase among PMWH in their 20s and the gap in occurrence of joint disease between PWMH and the sample from general population increased among the older age groups. Soucie *et al*. have reported reduced ROM among PWMH aged 2-19 years [65]. The authors reported that, PWMH who had their first HTC visit after age 2, showed greater reductions in ROM. Many PWMH are diagnosed later in life and some during adulthood. Subclinical haemarthrosis [62] and delayed treatment can result in progressive joint damage.

Our results showed milder joint problems than those observed by Zhang *et al*. [63] and Ling *et al*. [64] who reported substantial proportions of painful knees (37%) and ankles (47%), respectively, in their studies. Our joint disease estimates, however, were similar to those reported in a large study from Korea which also included a wide range of joint outcomes [66].

Several issues are important to note when interpreting the results of our investigation and those conducted on this subject in the past. PWMH, do not generally visit the HTCs unless they have a more severe bleeding phenotype or are suffering from comorbidities. For this reason, PWMH with poorer outcomes are more likely to take part in studies in which the entire cohort is not included. In addition, surveys are prone to recall bias that overestimate the risk among patients compared to comparisons. In Sweden, due to high diagnostic accuracy and partly because of the outreach research activities, the acquisition of mild haemophilia is very good. The population of mild haemophilia in our study is expectedly by far the most representative among all. However, some diagnostic factors, especially among the older persons, may have resulted in misclassification of moderate haemophilia as mild haemophilia [67, 68].

Burden of joint disease among carriers of haemophilia

While, in general, evidence on outcomes for carriers of haemophilia is scarce, some reports suggest that they experience frequent joint bleeding [45-47], MRI (magnetic resonance imaging)-detectable structural joint changes [49], and reduction in ROM [48]. With an aim to address some of the shortcomings of previous studies and investigate the validity of their results, we examined a wider range of joint outcomes, included a national cohort of carriers, added a large random sample of women without bleeding disorders and, finally, obtained more than two decades of data on joint outcomes from the National Patient Register in Sweden. Also, for the first time, we evaluated disease related hospitalizations among carriers.

Based on our observations, carriers have experienced a higher burden of joint disease, as well as surgery, than the comparison group. The index joints were more likely to undergo surgery among carriers aged 40-68 years. Carriers also experienced more hospitalizations than comparisons beyond age 20. Based on the cross sectional study by Paroskie *et al.,* approximately 20% of carriers compared to 0% of comparisons had experienced haemarthrosis [47]. Taking a conservative view, potential confounding factors have been proposed to explain higher rates of joint disease and bleeding among carriers. For example Plug *et al*., stated that the observed excess risk among carriers in their study could be an effect of misclassification of superficial bleeding of tissue in the joint region [46]. However,

more recent studies showed that even carriers younger than 20 years [48] and those with factor levels within normal ranges [49] have joint abnormalities.

In our study, the incidence of joint disease was also higher among carriers than comparisons even before age 20. However, there were no additional joint disease related hospitalizations among carriers in that age group. These observations, may have implications when assessing the adequacy of monitoring of joint outcomes among carriers who are less likely to visit HTCs.

Overall, surgery was observed among approximately 3% of carriers (all age groups) in our study. While this may seem a small proportion, it should be noted that surgery is one of the ultimate outcomes of joint disease. For many years prior to undergoing the surgery, people suffer from pain, mobility reduction and hospitalizations and lose substantial numbers of days from work or school. Some evidence suggests that carriers with a high bleeding tendency may have impaired HRQL [69]. Further studies should assess HRQL in relation to burden of joint disease and bleeding among carriers.

The WFH guideline for management of symptomatic carriers has recommended that carriers with CF below normal ranges and those with clinical symptoms should be followed up in HTCs [44]. However, based on our knowledge, monitoring of carriers in these facilities is still a rare practice. As reported by Baker *et al*., the absolute number of carriers treated in HTCs across the US increased by 62% between 2002 and 2010 [70]. Similar to persons with hemophilia, carriers benefit from follow-up at HTCs for their bleeding and joint evaluation. Use of sensitive and available techniques, e.g. ultrasound [71], can help in early detection of soft tissue changes in the joints of carriers allowing the provision of treatment when needed.

We did not have data on CF level of carriers to investigate the association of joint disease with that variable. We also could not adjust for potential confounders such as trauma or physical activity. The results of our study should be interpreted in light of those limitations.

Health utility and correlates in severe haemophilia

Health utility estimates are increasingly used to assess improvements in health status in regard to quality-adjusted life years following medical interventions or treatments. Several studies have used different instruments and methods, reporting substantially varied utility estimates. Based on Scott Grosse *et al*., difficulties in adjusting for multiple predictors, selection bias in (observational studies) and lack of country specific preference-data remain the most important challenges in estimating utility estimates to compare treatment regimens [72].

Data from the KAPPA international study (Denmark, Norway and Sweden) showed that about half of persons with severe haemophilia and negative inhibitor status between age 15-44 and on prophylaxis have high health utility and healthy joints. The utility estimates for prophylaxis obtained in the KAPPA study exceeded the highest reported utilities from the Dutch-Swedish comparison observations [15] and another study from the Netherlands [73]. In the KAPPA study, among participants aged ≥30, the lowest utility estimates belonged to participants treated episodic and those on prophylaxis started after the age of three.

In a recent publication, Manco-Johnson *et al*. reported on 12 years of observation among persons with severe haemophilia monitored at HTCs in the US [8]. They showed that prophylaxis is more efficient on protecting joints when started before the age of four. In the KAPPA study, participants 15-29 years of age on prophylaxis started by age three and those who started at greater than three years had similar and relatively high utilities. In addition, among participants above age 29, after adjusting for age, prophylaxis started after age three years and episodic treatment yielded comparable utilities. Under age 30 could be too early to capture utility reductions associated with the later onset of prophylaxis. Among older adults, switching from episodic treatment to prophylaxis among those with poor bleeding and joint outcomes makes both groups highly selective [8].

In the KAPPA study, the HJHS was the only variable associated with clinically and statistically significant reductions in utility after adjusting for other covariates. The increase in HJHS was associated with a decrease in utility in categories of HJHS greater than 15. In their recent publication, Fischer *et al*. reported that Pettersson scores greater than 21 were associated with reduction of utility estimates obtained using SF36 instrument [74]. Even though the two studies used different joint and utility assessment tools their results strengthen the conclusions of both.

Prophylaxis has become the gold standard of treatment for haemophilia [9, 75]. However, the greatest challenge remains the identification of an optimal regimen in terms of feasibility and cost. The lack of inclusion of data on compliance and its influence on outcomes undermines the results of the comparisons of regimens across settings and studies. Collecting data on home treatment is quite difficult, although an earlier investigation in Sweden showed high compliance among those on prophylaxis [76]. Nevertheless, collection of daily treatment information remains a challenge for some HTCs.

Change in treatment of patients over time is a common practice. In the KAPPA study, quality of home treatment reporting was different across HTCs. Given its complexity, we did not include compliance as a variable in the analysis of this study. While the addition of such information helps to more accurately define treatment history, major drawback is loss of power due to more treatment sub-groups. This highlights the importance of pooling data across settings and countries. Registers, designed with similar objectives and uniform outcome assessment tools can be most

helpful for this purpose [77]. More innovative methods of data collection are needed to obtain accurate and comprehensive data on haemophilia treatment.

History of inhibitor and age were not associated with statistically significant utility changes in our study. While age has been reported as a strong determinant of HRQL among PWH [78] and the general population [79], the adjustment for age-related correlates of utility including concomitant disease and joint disease, together with the healthy survivor effect, may have resulted in diminished of its association with utility.

Impact of access to treatment on long-term outcomes in severe haemophilia

One of the most notable achievements of modern haemophilia care is the life expectancy. Before the availability of haemophilia treatment, many persons with severe haemophilia did not reach their third decades of life. Today, reports from several countries have demonstrated that the gap in survival between PWH and the general population has almost diminished [30, 59, 80, 81]. The impact of the HIV epidemic in the 1980s, however, is still affecting outcomes among populations that were infected [81].

Lövdahl *et al*, have previously investigated mortality among the national cohort of PWH in Sweden [82]. The authors reported that the mean ages of death among persons with severe haemophilia were 45.6, 40.5 and 50.6 for the periods 1981-1990, 1991-2000 and 2001-2008, respectively. Using data from the Malmö register and historical comparisons, we investigated trends of survival of persons with severe haemophilia. The Malmö cohort showed better survival than the national cohort from the UK even among those positive for HIV [59]. It is, however, important to note that a significant proportion of those who died in both cohorts had no access to prophylaxis until late adulthood. The persons with severe haemophilia from Sweden have benefitted from an earlier start and more intensive prophylaxis than other populations with severe haemophilia including the UK cohort.

Another observation from the Malmö cohort was the remarkable decrease in joint surgery among generations with access to better treatment through prophylaxis. For the first time, this study reported that those with severe haemophilia born from 1970 onwards who had access to prophylaxis prior to age three did not experience joint surgery up to age 30. A large European study has reported that prophylaxis does not fully protect joints against haemarthrosis [83]. Soft tissue and osteochondral changes have been reported in joints of boys with severe haemophilia treated using the Canadian tailored prophylaxis [84]. Joint bleeding episodes are quite rare among boys in Sweden treated with primary prophylaxis [15]. However, further follow-up

is needed to evaluate the long-term joint protection obtained by treatment with high dose prophylaxis.

Haemophilia registers and research: a state of the art and lessons learned

Over recent decades, interest in registers has generally increased in the healthcare community with haemophilia researchers not an exception. Until today, most of the evidence from national haemophilia registers has emanated from the UK [85], Canada [86], USA [70] and Italy [87]. Sweden has recently pooled data at the national level and conducted several studies with two of which are included in this thesis [82, 88, 89]. There are smaller registers such as the Malmö centre database [90] and the database of the Van Creveld clinic (Utrecht, The Netherlands) [91] that have extensively published their data. Other countries including Syria, Portugal, Switzerland, Czech Republic, and Serbia have also announced the launching of their national haemophilia registers. While haemophilia registers are growing in number, their quality and capacity for providing comparable evidence remain challenging issues [77].

One of the great challenges is harmonizing outcome assessment and reporting across registers. WFH has recently developed the world bleeding disorder register use by HTCs around the world. This would be an exceptional opportunity in settings with scarce resources –the possibility to have a register maintained at a high level with minimal or no cost. However, it may be of lesser interest for those HTCs that currently have a register.

Standardized tools appropriate for patients from all age groups and certain characteristics such as positive for inhibitor or on life-long episodic treatment or prophylaxis, to harmonize outcome monitoring. For example, HJHS has been designed and validated for assessing joint status among children on prophylaxis. In the absence of suitable instruments, it is also used for episodic treated adults with poor joint status, despite the lack of data on its validity among this group.

In addition, register holders need to provide sufficient and detailed information on database structure, variable set, data collection practice, and quality of data to all stakeholders including researchers. Any changes to those elements over time should be documented and available to users of the data or evidence retrieved from the registers. This information enables appraisal of the obtained evidence. Another benefit of harmonized would be Taking into account the rarity of haemophilia, data pulled from harmonized registers will substantially help to conduct larger studies with increased statistical power.

In this thesis, we used data obtained from registers at the local, national and international levels. Larger registers encompass a greater number of centres and geographic areas, the increased heterogeneity among patients and register staff could potentially jeopardize the quality of the data. Well-defined operational guidelines are essential for registers of any scale, especially those which are larger.

Current registers have some limitations including variability of data quality and definitions over time. For example, registers designed for administrative purposes, usually include a limited number of data points and, as they are not designed for research, the rigor of data collection and validation cannot be expected to compete with, for example, clinical trials. On the other hand, research registers have narrow assessment areas, but are very costly and generally have a short observation period. In both types of registers, the quality of data as well as definitions of variables over time may vary. If the barriers referenced above and legal issues are removed, registers have the potential to be used as complementary resources to clinical trials [92].

Strengths and limitations

Studies included in this thesis had several strengths. We extracted and used data from registers at local, national and international levels. Different study designs including: cross sectional, ecological and longitudinal studies were applied to maximize the use of data. Using the Malmö centre register and the NPR we included a well-defined cohort of persons with severe haemophilia (on prophylaxis since early age) and the entire cohort of PWMH and carriers, respectively. The reported outcomes for these populations have rarely been reported in full (national) coverage. We also included more than two decades of high quality data on joint disease and related surgeries and hospitalizations for participants using the NPR. PWMH and carriers have are very difficult to reach populations and their outcomes have been rarely described with such a long follow-up period. The KAPPA register included participants from three countries. Using an internet-based registry with two standardized outcome assessment tools, a uniform data collection, and regular site visits and data audits, the quality of data across centres was assured in the KAPPA study. This was one of the largest studies in haemophilia on utilities that also included data on treatment history and more importantly the HJHS.

The results of this thesis should be evaluated in light of some limitations. First, registers are prone to varying quality of data over time. For example, change of data collection forms, definition of variables as well as resources, can affect the quality of data. It is of great importance to be aware of and investigate such issues when conducting research using registers. We limited the observation period in our studies

to include years for which we had high coverage over the population and acceptable data quality.

Second, in the studies on mild haemophilia and carriers, we did not have data on potential determinants of joint disease including: joint bleeding, treatment history, and trauma. The NPR did not contain such data, and they were not available through HTCs.

Third, even registers may be limited when it comes to the analyses of outcomes across the full course of life. Data from the NPR was available from 1987 and onwards. In papers III and IV, more recent cohorts of carriers and PWMH were covered in their earlier years of life, when they had relatively good outcomes. Older cohorts on the other hand, contributed with data on their later years of life with poorer outcomes.

Fourth, the statistical analysis of HJHS and EQ-5D data is complicated because of their distribution. We used the HJHS as a categorical variable and estimated CIs for the regression model with robust standard errors to reduce the impact of those issues.

Fifth, the HJHS instrument has been primarily designed and validated for children on prophylaxis. It's validity for use among older adults, especially those with poor joint status has not been investigated.

Sixth, participants in the KAPPA register may not fully represent their background cohort from the included centres. Patients with poorer outcomes such as those with current inhibitor and/or poor joint status may be less willing participate in studies.

Seventh, the access to treatment among the Malmö cohort, in the paper V, does not necessarily reflect the receipt of treatment.

Finally, all the four studies using register-based data in this thesis, are prone to confounding and bias, as relevant in all types of observational studies. Therefore, the results of those studies are more suitable for hypothesis generation rather than assessing causality.

Clinical implications

- Many of the current haemophilia registers at the local, regional, or national level do not produce peer reviewed evidence. Small numbers of patients and lack of the resources and skills needed for research are among the potential barriers. Harmonizing database structure and outcome monitoring in registers can result in a greater number of collaborative efforts, pooling of data and enhancing credibility and resources for the generation of new evidence.
- However, there are standard definitions, both proposed and in use, for clinical descriptors of disease severity and complications, there is no organized effort to harmonize outcome reporting in peer reviewed publications. The WFH, ISTH, EAHAD and other key partners should construct such an initiative and call for this cause.
- Carriers of haemophilia and persons with mild haemophilia should be monitored for their joint outcomes at HTCs. Developing a joint screening program to detect early structural joint changes should be considered for these groups. The feasibility and cost-benefit of such programs must be assessed prior to implementation.
- Different ages have been suggested as the optimum time to start prophylaxis, particularly for persons with severe haemophilia. As prophylaxis does not reverse the established joint damages, the earlier it is started, the more effective it will be at protecting joints. Research is needed to identify ways to increase feasibility and reduce the cost of earlier initiation of prophylaxis (under age 3-4).
- Additional innovative approaches are needed to increase reporting of the specifics of home treatment and patient-reported outcomes in haemophilia. Development of mobile applications will likely improve the reporting. Smart devices can be developed and used to automatically capture data and send them to haemophilia registers.

Future research

- A multi-centre longitudinal study is needed to investigate occurrence, process and determinants of structural joint changes among carriers of haemophilia. Persons with mild haemophilia may also benefit from a similar investigation. In this study, the CF level, treatment practice, bleeding tendency and the status of joints should be followed from the early years of life through adulthood to demonstrate how these factors interact and result in joint health later in life. To increase their feasibility, register-based resources can be used for initiating such a studies.
- Little is known about life style and physical activity among carriers. This information is needed to understand potential needs for educational interventions or coping strategies.
- A higher burden of hospitalizations due to joint disease among both carriers of haemophilia and PWMH was observed in our studies. More research is needed to understand how this burden is related to treatment practice and whether and how it could be reduced.
- The follow-up in studies among persons with mild haemophilia and carriers of haemophilia, extended only until 68. The incidence of joint disease and the associated burden beyond that age, need to be investigated among those populations in future studies.
- Further investigation of bleeding as a potential determinant of joint disease among carriers of haemophilia is recommended.

Conclusion

We investigated the practice of register-based outcome monitoring and reporting in haemophilia through a scoping study. In addition, we conducted several register-based studies and evaluted several important long term outcomes among persons with mild haemophilia, persons with severe haemophilia, and carriers of haemophilia. Our results showed that persons with mild haemophilia and carriers of haemophilia experience higher incidence of joint disease, surgery and hospitalization compared to the general population. We also demonstrated that the advancement of treatment in Denmark, Norway and Sweden has resulted in remarkable joint protection and high utility, especially among those who have started prophylaxis under age three years. Based on our observation, persons with severe haemophilia born >1979 who had access to high dose prophylaxis in Sweden (Malmö), did not have joint surgery within approximately the first 30 years of life. Registers enable studies to investigate broad and representative populations over the life course. They can be used at minimum costs to explore long-term impacts of treatment strategies in haemophilia. However, to optimize the use of register data, we need to harmonize register structures and outcome assessment tools. In addition, supplementary information on registers including: data collection process and data quality should become available to the users of data to increase interpretability and credibility of the register-based evidence.

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I am sitting and writing this piece and thinking about my PhD journey that took nearly five years. In 2012, when I stepped into PhD, I had a fixed mindset, I was more concerned about being entitled, was caring a lot about what others thought about me, and was not capable to handle complex situations in which one must be brave, persistent and enable to make quick and sufficiently good decisions. Of course I was a positive, supportive, creative, funny, motivated, and hard-working young boy who thought is the best and most intelligent person in this world ☺ However, those qualifications were not enough to carry out high quality research at PhD level. I was challenged to great extent and had to rebuild some of my characters from the scratch. I started reading books, watching videos and talking to colleagues to get help. I learned a lot about my shortcomings and how to improve them and I tried. I learned that I am a perfectionist, do not live in the moment and often taking a long time for making decisions. Knowing about these and other issues mentioned above, were critical to become more productive, get things done and feel great about myself and my career. Now, I am done with my PhD, but I am not done yet with discovering myself further and having higher contribution in the society. I am truly thankful to all the people who treated me with respect and gave me the opportunity to grow my mindest and find my mission.

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Appendixes

Appendix 1. List of included joint disease/arthropathy diagnoses and surgeries in paper III and IV

	ICD X	Description	ICD VIII/IX	Description
Diagnosis	M13	Other arthritis	713	Arthropathy associated with other disorders classified elsewhere [a]
	M14	Arthropathy due to other diseases classified elsewhere	715	Osteo-arthrosis and allied disorders
	M16	Coxarthrosis (arthrosis of hip)	716	Other and unspecified arthropathies
	M17	Gonarthrosis (arthrosis of knee)	717	Internal derangement of knee
	M19	Other arthrosis	718	Other derangement of joint
	M20	Acquired deformities of fingers and toes	719	Other and unspecified disorder of joint
	M22	Disorders of patella	724	Internal derangement of joint
	M23	Internal derangement of knee	729	Other diseases of joint
	M24	Other specific joint derangements	731	Synovitis, bursitis and tenosynovitis
	M25	Other joint disorders, not elsewhere classified	733	Diffuse diseases of connective tissue or other diseases of bone
	M36	Systemic disorders of connective tissue in diseases classified elsewhere*	738	Other diseases of joint
Surgery	NCK	Surgeries of elbow or forearm	830	Operations on joints and joint structures (arthrotomy, arthroscopy)
	NFB	Hip plastic surgery	831	Operations on joints and joint structures (capsulotomy)
	NFC	Secondary hip prosthesis/procedures	839	Other operations which refer to removal of joint structures
	NGB	Arthrodesis of knee	840	Arthroplasty of hip without using extrinsic material
	NGC	Prosthesis for knee/patella	841	Arthroplasty of hip with using extrinsic material
	NHB	Prosthesis for ankle	842	Reconstructive surgery of the ankle and knee joints
	NHC	Secondary prosthesis for ankle or other foot joints	843	Reconstructive surgery of other joints
	NHG	Arthrodesis of ankle or other foot joints	845	Arthrodesis

* Includes: haemophilic arthropathy diagnosis

Appendix 2. Haemophilia Joint Health Score (HJHS) 2.1 summary sheet

Subject ID #:_____ **Name of Physiotherapist:**_____

Assessment # : _____ **Date:** _____
yyyy / mm / dd

Time: _____

Hemophilia Joint Health Score 2.1 - Summary Score Sheet

	Left Elbow		Right Elbow		Left Knee		Right Knee		Left Ankle		Right Ankle	
Swelling		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Duration (swelling)		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Muscle Atrophy		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Crepitus on motion		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Flexion Loss		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Extension Loss		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Joint Pain		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Strength		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Joint Total												

Sum of Joint Totals _____

+

Global Gait Score _____

(☐ NE included in Gait items)

=

HJHS Total Score _____

NE = Non-Evaluable

Swelling
0 = No swelling
1 = Mild
2 = Moderate
3 = Severe

Duration
0 = No swelling or < 6 months
1 = ≥ 6 months

Muscle Atrophy
0 = None
1 = Mild
2 = Severe

Crepitus on Motion
0 = None
1 = Mild
2 = Severe

Flexion Loss

	Contralateral:	Normative Tables:
0	< 5°	within range
1	5° - 10°	1° - 4°
2	11° - 20°	2 = 5° - 10°
3	> 20°	3 = > 10°

Extension loss (from hyperextension)

	Contralateral:	Normative tables:
0	< 5°	within range
1	5° - 10°	1° - 4°
2	11°- 20°	2 = 5° - 10°
3	> 20°	3 = > 10°

Joint Pain
0 = No pain through active range of motion
1 = No pain through active range; only pain on gentle overpressure or palpation
2 = Pain through active range

Strength (Using The Daniels & Worthingham's scale)
Within available ROM
0 = Holds test position against gravity with maximum resistance (gr.5)
1 = Holds test position against gravity with moderate resistance (but breaks with maximal resistance) (gr.4)
2 = Holds test position with minimal resistance (gr. 3+), or holds test position against gravity (gr.3)
3 = Able to partially complete ROM against gravity (gr.3-/2+), or able to move through ROM gravity eliminated (gr.2), or through partial ROM gravity eliminated (gr.2-)
4 = Trace (gr.1) or no muscle contraction (gr.0)
NE = Non-evaluable

Global Gait (walking, stairs, running, hopping on 1 leg)
0 = All skills are within normal limits
1 = One skill is not within normal limits
2 = Two skills are not within normal limits
3 = Three skills are not within normal limits
4 = No skills are within normal limits
NE = Non-evaluable

NOTE: There is an accompanying instruction manual and worksheets that are required when administering the HJHS

General Comments:

_____

_____

_____

_____

Appendix 3. EQ5D 3L (English version)

Health Questionnaire

English version for the UK
(validated for Ireland)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

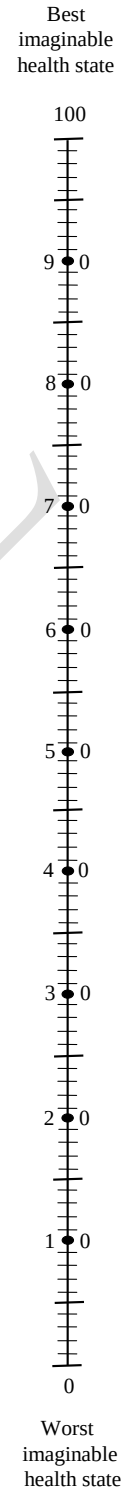
I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Paper I

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Registry-based outcome assessment in haemophilia: a scoping study to explore the available evidence

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Content List – Read more articles from the symposium: Future of haemophilia outcome assessment.

Abstract. Osooli M, Berntorp E (Lund University and Skåne University Hospital, Malmö, Sweden). Registry-based outcome assessment in haemophilia: a scoping study to explore the available evidence. (Review Symposium). *J Intern Med* 2016; **279**: 502–514.

Haemophilia is a congenital disorder with bleeding episodes as its primary symptom. These episodes can result in negative outcomes including joint damage, loss of active days due to hospitalization and reduced quality of life. Effective treatment, however, can improve the outcome. Registries have been used as a valuable source of information regarding the monitoring of treatment and outcome. The two main aims of this exploratory study were to establish which haemophilia registries publish peer-reviewed outcome assessment research and then to extract, classify and report the treatment outcomes and their extent of use in the retrieved registries. Using relevant keywords, we searched PubMed and Web of Science databases for publications during the period 1990–2015. Retrieved references were screened in a stepwise process. Eligible papers were original full articles on haemophilia outcomes that used data from a computerized patient database. Descriptive results were summarized. Of 2352 references reviewed, 25 full texts were eligible for inclusion in the study. These papers were published by 11 registries ranging from local to international in coverage. It is still relatively rare for registries to produce peer-reviewed publications about outcomes, and most that currently do produce such papers are located in Europe and North America. More information is available on traditional outcomes such as comorbidities and arthropathy than on health-related quality of life or the social and developmental impact of haemophilia on patients. Inhibitors, HIV and viral hepatitis are amongst the most commonly reported comorbidities. Research has focused more on factor consumption and less on hospitalization or time lost at school or work due to haemophilia. Haemophilia registries, especially those at the national level, are valuable resources for the delivery of effective health care to patients. Validated outcome measurement instruments are essential for the production of reliable and accurate evidence. Finally, such evidence should be communicated to physicians, patients, the public and health policymakers.

Keywords: factor VIII, factor IX, haemophilia, registries, treatment outcome.

Introduction

Haemophilia is a rare, congenital disorder with a prevalence of approximately 1/5000 live male births [1]. Treatment of the more severe forms of the disease is based on replacement of the missing or dysfunctional clotting factor protein, that is factor VIII or factor IX for haemophilia A or B, respectively. Whilst the main consequence of haemophilia is bleeding, multiple negative outcomes may result from bleeding events in a variety of organs in the absence of efficient treatment (Fig. 1). Most of these outcomes are the result of treatment strategy as well as the replacement products used. For example, products which are not free of viral contaminants increase the risk of hepatitis and HIV, and intense treatment increases the risk of inhibitor development amongst patients [1, 2].

The principal symptom of haemophilia is joint haemorrhage. Repeated haemorrhage in the same joints eventually causes cartilage destruction which affects the entire bone and soft tissue of the joint structure. If not adequately treated, patients eventually become disabled with reduced quality of life and shortened life expectancy [3–5].

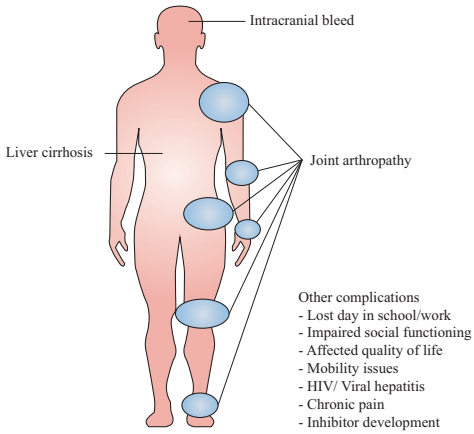

Fig. 1 *Some of the most common outcomes and complications of haemophilia.*

Development of joint disease in haemophilia is a process that occurs over many years and susceptibility varies between individuals; in some patients joint damage results from the occurrence of subclinical bleeding whereas others require a relatively large number of bleeding episodes [6]. Regular replacement therapy with modern concentrates (i.e. in prophylaxis) is extremely costly and therefore affordable only in high-income countries. Even in such countries, there is ongoing discussion about dosing (i.e. dose interval and dose for each infusion). The high costs, and particularly the time period needed for robust data collection to measure arthropathy development, make it virtually impossible to design high-quality studies to test different treatment schedules against one another. The foundation for the use of prophylaxis was established from data derived from registries and observational studies in Europe [7–9].

During the early 1990s, it became clear from long-term and relatively large studies in Europe that prophylaxis was far superior to on demand treatment [7, 8]. In some countries, however, methodologically stronger evidence was required. Results from such studies were published more recently [6, 10] and facilitated the introduction of prophylaxis as the best practice in children with severe haemophilia. Later, similar studies demonstrated the benefit of prophylaxis for adult patients [11]. These randomized studies were small and of relatively short duration. In Europe, where observational studies using registry data had been accepted for some time, it was clear that centres, or even countries, could be compared with respect to treatment regimens. The benefit of such studies was the size of the cohorts, the long-term follow-up and the degree to which the results could be generalized to large populations. In fact, comparing socio-economically similar countries is very similar to randomization, as country of birth is not chosen. For example, comparative studies in Sweden and Norway as well as in Sweden and the Netherlands have been conducted [8, 9].

Real-world treatment data also provide an extra dimension to such studies. Several comparisons have been conducted between the Netherlands and Sweden, two countries with long histories of the use of prophylaxis, albeit with different regimens. It was recently shown that the high cost of the Swedish treatment strategy provided only minor outcome benefits compared to the Dutch regimen with respect to bleeding frequency and physical joint score within the time frame studied [9]. In addition, quality of life did not differ between the two cohorts. It is likely that such studies will be impossible to complete using standard randomization strategies.

Although outcomes such as median survival time have been studied with large datasets, which outcome data should be collected to best monitor treatment remains unclear. Data from well-designed and managed registries are likely to be the best source for outcomes when comparing different methods of follow-up and treatment modalities.

Haemophilia registries

Registries are being used increasingly more frequently as a tool for clinical management and research in health science. They can provide a system for collection of large amounts of high-quality data and become a valuable component of the research infrastructure if built and maintained appropriately. The development of a multidisciplinary team, identification of clear specific aims for collecting data, selection and validation of variables for collection and regular updating of and improvement to database operations are all crucial to ensure the optimum functioning of the registry and quality of data output. The most challenging issues with respect to using registry-

based data are the minimization and management of missing data and loss to follow-up, handling changes in diagnosis and variable definitions and assuring the quality of data over time. Despite the obstacles that exist, outcome evaluation using registries is not only important for producing scientific evidence but also for healthcare planning and communication with patients, healthcare policymakers and the public [12–14].

Registries are useful tools for health research, and particular value can be derived from them for rare and chronic diseases such as haemophilia. (Fig. 2). In the case of haemophilia, the lifelong nature of the disease and treatment make it even more important to register and record patients' health status and treatment progress. As an example, by examining over time the patient's quality of life in association with a particular treatment, physicians can better evaluate its effectiveness. Although this can also be performed using paper-based documents, efficiency of organizing information and of providing graphical presentation of the data are some of the practical benefits of electronic registries. As noted above, registries have limitations. Using historical data may present challenges related to the variable quality of data over time as well as ethical considerations regarding their use in the performance of research.

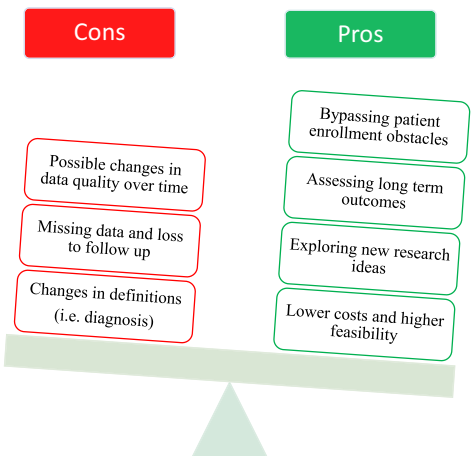

Fig. 2 *Advantages and disadvantages of using registries for haemophilia research.*

Early significant attempts to develop 'haemophilia outcome assessment' registries date back to the era of the HIV epidemic in the 1980s as a result of the infusion of contaminated blood products [15, 16]. Some registries were established to facilitate HIV surveillance amongst patients with haemophilia. More than 20 years later, the World Federation of Haemophilia (WFH) published guidelines for developing a national registry [17]. A few years after that, the European Association for Haemophilia and Allied Disorders (EAHAD) also recommended the establishment of national registries as one of the European principles of haemophilia care [18]. Useful information is freely available to provide guidance on the design and maintenance of a patient registry [19]. Useful information has been published to provide guidance on the design and maintenance of a haemophilia patient registry [14, 20–23].

Inhibitor development and joint arthropathy are amongst the most important outcomes for patients with haemophilia. We have previously investigated registries developed specifically for the study of inhibitors and explored the choice of variables for inhibitor prediction and outcome [24]; we concluded that registry-based evidence, with respect to these factors, remains insufficient.

We had two main objectives in this study. We aimed first to establish which haemophilia registries have produced peer-reviewed evidence about treatment outcomes and secondly to extract, classify and report the treatment outcomes and the extent of their inclusion in the retrieved registries. This information could be useful to explain current practice and to improve haemophilia outcome assessment.

Methods

In this scoping study, registry-based evidence regarding haemophilia treatment outcomes was retrieved for analysis. The scoping review is a social science research method that aims to broadly explore evidence in a given research area [25, 26]. With some exceptions, this research method is similar to the systematic review. A scoping review can reveal the extent of available evidence for a scientific subject area and result in the development of more specific research questions. This methodology is especially useful for retrieval, organization and reporting of findings.

Identification of relevant studies

PubMed and Web of Science databases were the two main sources for identification of relevant studies. Additional information was retrieved using Google and through personal communication with registry holders and corresponding authors of the included papers.

Using a relatively broad search strategy, references to haemophilia treatment outcome studies published between January 1990 and January 2015 were searched and obtained. Database-specific search strategies were developed to optimize the search results. MeSH (Medical Subject Headings) terms were used to search in PubMed to cover the majority of relevant references whilst a free-text search was implemented to retrieve the most recent references not yet labelled with MeSH terms. In the Web of Science, the title field was searched to increase specificity of the search results.

Keywords were selected combining the authors' knowledge and 'key word selection' guides and facilities available for each database. Use of the term 'registry' could result in the exclusion of some publications that had used alternative terminologies to describe their patient database; therefore, this term was not used. The following groups of keywords were combined according to the search rules of each database using the operators 'AND' and 'OR'.

1 'Haemophilia A', 'Haemophilia B', 'Factor VIII', 'Factor IX'

2 'Treatment'

3 'Treatment Outcome', 'Joint Arthropathy', 'Health Related Quality of Life', 'Cost', 'Cost Utility', 'Cost Effectiveness Analysis', 'Bleed', 'Survival', 'Life Expectancy', 'Hospitalization', 'Death'.

Treatment Outcome

The following search strategies in PubMed and Web of Science were used.

1 *'MeSH empowered search' in PubMed:* (((''Factor VIII'[MeSH]) OR 'Factor IX'[MeSH]) OR ('Hemophilia A'[MeSH] OR 'Hemophilia B'[MeSH])) AND 'Treatment Outcome'[MeSH]

2 *Web of Science database:* ('Hemophilia A' OR 'Haemophilia A' OR 'Hemophilia B' OR 'Haemophilia B') AND ('Treatment Outcome' OR 'Joint Arthropathy' OR 'Health Related Quality of Life' OR 'Cost' OR 'Cost Utility' OR 'Cost Effectiveness Analysis' OR Bleed* OR 'Treatment' OR 'Survival' OR 'Life Expectancy' OR 'Treatment' OR 'Hospitalization' OR 'Death').

Study selection criteria

Eligible papers were original articles published between January 1990 and February 2015 on haemophilia treatment outcomes using registry data. A registry was defined as any computerized database with patient follow-up that serves as a platform for research and clinical practice. The registry-based evidence was the main focus of this study; therefore, we used a broad definition of registry. Papers published from genetic haemophilia registries in which no outcome data were reported were not within the scope of this study and consequently not included. There was no eligibility criterion for the number of patients included in a registry.

Amongst multiple similar updates published from the same registry, the most recent and complete data were included. Paper screening and enrolment was performed by a single reviewer in a stepwise process. First, through title screening, the clearly irrelevant papers were excluded. Selected titles and those that were unclear were included for abstract screening. In the second stage, the abstracts were assessed. Relevant papers, those lacking abstracts or with an unclear methodology, were included in the full-text assessment. In the last screening stage, the final decision on inclusion of each individual paper was made by reading the retrieved full texts. Nonobservational and nonhuman studies, reviews and those papers without full text (such as meeting abstracts) were excluded.

Charting the data

Data extraction was performed using two themes: characteristics of registries and reported outcomes. In an iterative process, data extraction tables were prepared. A single reviewer extracted data by viewing the Methods and Results sections of each included paper.

Collating, summarizing and reporting the results

Table 1 shows the basic characteristics of each registry. Any reported outcome measure was extracted, citing the source paper. Based on their

Table 1 *Characteristics of haemophilia registries as data sources for peer-reviewed publications about treatment outcomes*

Registry	Year initiated	Number of patients	Prophylaxis available	Source of funding	Number of publications[a]
Canadian Haemophilia Registry [53]	1988	3307	Yes	Public	2
Emilia-Romagna Regional Registry (Italy) [13]	2003	312	Yes	Public	2
Haemophilia database of the Van Creveld clinic (Utrecht, The Netherlands) [42]	1972	1060	Yes	Public	1
Haemophilia registry of the Centre for Thrombosis and Haemostasis, Malmö [54]	1986	333	Yes	Public	5
HemoRec Registry (Poland) [29]	2006	1102[b]	Yes	Industry	4
Registry of Italian Regional Haemophilia Centre of Pescara [55]	Unknown	95	Yes	Unknown	1
Italian Registry of Haemophilia and Allied Disorders [22]	2003	3246	Yes	Unknown	1
PedNet Haemophilia Registry (international) [31]	2004	1094	Yes	Industry	3
Swiss Haemophilia Registry [14]	2000	950	Yes	Public	2
UK Haemophilia Registry [41]	1969	6891	Yes	Public	2
Universal Data Collection database (USA) [39, 56]	1990	15 527	Yes	Public	2

[a]Only those including haemophilia outcomes (and retrieved in this study).
[b]Only the patient subgroup from Poland.

relevance, outcome measures were categorized as 'joint outcomes', 'comorbidity and mortality', 'bleeding-related outcomes' and 'burden of disease and cost of treatment'. If outcome measures could not be matched to any of these categories, or if such categories were only of minor importance, outcomes were recorded separately. For each reported outcome, the reference to the source paper is included in the Tables 2–5 for ease of tracking and to identify further information. Data extraction for all included papers was rechecked to minimize the possibility of error or omission.

Results

A total of 2352 references were screened, and 25 full-text articles were considered eligible and included in the study. In the first step after duplicate removal, 2348 titles were included for screening (Fig. 3). Overall, 822 titles were selected for abstract assessment. Of these, 295 abstracts were eligible and full text was available for 248. These were included in the next step of full-text evaluation. Twenty-five papers were abstracts only, and these were excluded. Access to the full text of 26 references was not possible. By screening the reference list of each full-text paper, four additional references were found to be relevant for assessment and included in the study.

Characteristics of haemophilia registries

We included 25 papers published by 11 registries including two international, four national, two regional and three single-centre registries (Table 1). The oldest registry was established in 1969 in the UK, and the largest registry [15 527 patients in the Universal Data Collection (UDC) system] was initiated in the USA. Most of the registries were located in Europe. Patients in the majority of the registries had access to long-term prophylaxis.

Comorbidities and mortality

Most of the reported evidence regarding treatment complications and comorbidities was related to

Table 2 *Comorbidities and mortality reported by haemophilia registries*

Registry	Inhibitors	Adverse events	HIV/viral hepatitis	Cause of death	Survival/ mortality	Other comorbidities[a]
Canadian Haemophilia Registry	[38]	–	[38]	[38]	[38]	[38, 57]
Emilia-Romagna Regional Registry	[13, 58]	[58]	[13, 58]	–	–	–
Haemophilia database of the Van Creveld clinic	[42]	–	–	–	–	–
Haemophilia registry of the Centre for Thrombosis and Haemostasis, Malmö	[59]	–	[3, 54, 59, 60]	[3]	[3]	–
HemoRec Registry	[27, 29, 30]	[30]	[30]	–	–	–
Italian Registry of Haemophilia and Allied Disorders	[22]	–	[22]	–	–	–
PedNet Haemophilia Registry	[61, 62]	–	–	–	–	–
Registry of Italian Regional Haemophilia Centre of Pescara	[55]	–	[55]	–	–	–
Swiss Haemophilia Registry	–	–	–	[40]	[40]	–
UK Haemophilia Registry	[4, 41]	–	[4, 41]	[4, 41]	[4, 41]	[41]
Universal Data Collection database	[56]	–	[56]	[39]	[39]	–
Total	10	2	8	5	5	2

[a]Excluding HIV/viral hepatitis.

Table 3 *Joint outcomes reported by haemophilia registries*

Registry	Joint bleeding	Target joint	Arthropathy	Range of motion	Gilbert score	HJHS	Joint surgery
Emilia-Romagna Regional Registry	[13]	–	[13]	–	–	–	–
Haemophilia database of the Van Creveld clinic	[42]	–	[42]	–	[42]	–	–
Haemophilia registry of the Centre for Thrombosis and Haemostasis, Malmö	[43, 54]	[43]	–	[43]	–	[54]	[59]
HemoRec Registry	[27]	[28, 30]	–	–	–	–	–
Universal Data Collection database	–	[56]	–	[56]	–	–	–
Total	4	3	2	2	1	1	1

HJHS, Haemophilia Joint Health Score.

inhibitor development and the presence of HIV and viral hepatitis (Table 2). Other comorbidities were reported only by Canadian and UK registries. Longevity was assessed from different perspectives; some registries recorded life expectancy and others reported survival.

Joint outcomes

The most frequent joint outcomes reported by registries were joint bleeds and target joints (TJs) (Table 3). Arthropathy and range of motion (ROM) were reported by two registries, and joint surgery was reported by one registry. Haemophilia Joint Health Score (HJHS) and Gilbert score were each reported by one registry. Age at development of TJ was only reported by the UDC registry.

Bleeding specifications and outcomes

The frequency of bleeding was reported in only two of the registries. All four registries that reported on

bleeding episodes included the location but only two provided information on the cause (Table 4). Minor bleeding has been defined as bleeding episodes characterized by mild pain, minimal swelling, minimal restriction of motion/function and resolution within 24 h of initial treatment; major bleeding was characterized by pain, swelling, limitation of motion/function and failure to respond within 24 h of treatment. The HemoRec registry also reported on outcomes of treatment of bleeding events. Measures including time to resolution [27–29], effectiveness of treatment [27] and rebleeding [27, 28, 30] were introduced to evaluate treatment efficiency. The PedNet registry introduced the extent of bleed as an outcome measure [31].

Burden of disease and 'cost of treatment'

Of the 11 registries, six reported on factor consumption (Table 5). Two commonly reported outcomes of the impact of haemophilia were patients' school or work attendance and the number of hospitalization days per year. Loss of time at school/work was reported by two registries and hospitalization due to haemophilia was reported by two single-centre and one regional registry. The HemoRec registry further reported on hospital costs. The burden of haemophilia on family life was reported by the Malmö haemophilia registry.

Table 4 *Bleeding characteristics reported by haemophilia registries*

Registry	Frequency	Location	Cause
Emilia-Romagna Regional Registry	[13]	[13, 58]	[58]
HemoRec Registry	[27, 29]	[27, 29, 30]	[27, 28]
PedNet Haemophilia Registry	–	[63]	–
Universal Data Collection database	–	[56]	–
Total	2	4	2

Other reported outcomes

Health-related quality of life (HRQoL) using the 36-item Short Form Health Survey was reported by the Malmö registry. The HemoRec registry reported on the effectiveness of treatment of bleeding (effective, partially effective or ineffective). Other outcomes such as number of patient visits for care per year, impact of haemophilia on patients' social and family life and body mass index were each reported by one registry. The Gilbert score was reported by a single-centre registry. No radiological assessment tools were reported by any registries.

Discussion

The aim of this study was to map registries that provide haemophilia-related data to classify and report the treatment outcomes and the extent of their inclusion in retrieved registries. The results of this study showed that most of the outcome registries are located in Europe, and indeed, such registries are rare outside Europe. The focus of the outcome assessment has been on outcomes such as bleeding events and joint arthropathy.

Table 5 *Cost of treatment and burden of disease reported by haemophilia registries*

Registry	Factor consumption	Hospitalization due to haemophilia	Time lost at school/work[a]
Emilia-Romagna Regional Registry	[13, 58]	[13]	[13, 58]
Haemophilia database of the Van Creveld clinic	[42]	–	–
Haemophilia registry of the Centre for Thrombosis and Haemostasis, Malmö	[43, 54]	–	[43]
HemoRec Registry	[27, 29]	[27, 28]	–
PedNet Haemophilia Registry	[63]	–	–
Registry of Pescara Haemophilia centre registry	–	[55]	–
Swiss Haemophilia Registry	[14, 40]	–	–
Total	6	3	2

[a]Due to haemophilia.

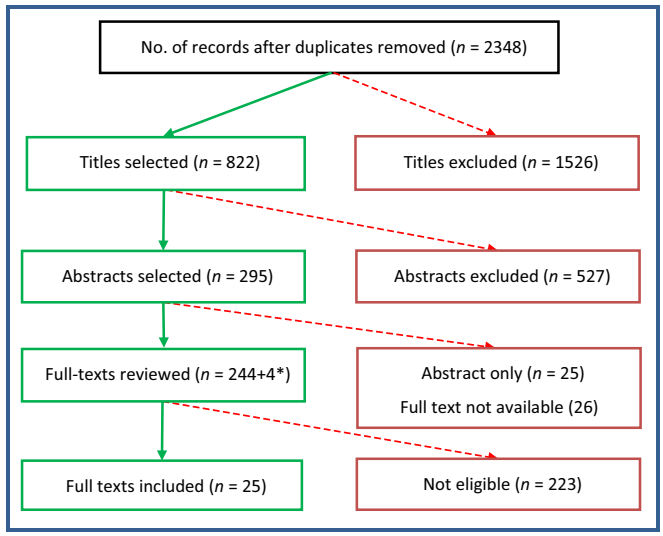

Fig. 3 *Literature search and manuscript selection process. *Four papers were added through reference searching during full-text assessment.*

Haemophilia outcome assessment as a helpful tool in delivering more effective healthcare services has received increased attention in recent years. There are a variety of publications, including review papers, approaching the topic from different perspectives. Blanchette *et al.* has examined outcome assessment from the viewpoints of clinicians, patients, family and funders [32]. In their study, they touched upon issues related to selection of appropriate assessment tools for each outcome category, the role of patients and patient organizations in collecting data, and practical experience in securing funding for outcome assessment activities. Another study by Poonnoose *et al.* reviewed the limitations and challenges of haemophilia outcome assessment focusing on HRQoL and musculoskeletal outcomes [33]. They listed available instruments, discussed their validity, reliability and use in haemophilia assessment. The aim of the current study has been to show the progress in registry development and provided a comprehensive inventory of outcomes reported from registry-based data.

Current haemophilia registries and their characteristics

Haemophilia registries that have been used to publish evidence on outcomes are rare. Apart from one international registry, most were located in Europe ($n = 8$). The remaining two were maintained in North America. Activities to promote their development have begun in Asia and Africa [20, 34], but registries and registry-based evidence are still lacking in these settings. According to the WFH, about 75% of the world's population with haemophilia does not have access to treatment [35]. Outcome assessment and evidence dissemination have not been a priority for countries that cannot afford treatment. Cost is not the only challenge for registry set-up. Effective coordination amongst centres in managing the work process at the national or international level is difficult.

Several years have passed since EAHAD highlighted the importance of a national registry for haemophilia care for European countries [18]. Based on a survey performed in 2013, there are 27 national haemophilia registries in Europe [36]; we found publications from three of these. The remainder may be newly implemented with insufficient data for publication. Moreover, the publication of scientific papers is not a routine practice in some settings.

Comorbidities and mortality outcomes

Inhibitory antibodies, HIV and viral hepatitis were the most commonly reported comorbidities. There are registries built specifically for research on inhibitor development and its consequences. The status of these and the choice of predicting factors and outcome variables are presented elsewhere

[24]. HIV and viral hepatitis were, a few decades ago, amongst the most important comorbidities in haemophilia. Today, in some countries including Sweden and Canada, because of long-term provision of safe products for treatment and regular monitoring, these comorbidities have, fortunately, declined in occurrence. In low-income settings where unsafe products are still in use, however, ascertainment of these conditions should be continued. On the other hand, the haemophilia population is growing older and increased longevity is likely to result in an increase in age-related morbidities. For example, the risk of cardiovascular disease amongst people with haemophilia has been a topic of discussion for a number of years. The lack of evidence of its effect in the haemophilia population has been highlighted [37].

Longevity has been assessed and reported for patients with inhibitors, those with HIV or hepatitis and the general haemophilia population. Cause-specific mortality is a useful mechanism for reporting patient survival. Evidence is available from multiple registries on 'cause-specific mortality' in haemophilia [3, 4, 38–41].

Adverse events, particularly adverse drug reactions (ADRs), have not been sufficiently covered by registries. ADRs, although rare, are quite important due to their impact on patients' health through the choice of treatment products. ADRs should be a part of routine outcome assessment.

Joint outcomes

Joint bleeding, when repeated in the same joint in the absence of proper treatment, is the starting point for the joint arthropathy process. Clinicians must identify any and every joint bleed early and treat it immediately. A TJ is one that has experienced multiple bleeding episodes within a short period of time. There are a variety of definitions for a TJ, differing on the number of bleeding events or the time period during which they occurred. A TJ may result in development of joint arthropathy and loss of mobility and ROM. Of note, ROM is a useful and easy method of assessing joint function, but it cannot replace standardized joint assessment tools such as the Gilbert score or the HJHS. Gilbert score was reported by one of the registries [42].

Five registries reported joint outcomes. Of these, four registries included the number of joint bleeding events whilst only three noted TJ. In three of the four papers reported on TJ, the definition used was missing [28, 30, 43]. Arthropathy and ROM were each reported by two registries. There are no reported data from registries on outcome assessments using imaging techniques. The techniques of ultrasound and magnetic resonance imaging are under evaluation [44] and it seems likely that these will, to some degree, replace plain X-rays in the future.

Joint surgery is another reported outcome. It is the ultimate solution for an affected joint but complex due to its dependence on access to resources. When comparing the age at joint surgery amongst patient populations, it is necessary to adjust for the socio-economic status of each and the resources available for performing the surgery.

Bleeding specifications and outcomes

Bleeding episodes are usually described in terms of their frequency, location and cause. The extent of bleeding, which has been reported by PedNet, can give further information on their impact. Five registries elaborated on the characteristics of bleeding, mostly focusing on the localization. Outcome of treatment of a bleeding event is one of the most important aspects of haemophilia care, although there is no consensus as to how to report it. The HemoRec registry reported on different indexes of bleeding treatment outcome [27–30]. Because bleeding events are generally patient-reported outcomes, efforts should be made to reduce the amount of information by focusing on the most important questions. At the same time, use of easier reporting methods such as mobile apps could be valuable [45].

Burden of disease and 'cost of treatment'

Due to its high cost, haemophilia treatment has been the subject of numerous health economic evaluations. Most of these studies have relied on nonregistry-based and cross-sectional data [46]. Many of them suffered from some design issues resulting in huge variations of their results [47]. Two economic evaluation papers published using HemoRec registry based data were enrolled in this study [27, 28]. Clotting factor consumption, as one of the main determinants of haemophilia treatment cost, has been reported more frequently than other, less direct outcomes such as loss of days at school/work or hospitalization due to haemophilia. In fact, there is little published evidence regarding loss of days at school/work.

Further, it is not clear how reliable the data are and how much the time spent by parents and caregivers in the care of their children with haemophilia have been considered. Overall, it appears that given the considerable expense of clotting factor, other costs of haemophilia treatment have received less attention.

Patient-reported outcomes

The patient's perspective of outcomes has more recently become of major interest and importance. The term patient-reported outcome is used to reflect the patient's perceptions of disease and its consequences. In the case of haemophilia, HRQoL and patient preferences are important but do not appear to be well addressed. Increased use of patient-reported outcomes has been recommended [48] and highlighted by the International Prophylaxis Study Group [49]. In the present study, we found that these measures are not generally reported in registries.

Other issues

Helpful general guidelines for registry development [19], as well as registries specifically for haemophilia [17, 20], are available for use. There are also good examples of applications of modern database functions to provide services for patients and other stakeholders. The Emmilia Romanga Registry has offered complete online access to its data. The registry's website is directly linked to the database, thus combining the data from the various haemophilia centres; the results are presented in the form of tables, lists and graphs on various pages of the site [13]. This information is available for the registry contributors.

There are several established genetics registries, including the Italian AICE genetic haemophilia A database [50] and the Factor VIII Variant Database [51]. These were not included in this study due to their lack of reported outcome measures.

Limitations

One of the aims of this study was to collect and present published evidence from registry-based haemophilia outcome studies. Larger registries, and those from high-income countries, publish more often. We included in our study only English language publications, but using a wide search strategy we attempted to capture most of the available evidence in the databases searched. The results are primarily from Europe and North America. There were no publications from Asia and Africa. Thus, conclusions might be biased towards the perspectives of high-income countries.

Table 6 *Recommended outcome categories to be included in haemophilia registries*

Anthropometric and vital sign evaluations (such as weight, height and blood pressure)
Antibodies against factor VIII/IX
Bleeding episodes
Comorbidities
Joint outcomes
Patient preferences
Relevant laboratory measures
Social and economic burden (including HRQoL)
Treatment complications

HRQoL, health-related quality of life.

Recommendations

Combining authors' experience and findings from this scoping review some recommendations can be provided about outcomes to be included in registries and methods to keep a registry viable and valid. The authors' suggested outcome categories are listed in Table 6. The ultimate decision with respect to variables and data to be collected at each setting must be adjusted based on the needs of the patient population and the available infrastructure, expertise and resources.

To keep a registry viable and up to date, it is of major importance to use standardized tools for assessment. Registries must use exactly defined outcomes and, optimally, consensus and standardization amongst registries should be a goal. They must be updated and maintained by staff with competence and interest in registries and their use in daily practice as well as in research. Ideally, an international body such as EAHAD or WFH should take on the task of aligning the most substantial registries to improve the possibilities for their use and increase the feasibility of obtaining output from these valuable sources.

Conclusion

Haemophilia registries, especially those at the national level, are valuable resources for organizing

outcome assessment and production of evidence for delivering more effective health care to patients. This message has been highlighted by others [52]. As our knowledge of care and treatment advances, we need to improve our capabilities and assessment tools to adequately address the critical outcomes. Gaps in knowledge remain regarding the outcomes of different haemophilia treatment strategies. Registries can provide a platform for documenting evidence on assessment of these. Use of validated instruments will save time, will save resources and will result in more reliable and accurate measurements. Outcome assessment is the first step. It should be followed by generation of sound results and dissemination of these to physicians, their patients, the public and health policymakers.

Conflict of interest statement

MO and EB are conducting research with data from the Malmö haemophilia registry.

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Paper II

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ORIGINAL ARTICLE

The association between health utility and joint status among people with severe haemophilia A: findings from the KAPPA register

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Introduction: People with severe haemophilia A have reportedly impaired health related quality of life (utility) mainly due to recurrent bleeding, arthropathy and treatment burden. **Aim:** To estimate utilities and evaluate their potential correlates – most importantly the joint status – among people with severe haemophilia A. **Methods:** In this cross-sectional study, eligible participants had severe haemophilia A, were aged ≥15, negative for factor VIII inhibitor and included in the KAPPA register of Denmark, Norway and Sweden. Data on demographics, treatment history, haemophilia joint health score, and EQ-5D utility were obtained from the register. We used box plots to present utilities and joint status and ordinary least squares regression to evaluate correlates of utilities. Participants were consecutively enrolled in the KAPPA register between April 2013 and June 2016. **Results:** Overall, 173 participants with median age of 34 (interquartile range: 25–45) were included. Twelve (6.9%) participants were on episodic treatment while 161 (93.1%) were treated using prophylaxis. Concomitant diseases and positive inhibitor history were reported for 73 (43.2%) and 21 (12.1%) participants, respectively. The highest median utility (1.0) was observed among those aged <29 on prophylaxis and those aged 30–44 who had started prophylaxis by age 3. In the multi-variable regression, joint scores of 16–25 (Coef. −0.18, 95% CI: −0.30, −0.06), 26–35 (Coef. −0.21, 95% CI: −0.36, −0.06) and >35 (Coef. −0.37, 95% CI: −0.52, −0.23) were associated with lower utilities. **Conclusion:** Moderate to severe joint manifestations are associated with reduced utilities among persons with severe haemophilia A.

Keywords: EQ-5D, haemophilia A, haemophilia joint health score, health utility, treatment outcomes

Introduction

People with severe haemophilia A have a clotting factor (CF) VIII level of <0.01 kIU L^{-1} in plasma [1]. Bleeding episodes are the main consequence of haemophilia A. These can be life threatening or result in irreversible joint damage and disability in the absence of efficient and timely treatment. The advent of regular factor replacement treatment (prophylaxis) in the late 1960s was a turning point in the management of haemophilia [2]. Prophylaxis and improvements in follow-up care [3] have closed the gap in life expectancy [4,5] and resulted in improvements in health-related quality of life (HRQOL) among people with haemophilia (PWH) [6]. Prophylaxis, however, may be jeopardized by the development of neutralizing antibodies (inhibitors) against the

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infused clotting factor product [7]. More importantly, prophylaxis may not fully protect joints against bleeding [8] and is not affordable in many settings [9].

Bleeding events and their associated complications (most importantly joint damage), treatment burden and the perceived limitations in activities of daily life due to risk of bleeding can potentially reduce HRQOL among PWH. Health utilities (HU) as generic measures of HRQOL are increasingly used for making treatment decisions and resource allocation in haemophilia. In a recently completed review by Grosse *et al.* [10], however, the authors reported that complexity of the adjustment for predictors of HU, selection bias (in observational studies), and lack of availability of preference-based data from PWH on a variety of treatment regimens pose challenges in estimating suitable utility weights for treatment decision making. Despite the importance of the topic, the literature remains scarce and often controversial with respect to health utilities and their correlates in haemophilia [11–13].

Sweden, the first country to have adopted prophylaxis, provides lifelong access to what is termed a high-dose treatment regimen to persons with moderate or severe haemophilia [14]. Denmark and Norway began use of prophylaxis some years after Sweden and, today, the majority of the PWH with a severe phenotype are treated using prophylaxis in those countries. In 2013, Lund University established an international prospective register to monitor long term outcomes of different treatment regimens for moderate to severe haemophilia A. The project was named 'Key Aspects of medical Practice in Patients with haemophilia A (KAPPA)'. In this study, we used data from the KAPPA register to: 1. estimate health utilities; and 2. evaluate their potential correlates including demographics and clinical characteristics, with emphasis on the joint status among adult persons with severe haemophilia A.

Methods

Study design, setting and participants

This was a cross-sectional study. Eligible participants had severe (CF <0.01 kIU L^{-1}) haemophilia A, were $\geq$15 years of age, and did not currently have an inhibitor to factor VIII. Participants were from centres in Denmark, Norway and Sweden that were included in the KAPPA register. KAPPA is a web-based register [15] developed by Hemophilia Systems (Munkeby Systems, Malmö, Sweden) using components of the haemophilia register in place for many years in Malmö (UMAS Hemophilia register) [16]. At the time of this study, the KAPPA register included participants from 17 centres in seven countries. This report was confined to the Scandinavian centres as the enrolment and data collection were most complete for those sites. Moreover, the standard of haemophilia care, socioeconomics and demographics were homogenous across these centres. Trained physiotherapists from participating centres performed the HJHS examinations. The participants were consecutively enrolled in the KAPPA register between April 2013 and June 2016 during routine clinical visits.

Study variables

Health utility – our primary outcome – was measured using the EQ-5D-3L [17]. We estimated preference-based utilities in two steps. First, the study participants answered five multiple-choice questions (attributes): mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each EQ-5D attribute has three states: (i) 'no problem', (ii) 'some or moderate problems', and (iii) 'extreme problems'. In the second step, reported health states were assigned utility values based on a weighting protocol also known as tariff. We used the UK tariff [18] where health states are ranked on a scale between 1 (full health) and 0 (death). However, we had data on EQ-5D VAS (Visual Analogue Scale), we did not use it in this study. The EQ-5D VAS has limited value for economic evaluations and it poses some methodological challenges when used for this purpose.

The independent variables included: age, treatment history, concomitant disease, inhibitor history, education level, and body mass index (BMI) calculated from weight and height. We used the Haemophilia Joint Health Score (HJHS) 2.1 for the assessment of joints [19]. HJHS assessment includes examination of elbows, knees, and ankles. There is an assessment of overall joint function and a global gait score (range: 0–4). The HJHS ranges from 0 (best joint health) to 124 (the worst score). Human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infection status variables were integrated with concomitant disease in the regression analysis. Treatment was defined as episodic (on-demand) if participants only infused factor VIII upon the onset of bleeding. We defined prophylaxis as receipt of at least one infusion per week for more than 40 weeks in a year. We divided those on prophylaxis into two groups: prophylaxis started $\leq$3 years of age (early prophylaxis) and prophylaxis started >3 years of age (late prophylaxis) [20]. Definition of positive inhibitor was at the discretion of the investigators.

Statistical analysis

For describing subject characteristics and clinical data, we used means (95% confidence interval) and medians (inter-quartile range, IQR) for normally and non-normally distributed quantitative variables, respectively. The categorical variables were presented in

numbers and percentages. Using box-plots, we presented HJHS and EQ-5D (utilities) based on age and treatment categories. To assess demographic and clinical correlates of health utilities among participants we performed ordinary least squares (OLS) regression analysis with robust standard errors. OLS has been proposed as an unbiased approach with valid confidence intervals to produce utility estimates for economic evaluations [21]. Using iterative chained equations (ICEs) imputation with 20 iterations [22] missing values in EQ-5D, HJHS, BMI, inhibitor history, concomitant disease, and education were imputed. Age, weight, height, and treatment history were used as auxiliary variables to improve the precision of imputations. We chose the imputed data model as the main model. We presented both regression models (before and after imputation) to check the robustness of the results. We adjusted for the country of residence to account for local variations and potential confounders [10]. Analysis was done using STATA 13 (StataCorp LP, College Station, TX, USA). For hypothesis testing, 95% confidence intervals (CI) for estimates were reported and $P < 0.05$ was considered statistically significant.

Ethics

The Regional Ethical Review Board of Lund University (dnr.: 2012/118) reviewed and approved the KAPPA register protocol. This approval was valid for Sweden and Denmark. We obtained an additional approval from The Regional Committees for Medical and Health Research Ethics for the Oslo centre (ref nr.: 2014/453). Patients had the opportunity to decide on their participation in or withdrawal from the study and provided written informed consent prior to enrolment in the KAPPA register.

Results

We included 173 participants with severe haemophilia and no current inhibitor. At the time of this study, the KAPPA investigators from the included centres had enrolled 49% of their eligible PWH (severe phenotype) in the register – the inclusion rate ranged from 30% to 71% across centres. The majority of the participants were from Sweden (53%). As shown in Table 1 the oldest and youngest participant groups were those on episodic treatment (median age: 53 years) and early prophylaxis (median age: 26 years), respectively. The median BMI was 24.6 (IQR: 22.8–27.5). Late prophylaxis was the most common category of treatment (101 participants, 58.4%). Only 12 (6.9%) participants were on episodic treatment. Twenty-one (12.1%) of participants had positive inhibitor history. More than half of the participants had no reported concomitant diseases and the information was missing for 10 (5.8%) participants. HIV and HCV (PCR) status were positive for 13 (7.5%) and 32 (18.5%) participants, respectively.

Table 1. Demographic and clinical characteristics of participants presented by treatment history.

	Prophylaxis started age ≤3 (n = 60)	Prophylaxis started age >3 (n = 101)	Episodic (n = 12)	All treatments (n = 173)
Country of residence, n (%)				
Denmark	10 (16.7)	18 (17.8)	10 (83.3)	38 (22.0)
Norway	6 (10.0)	35 (34.6)	2 (16.7)	43 (24.9)
Sweden	44 (73.3)	48 (47.5)	0	92 (53.2)
Factor VIII inhibitor status, n (%)				
Negative	47 (78.3)	90 (89.1)	11 (91.7)	148 (85.6)
Positive history	10 (16.7)	10 (9.9)	1 (8.3)	21 (12.1)
Unknown history (currently negative)	3 (5.0)	1 (1.0)	0	4 (2.3)
Concomitant disease, n (%)				
No	40 (66.7)	48 (47.5)	2 (16.7)	90 (52.0)
Yes	15 (25.0)	48 (47.5)	10 (83.3)	73 (42.2)
Unknown	5 (8.3)	5 (5.0)	0	10 (5.8)
Human immunodeficiency virus (HIV), n (%)				
Negative	46 (76.7)	78 (77.2)	11 (91.7)	135 (78.0)
Positive	2 (3.3)	10 (9.9)	1 (8.3)	13 (7.5)
Unknown	12 (20.0)	13 (12.9)	0	25 (14.4)
Hepatitis C virus (HCV), n (%)				
Negative	45 (75.0)	68 (67.3)	7 (58.3)	120 (69.4)
Positive	4 (6.7)	23 (22.8)	5 (41.7)	32 (18.5)
Unknown	11 (18.3)	10 (9.9)	0	21 (12.1)
Education level, n (%)				
Academic	13 (21.7)	33 (32.7)	5 (41.7)	51 (29.5)
High school diploma or lower*	43 (71.7)	58 (57.4)	7 (58.3)	108 (62.4)
Unknown	4 (6.6)	10 (9.9)	0	14 (8.1)
Age at enrolment, median (IQR)	26.5 (20.0, 32.5)	39.0 (30.0, 50.0)	53.0 (39.5, 64.0)	34.0 (25.0, 45.0)
Body Mass Index (BMI), median (IQR)	24.3 (22.9, 27.8)	24.6 (22.6, 26.9)	26.6 (23.4, 29.2)	24.6 (22.8, 27.5)
Haemophilia Joint Health Score (HJHS), median (IQR)	2.0 (1.0, 6.0)	22.0 (7.0, 41.0)	37.5 (24.0, 47.0)	12.5 (2.0, 28.0)
EQ-5D utility, median (IQR)	1.0 (0.796, 1.0)	0.727 (0.691, 1.0)	0.718 (0.587, 0.823)	0.796 (0.725, 1.0)

IQR, inter-quartile range.
*Including current high school students.

HJHS were available for 154 (89%) and EQ-5D scores from 161 (93.1%) participants. For the entire sample, the median HJHS and utility were 12.5 (IQR: 2.0–28.0) and 0.796 (IQR: 0.725, 1.0), respectively. The highest and lowest median HJHS were observed among those on episodic treatment (median 37.5) and on early prophylaxis (median 2.0), respectively. The median utility was highest among those on early prophylaxis (1.0) and lowest in the episodic treatment group (0.718).

Figure 1 presents HJHS by age group and history of treatment. Among those on early prophylaxis, the median HJHS was slightly higher in the age group 30–44 years compared to those 15–29 years (3.0 vs. 2.0). In comparison, among subjects who began prophylaxis late, the median HJHS was considerably higher in the 30–44 age group compared to those 15–29 years. The median HJHS in the late prophylaxis group showed a positive and strong correlation with age. At every age group, those on episodic treatment had a slightly higher median HJHS than the late prophylaxis group. None of the participants under age 30 were on episodic treatment and no one greater than 44 years had been placed on prophylaxis early in life.

EQ-5D utilities

Overall, utilities were stable among those on prophylaxis. Participants on early prophylaxis (aged 15–29 and 30–44 years) and those on late prophylaxis (aged 15–29 years) had the highest utility (median 1.0; Fig. 2). For those on late prophylaxis, the median utility was higher among participants 15–29 years (1.0) but lower and similar (0.727) among older age groups: 30–44, 45–59 and ≥60 years. For those on episodic treatment, the median utility was higher among those 30–44 years (0.778) compared to those aged 45–59 (0.656) or those ≥60 years (0.710).

We also examined EQ-5D attributes (Table 2). Overall, mobility and pain/discomfort were the most affected domains. In addition, usual activities were curtailed among those treated episodically (50% moderate problems). Table S1, presents EQ-5D attributes reported by participants from different age and treatment backgrounds.

Correlates of EQ-5D utilities

The results from multiple regression analysis showed that after adjusting for age, treatment and other clinical and socioeconomic factors, increase of HJHS was associated with reduced utility (Table 3). However, early joint manifestations identified by HJHS in ranges 1–15 did not yield statistically significant reduced utility compared to the reference category. In the imputed-based regression model, HJHS 16–25, 26–35 and ≥35 was associated with utility reductions of 0.18, 0.21, and 0.37, respectively, compared to the reference category (HJHS = 0). In both models, BMI, treatment history, inhibitor history, concomitant disease and education level did not show any statistically significant associations with utility controlling for age, HJHS and country of residence.

Discussion

To best of the authors' knowledge, this is the largest international study to investigate (EQ-5D) utilities

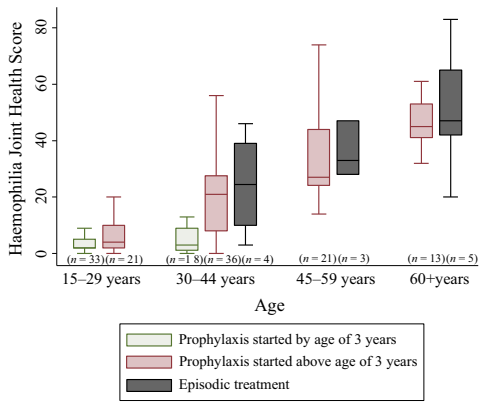

Fig. 1. Haemophilia Joint Health Score (HJHS) presented by age and treatment history. The vertical axis represents the median, inter-quartile range and range of Haemophilia Joint Health Scores. The horizontal axis represents age groups. Groups on prophylaxis started by age 3, prophylaxis started above age 3 and episodic treatment were differentiated with green, maroon and black colours, respectively.

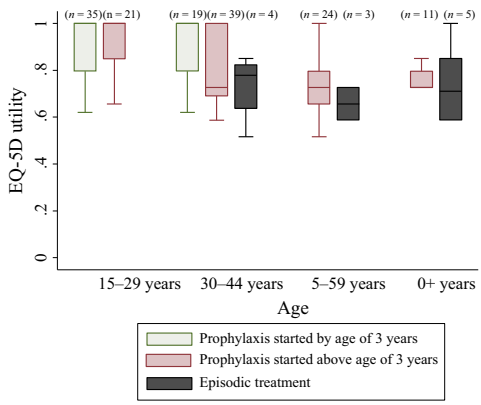

Fig. 2. Preference-based EQ-5D utilities presented by age and treatment history. The vertical axis represents the median, inter-quartile range and range of EQ-5D utility scores. The horizontal axis represents age groups. Groups on prophylaxis started by age 3, prophylaxis started above age 3 and episodic treatment were differentiated with green, maroon and black colours, respectively.

Table 2. Numbers and proportions reporting levels within EQ-5D dimensions presented by treatment history.

	Prophylaxis started age ≤3 (*n* = 54)	Prophylaxis started age >3 (*n* = 95)	Episodic treatment (*n* = 12)	All treatments (*n* = 161)
Mobility, *n* (%)				
No problem	46 (85.2)	47 (49.5)	3 (25.0)	96 (59.6)
Some problem	8 (14.8)	48 (50.5)	9 (75.0)	65 (40.4)
Extreme problem	0	0	0	0
Self-care, *n* (%)				
No problem	53 (98.1)	92 (96.8)	8 (66.7)	153 (95.0)
Some problem	1 (1.9)	3 (3.2)	4 (33.3)	11 (5.0)
Extreme problem	0	0	0	0
Usual activities, *n* (%)				
No problem	49 (90.7)	76 (80.0)	6 (50.0)	131 (81.4)
Some problem	5 (9.3)	18 (18.9)	6 (50.0)	29 (18.0)
Extreme problem	0	1 (1.0)	0	1 (0.6)
Pain/discomfort, *n* (%)				
No problem	33 (61.1)	36 (37.9)	4 (33.3)	73 (45.3)
Some problem	20 (37.0)	55 (57.9)	7 (58.3)	82 (50.9)
Extreme problem	1 (1.9)	4 (4.2)	1 (8.3)	6 (3.7)
Anxiety/depression, *n* (%)				
No problem	48 (88.9)	76 (80.0)	9 (75.0)	133 (82.6)
Some problem	6 (11.1)	19 (20.0)	3 (25.0)	28 (17.4)
Extreme problem	0	0	0	0

among persons with haemophilia. Optimally, the decision on treatment should be based on the trade-off between costs and gains from alternative treatment options and use advice in clinical guidelines. However, real-world practice clinicians adapt to the presence of limited information on all relevant aspects and use experience in clinical decision making. There is a growing demand for evidence from daily practice and register-based studies such as the KAPPA are among the best sources of such data. Based on the results of this study, onset of prophylaxis early in life maintains high utility and low HJHS to the fifth decade of life. Medium to high HJHS were associated with reduced utility among study participants and the regression analyses showed that the HJHS was the only statistically significant factor impacting health utility.

Table 3. Assessing correlates of EQ-5D utilities using ordinary least square regression analysis.

	Complete data, Coef. (95% CI) (*n* = 134)	Imputed data, Coef. (95% CI) (*n* = 161)
Age		
15–29 (ref)	–	–
30–44	0.04 (−0.06, 0.15)	0.02 (−0.06, 0.11)
45–59	0.06 (−0.07, 0.19)	0.07 (−0.06, 0.19)
≥60	0.17* (0.02, 0.32)	0.14 (−0.02, 0.30)
Haemophilia Joint Health Score		
0 (ref)	–	–
1–5	−0.06 (−0.13, 0.02)	−0.01 (−0.11, 0.08)
6–15	−0.10 (−0.21, 0.01)	−0.08 (−0.20, 0.04)
16–25	−0.17** (−0.28, −0.06)	−0.18** (−0.30, −0.06)
26–35	−0.24** (−0.40, −0.09)	−0.21** (−0.36, −0.06)
>35	−0.40*** (−0.51, −0.28)	−0.37*** (−0.52, −0.23)
Treatment history		
Primary started ≤3 years age (ref)	–	–
Prophylaxis started >3 years age	0.03 (−0.04, 0.10)	0.02 (−0.05, 0.09)
Episodic treatment	−0.02 (−0.14, 0.10)	−0.02 (−0.15, 0.11)
Inhibitor history		
Negative (ref)	–	–
Positive	0.06 (−0.03, 0.16)	0.03 (−0.05, 0.12)
Concomitant disease		
No (ref)	–	–
Yes	−0.08 (−0.17, 0.01)	−0.04 (−0.12, 0.04)
Education level		
Academic level (ref)	–	–
Non-academic education	0.01 (−0.06, 0.08)	−0.02 (−0.05, 0.10)
Body mass index		
18.5–24.99 (ref)	–	–
<18.5	−0.12 (−0.37, 0.13)	−0.02 (−0.24, 0.21)
25–29.99	−0.02 (−0.09, 0.05)	−0.01 (−0.07, 0.06)
≥30	0.06 (−0.02, 0.15)	0.06 (−0.03, 0.14)

CI, confidence interval.
We adjusted for the country of residence in crude and adjusted models.
*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$.

Estimated health utilities

Our utility estimates for episodically treated adults were comparable to those reported by Noone *et al.* [23,24] in two international studies in 2011 (0.720) and 2013 (0.619). In the age group 30–44 years, those on episodic treatment had a higher median utility than those on prophylaxis started after age 3. This finding might be explained by reverse causality arising from switching those on episodic treatment to prophylaxis for their poor outcomes under episodic treatment and keeping those with milder bleeding phenotypes on the episodic treatment [25]. Evidence remains scarce on the natural history and outcomes of individuals with severe haemophilia treated episodically although the randomized, prospective, joint outcome study clearly showed a better outcome with use of prophylaxis compared to a modern, and even strengthened, protocol for treatment on-demand [26]. In the setting of the current study (Sweden, Norway and Denmark) episodically treated patients with severe haemophilia are quite rare.

Treatment assignment in observational data is likely to be linked to unmeasurable factors of disease severity. For example, the late prophylaxis group includes PWH on tertiary prophylaxis who were placed on the regimen because of poor joints and frequent bleeding indicating the presence of a more severe phenotype compared to those who remained on episodic treatment. While secondary or tertiary prophylaxis cannot repair the established joint damage, it can prevent further bleeding, especially in target joints [27–29]. As reported among patients with inhibitors, reduction in joint bleeding decreases pain, loss of time at work/school and mobility restrictions and consequently improves HRQOL [30]. It is the case, however, that

patients with current inhibitors do have a markedly reduced HRQOL [31] and a different prophylaxis experience. We did not include patients with current inhibitors in our study because this group could bring heterogeneity into the sample for their different treatment and curtailed outcomes.

Among those treated with early prophylaxis health utilities were similar between the age groups 15–29 and 30–44. According to our results, half of those with early prophylaxis did not report reduced health utility up to the fifth decade of life. The health utility among the age group 15–29 on early prophylaxis exceeded the estimates from a previous Dutch-Swedish comparative study [32] and the investigation by den Uijl *et al.* [33] both of which examined patients with severe haemophilia.

Our participants' domain-specific EQ-5D results were better than those observed in the study by Kodra *et al.* [34]. Similar to their findings, however, mobility and pain/discomfort were the two most affected EQ-5D domains in our study. In contrast to the results from Kodra *et al.*, self-care and anxiety/depression were not severely affected in our study. However, this finding was in agreement with a previous observation [11].

Correlates of utilities

Analysis of the HRQOL outcomes of haemophilia treatment is complicated and requires inclusion of information on numerous clinical and demographic characteristics of patients [10]. In addition, the relatively short duration of availability of some treatments and the evolving quality of factor products and regimens makes the comparison of outcomes across treatments and age groups difficult, if not impossible. In addition to HJHS, we investigated several potential correlates of utilities in the multivariate regression model including age, treatment history, inhibitor history, education level, and concomitant diseases. Except for age, and in only one age group, none of the covariates were significantly associated with utility after adjusting for HJHS.

Age has been reported to be associated with declining utility in previous studies on PWH [12] and from the general population [35,36]. In our regression model we controlled for variables that may be associated with increasing burden of haemophilia with age including HJHS and age at start of prophylaxis as a proxy for cumulative burden, and the remaining age effects may be less clear cut. In addition, in haemophilia there may be a healthy survivor effect and adaptation to the disease in mid age whereas adolescents and young adults may struggle more with being disease related impairments in comparisons to people of the same age.

In their study, Fischer *et al.* [37] recently reported clinically important and statistically significant reduction of utilities among adult persons with severe haemophilia and Pettersson scores (PS) >21. In our study, the EQ-5D utility was negatively correlated with HJHS; however, only the HJHS scores above 15 reached statistical significance. As noted earlier in the discussion, pain/discomfort and mobility reduction were the two main sources of worsening utility in this study. These attributes may reflect on joint problems but also on other conditions not necessarily related to haemophilia *per se* such as low back pain due to muscle strain or nerve root compression. Early joint damages which do not affect these attributes are less likely to reduce utilities. Identifying a cut-off for HJHS that would distinguish those with reduced utilities is of clinical importance. However, since detectable joint damage is generally irreversible, and may progress, intensifying treatment below such a cut-off should be considered.

Inhibitors to clotting factor can affect HRQOL through more frequent bleeding into joints, the subsequent joint damage and the extensive treatment to resolve them [31]. There is limited evidence on health utility among those with positive inhibitor history. Our data may suggest that eradication of an inhibitor can potentially minimize or even reverse its negative impact on patient HRQOL. However, as only a small number of patients with a positive history but no current inhibitor were included in our study, this observation might have resulted from the lack of sufficient statistical power.

There is evidence suggesting that persons with haemophilia and positive HIV and or HCV may experience reduced HRQL [38,39]. Due to the limited number of participants positive for HIV/HCV in our study, we could not enter HIV/HCV status independently in the multivariate regression analysis. In our future reports using the entire KAPPA register cohort we may obtain sufficient number of participants with HIV/HCV to assess association of those conditions with EQ-5D utility.

There were some limitations to our study. First, historical data on type of prophylaxis regimens, number and type of bleeding episodes and treatment compliance were not available. Based on prior research, treatment compliance is expected to be high in the setting of this study [40]. Some differences in definition and dosing of prophylaxis, particularly in past decades, are likely across participating HTCs. Second, the statistical analysis of EQ-5D data is complicated due to its ceiling effects, heteroscedasticity and non-normal distribution [41]. Some of these problems apply to HJHS data as well. To address those issues, we categorized HJHS and reported CIs for the regression model with robust standard errors. Third, the HJHS instrument has been designed and validated for use among children. Fourth, for a limited number of participants who did not have HJHS or EQ-5D

reports at enrolment we included the assessment results from the first follow-up visit. Fifth, we used EQ-5D-3L because it had language translations and tariffs required across our study countries during the launch of KAPPA project. While it may be argued that the updated version EQ-5D-5L is more sensitive and could pick up smaller differences in utilities between subjects, the vast majority of studies published to date are based on EQ-5D-3L. The results reported here are more straightforward to be compared with other published work. Lastly, participants enrolled in this study might not be fully representative of all patients with severe haemophilia in their respective centres possibly due to higher likelihood of the inclusion of more compliant patients (selection bias).

Conclusion

This study confirmed previous reports on the significance of the impact of joint manifestations on HRQOL among PWH. In fact, moderate to severe joint manifestations were the only statistically significant correlates of utilities in this study. Moreover, the study showed that a substantial proportion of those on prophylaxis maintained healthy joints and high health utility for several decades of their life. However, it is important to note that a considerable proportion of adults with severe haemophilia who received episodic treatment or began prophylaxis later in life have impaired joints and HRQL. The treatment and monitoring of outcomes in this group should be intensified.

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Disclosures

M.O. has received speaker/consultant fees from NovoNordisk and Bayer AG. F.B. has received honoraria as a member of an advisory board and/or speaker from Shire, NovoNordisk, Sobi, Pfizer, Bayer AG. L.H. has served on the advisory boards of Bayer Healthcare, Pfizer, Sobi, and NovoNordisk. L.H. has also received investigator payments for clinical trials from NovoNordisk and Bayer Healthcare. S.R. works for Bayer AG. E.B. has acted as a paid consultant to Bayer AG and has received funding for research carried out in this work. All authors declared that they had no conflict of interest in relation to the findings of this study.

Authorship

F.B., M.H., P.A.H., L.H., J.A., and E.B. contributed with inclusion of participants in the KAPPA register; M.O., K.S.C., S.R. and E.B. designed the study; M.O. and K.S.C. designed the statistical analysis; M.O. carried out the statistical analysis and drafted the manuscript; all authors contributed in the interpretation of results and process of writing; all authors have read and approved the final version of manuscript.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Numbers and proportions reporting levels within EQ-5D dimensions presented by age and treatment history.

Paper III

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ORIGINAL ARTICLE

Comparative burden of arthropathy in mild haemophilia: a register-based study in Sweden

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Introduction: Mild haemophilia is a congenital bleeding disorder affecting males. The burden of arthropathy in mild haemophilia has not been comprehensively described. **Aim:** The aim of this study was to compare the incidence, age at diagnosis and surgery for arthropathy and related hospitalizations between people with mild haemophilia and the general population in Sweden. **Methods:** This was a register-based cohort study. Eligible participants were those with mild haemophilia born between 1941 and 2008 and a randomly selected, birthdate and sex-matched comparison group from the general population. Follow-up was from birth (or earliest 1984) until death, emigration or end of the study in 2008. Data on arthropathy were obtained from a national patient register. Negative binomial and competing risk regression and Kaplan–Meier estimate curves were used in the analysis. **Results:** Overall, 315 people with haemophilia and 1529 people in the comparison group were included. Participants with haemophilia born between 1984 and 2008 had a ninefold (95% CI: 3.3–27.2) and 16-fold (95% CI: 6.7–36.5) increased incidence of arthropathy-related hospital admission and arthropathy diagnosis respectively. None in this cohort underwent surgery. Among participants with haemophilia born prior to 1984, the rates of arthropathy diagnosis and surgery of the index joints (knee, elbow, ankle) were increased twofold (95% CI: 1.0–3.2) and fivefold (95% CI: 1.7–17.8) respectively. **Conclusion:** Our data suggested a higher burden of arthropathy among individuals with mild haemophilia compared to the general population. Further research should investigate the need for targeted joint screening programmes among individuals with mild haemophilia.

Keywords: follow-up studies, haemophilia A, haemophilia B, joint diseases, orthopaedic procedures, outcome assessment

Introduction

Mild haemophilia is an X-linked bleeding disorder characterized by a blood coagulation factor (CF) VIII/IX level of >0.05–0.40 kIU L^{-1} [1]. People with mild haemophilia (PWMH) experience sporadic trauma-related bleeds. Compared to those with moderate or severe haemophilia, PWMH are less likely to receive an early diagnosis of haemophilia and an appropriate treatment [2]. Moreover, less frequent clinical evaluations have been recommended for this group than for those with severe haemophilia [3]. Additionally, less research has been conducted on this population, resulting in a scarcity of evidence regarding many aspects of this phenotype including its natural history and comorbidities [4].

Arthropathy is a major determinant of health-related quality of life (HRQL) [5–7]. Frequent joint bleeding in the absence of effective treatment can promote the onset of arthropathy. This multifactorial process includes degenerative cartilage-mediated and inflammatory synovium-mediated components [8]. Among individuals with haemophilia, arthropathy is referred to as chronic arthropathy or haemophilic arthropathy. Age, sex, obesity and joint-related factors

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including injury and abnormal loading of joints have been proposed as important determinants of arthropathy [9]. However, receiving an arthropathy diagnosis or surgery among PWMH depends somewhat on healthcare system-related factors such as: frequency of healthcare visits, a clinician's decision to further evaluate joint status and the outcome of risk–benefit analysis for performance of joint surgery.

Although clinically evident joint bleeds, the main cause of arthropathy, are considered to be rare in mild haemophilia, few studies have reported unexpectedly high prevalence of joint disease among PWMH [5,10–12]. Those studies, however, had some limitations: lack of control groups, examination of a limited number of joint diagnoses, small numbers of subjects and non-representative samples.

An estimated 43% of the haemophilia population in Sweden have mild haemophilia [13] and the ascertainment of mild haemophilia is reasonably good [4]. Availability of high-quality national registers allows the possibility of long-term follow-up of patients, providing the opportunity to study rare conditions and long-term outcomes in Sweden [14]. Using unique personal identification numbers, data on various aspects of health, treatment and care for the entire population are retrievable from these registers. This study assessed the comparative burden of arthropathy among PWMH compared to the general population in Sweden. The evaluation focused on the incidence of arthropathy and hospitalizations due to arthropathy and age at first diagnosis/surgery.

Materials and methods

The ethical review board of Lund University, Sweden approved this study (reg. number: 706/2008).

Study population

This was a register-based cohort study. Eligible participants were PWMH born between 1941 and 2008 and a sex and birthdate-matched comparison group with no congenital bleeding disorders randomly selected from the general population. Participants were permanent residents of Sweden and lived in the country for some period between 1984 and 2008. The definition of mild haemophilia was a clotting factor (CF) VIII/IX >0.05–0.25 kIU L^{-1} prior to 2001 and a CF VIII/IX >0.05–0.40 kIU L^{-1} from 2001 onwards [1]. We did not have individual-level data on CF levels for PWMH in this study. Based on year of birth, we divided the sample into two birth cohorts (BC). Participants from the BC1 and BC2 were born between 1941–83 and 1984–2008 respectively. The reason for this categorization was to separate those for whom we did not have follow-up from birth (BC2) from the remainder of the sample (BC1). During follow-up, the age of participants in BC1 ranged from 16 to 68 and in BC2, 1 to 25 years. The follow–up period began in 1984 or at participants' date of birth for those born after this year. Follow-up continued until participants emigrated, died or the end of study (December 2008).

Registers

The study investigators from haemophilia comprehensive care centres (HCC) in Gothenburg, Malmö and Stockholm identified PWMH using Congenital Bleeding Disorders Register in Sweden (CBDS register study) and their local records. These three HCCs provide care to all individuals with haemophilia in the country. The National Board of Health and Welfare of Sweden (NBHW) selected the comparison group from the Swedish population register. The data were pseudo-anonymized prior to delivery to the research team. A unique study ID was used to link the data across registers. We used the National Patient Register (NPR) as the data source for arthropathy diagnosis and surgery. The NPR contains national data on all inpatient and outpatient admissions [15]. The NPR began registration of inpatient hospitalizations in 1964, while outpatient registrations began in 2001. The inpatient and outpatient registrations in NPR achieved full coverage by 1987 and 2004 respectively. In the NPR, for each admission, it is possible to register up to six and 11 accompanying diagnoses and surgical procedures respectively. By year 1984 (the start of study follow-up), the coverage of inpatient registrations was over 97%. Additional information from other registers used in this study including: emigration, medical birth and death registers have been published previously [13] and are available on the web page of NBHW [16].

Data preparation and variable definitions

We used international classification of disease (ICD) codes to extract data from the NPR for arthropathy diagnoses and surgeries. The included ICD codes and their definitions are available in the results section. Most of the included diagnoses belong to the index joints (knee, elbow and ankle) and hip. We defined the following outcome variables: number of hospital admissions with a arthropathy diagnosis, number of arthropathy diagnoses/surgeries and age at first arthropathy diagnosis/surgery. To calculate the number of admissions for arthropathy, we only included those that identified this as the primary reason for admission. To calculate number of arthropathy diagnoses and surgeries, we included any ICD code, regardless of whether it was the primary or accompanying diagnosis or surgery. To exclude multiple referrals for the same diagnosis in calculation of number

of arthropathy diagnoses, we omitted repeated ICD codes for each participant.

Statistical methods and ethical considerations

The observed and relative frequencies for categorical variables and median and interquartile range (IQR) for quantitative variables were reported. We used Kaplan–Meier estimates curves to plot age at first arthropathy diagnosis and surgery. The independence of curves was evaluated using the log-rank test (LRT). Using negative binomial regression (NBreg), we estimated the incidence rate ratios (IRR) of hospital admissions (count variable) primarily for arthropathy diagnoses or surgeries [17]. With death and emigration considered as competing risk (CR) events, we performed competing risk Cox regression to estimate sub-hazard ratios (SHR) of arthropathy diagnosis and surgery. We adjusted for birthdate and the number of hospital admissions primarily for non-musculoskeletal diagnoses/surgeries in both NBreg and CR models. For quantitative estimates, the 95% confidence intervals (CI) were reported considering a *P*-value (*P*) <0.05 as statistically significant. Authors used STATA release 13.0 (StataCorp LP, College Station, TX, USA) for data analysis.

Results

Characteristics of participants

Overall, 1844 participants including 315 PWMH and 1529 in the comparison group were included in this study. Among PWMH, 239 (75.9%) and 76 (24.1%) had haemophilia A and haemophilia B respectively. The study collected 36 798 person-years of follow-up including 6366 and 30 432 person-years from PWMH and the comparison group respectively. In total, 660 (35.8%) of participants including 110 (35.6%) PWMH and 550 (36.0%) in the comparison group were followed from birth (≥1984). Duration of follow-up ranged from <1 to 25 years (median: 25 years, IQR: 16.0–25.0). Death and emigration were the only reasons for loss to follow-up. Among PWMH and the comparators, 18 (5.7%) and 50 (3.3%) died during follow-up ($P = 0.036$) respectively. Five (1.6%) PWMH and 88 (5.8%) of the comparison group emigrated during follow-up ($P = 0.002$).

Age at first joint arthropathy diagnosis/surgery

In Fig. 1, we have presented the age at first arthropathy diagnosis using Kaplan–Meier survival estimate curves. Among PWMH, joint diagnosis rapidly increased from the age of 10. This can be compared to the age of 20 among those in the comparison group. By the age of 60 years, 50.0% of PWMH and 88.8% of those in the comparison group were living without arthropathy. Overall, PWMH received a joint diagnosis at earlier ages than their comparators ($P < 0.001$). The age at first joint surgery has been presented in Fig. 2. Based on this graph, until the age of 50, surgery is quite rare in both groups. From approximately 55 years, more frequent surgeries were experienced among PWMH than those in the comparison group. By the age of 60 years, 86.1% of PWMH and 96.0% of the comparison group were living without having had a arthropathy surgery. The difference in age at first arthropathy surgery between PWMH and their comparison group did not reach statistical significance ($P = 0.103$).

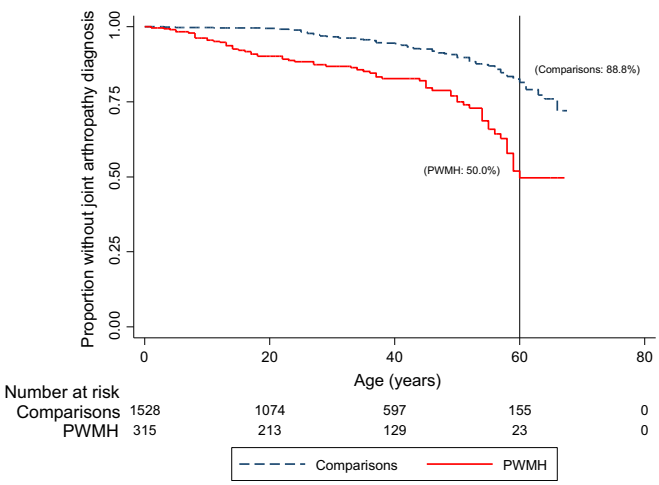

Fig. 1. Kaplan–Meier survivor function for age at first joint arthropathy diagnosis among people with mild haemophilia (PWMH) and the comparison group born 1941–2008. The vertical axis represents the proportion of participants remained without joint arthropathy diagnosis. [Colour figure can be viewed at wileyonlinelibrary.com].

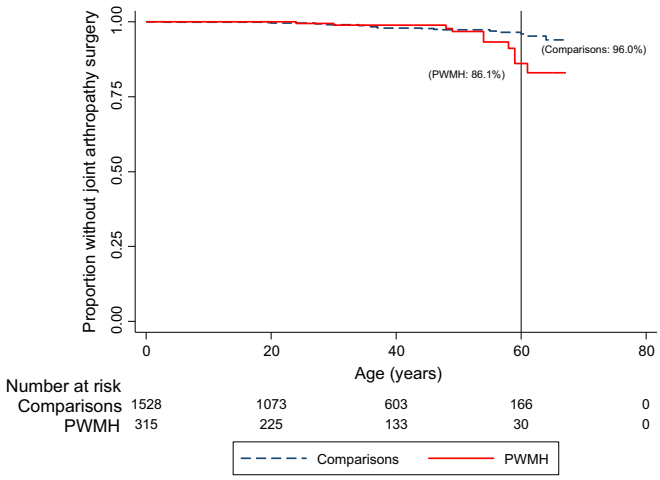

Fig. 2. Kaplan–Meier survivor function for age at first joint arthropathy surgery among people with mild haemophilia (PWMH) and the comparison group born 1941–2008. The vertical axis represents the proportion of participants remained without joint arthropathy surgery. [Colour figure can be viewed at wileyonlinelibrary.com].

Arthropathy diagnoses

During the observation period, 66 (20.9%) PWMH and 102 (6.7%) in the comparison group received at least one arthropathy diagnosis. In both birth cohorts for all selected arthropathy diagnoses, after adjusting for number of hospital admissions for non-musculoskeletal diagnoses, the hazard of arthropathy was higher among PWMH than the comparison group (Table 1). The sub-hazard of arthropathy diagnosis in both BC1 (SHR = 2.2, 95% CI: 1.6–3.1) and BC2 (SHR = 15.6, 95% CI: 6.7–36.5) was higher among PWMH. Looking at the index joints, in BC1, the hazard of arthropathy was nearly twofold among PWMH after adjustment (SHR = 1.8, 95% CI: 1.0–3.2). In BC2, only three participants (one of the PWMH and two in the comparison group) had an arthropathy diagnosis for an index joint. In this group, there was a twofold hazard of index joint surgery among PWMH (SHR = 2.0, 95% CI: 0.2–23.8).

The number (%) of each arthropathy diagnosis has been presented in Table 2. Among both PWMH and their comparators, 'other joint disorders-not elsewhere classified' (M25), 'internal derangement of knee' (M23, 717) and gonarthrosis (M17) were the most frequently registered joint diagnoses. PWMH did not have the following diagnoses: 'other and unspecified arthropathies' (716), synovitis, 'bursitis and tenosynovitis' (731), 'other diseases of joint' (738) and 'arthropathy due to other diseases classified elsewhere' (M14).

Arthropathy surgeries

There was no joint surgery performed among those from BC2. In BC1, 10 (4.9%) and 25 (2.5%) of PWMH and comparisons had at least one joint surgery respectively. In BC1 the hazard of surgery of the index joints was fivefold among PWMH (SHR: 5.6,

Table 1. Sub-hazard ratio (SHR) estimates for joint arthropathy diagnosis and surgery in people with mild haemophilia (PWMH) in relation to comparison group stratified by birth cohort (BC).

	BC1*, SHR (95% CI; PWMH = 205 and comparisons = 979)		BC2†, SHR (95% CI; PWMH = 110 and comparisons = 550)	
	Crude	Adjusted‡	Crude	Adjusted‡
Joint arthropathy diagnosis				
Index joints§	1.9 (1.1–1.4)	1.8 (1.0–3.2)	2.5 (0.2–29.3)	2.0 (0.2–23.8)
All included diagnoses	2.4 (1.7–3.4)	2.2 (1.6–3.1)	18.2 (7.8–42.4)	15.6 (6.7–36.5)
Joint arthropathy surgery¶				
Index joints**	6.1 (1.9–19.8)	5.6 (1.7–17.8)	–	–
All included surgeries	1.9 (1.0–3.8)	1.8 (0.9–3.5)	–	–

*BC1 born 1941–83.
†BC2 born 1984–2008.
‡Adjusted based on the number of hospital admissions with a primary diagnosis of non-musculoskeletal diseases.
§Included joint arthropathy diagnoses: M17, M22, M23 and 717.
¶No one had joint arthropathy surgery in BC2.
**Included surgery codes: NCK, NGB, NGC, NHB, NHC, NHG, 842.

Table 2. Observed frequency (%) of joint diagnoses among people with mild haemophilia (PWMH) born 1941–2008 and birthdate and an age-matched comparison group.

ICD code*		PWMH (N = 315), n (%)	Comparisons (N = 1529), n (%)
713	Arthropathy associated with other disorders classified elsewhere†	3 (0.9%)	0
715	Osteoarthrosis and allied disorders	2 (0.6)	6 (0.4)
716	Other and unspecified arthropathies	0	2 (0.1)
717	Internal derangement of knee	3 (0.9)	6 (0.4)
718	Other derangement of joint	1 (0.3)	6 (0.4)
719	Other and unspecified disorder of joint	7 (2.2)	1 (0.1)
724	Internal derangement of joint	1 (0.3)	8 (0.5)
729	Other diseases of joint	2 (0.6)	3 (0.2)
731	Synovitis, bursitis and tenosynovitis	0	1 (0.1)
733	Diffuse diseases of connective tissue or other diseases of bone	1 (0.3)	2 (0.1)
738	Other diseases of joint	0	1 (0.1)
M13	Other arthritis	4 (1.3)	3 (0.2)
M14	Arthropathy due to other diseases classified elsewhere	0	1 (0.1)
M16	Coxarthrosis (arthrosis of hip)	4 (1.3)	8 (0.5)
M17	Gonarthrosis (arthrosis of knee)	12 (3.8)	22 (1.4)
M19	Other arthrosis	7 (2.2)	6 (0.4)
M20	Acquired deformities of fingers and toes	4 (1.3)	3 (0.2)
M22	Disorders of patella	2 (0.6)	4 (0.3)
M23	Internal derangement of knee	11 (3.5)	27 (1.8)
M24	Other specific joint derangements	2 (0.6)	7 (0.5)
M25	Other joint disorders, not elsewhere classified	26 (8.2)	17 (1.1)
M36	Systemic disorders of connective tissue in diseases classified elsewhere†	7 (2.2)	0

*Each individual may have more than one diagnosis.
†Includes haemophilic arthropathy diagnosis (M36.2).

Table 3. Observed frequency (%) of joint surgeries for people with mild haemophilia (PWMH) born 1941–83 and an sex and birthdate-matched comparison group.

Surgical intervention*		PWMH (N = 205), n (%)	Comparisons (N = 979), n (%)
830	Operations on joints and joint structures (arthrotomy, arthroscopy)	0	3 (0.3)
831	Operations on joints and joint structures (capsulotomy)	0	4 (0.4)
839	Other surgeries which refer to removal of joint structures	2 (1.0)	2 (0.2)
840	Arthroplasty of hip without using extrinsic material	0	0
841	Arthroplasty of hip with using extrinsic material	0	2 (0.2)
842	Reconstructive surgery of the ankle and knee joints	0	1 (0.1)
843	Reconstructive surgery of other joints	0	9 (0.9)
845	Arthrodesis	0	1 (0.1)
NCK	Surgeries of elbow or forearm	0	0
NFB	Hip plastic surgery	4 (1.9)	5 (0.5)
NFC	Secondary hip prosthesis/procedures	0	0
NGB	Arthrodesis of knee	4 (1.9)	2 (0.2)
NGC	Prosthesis for knee/patella	1 (0.5)	0
NHB	Prosthesis for ankle	0	0
NHC	Secondary prosthesis for ankle or other foot joints	0	0
NHG	Arthrodesis of ankle or other foot joints	1 (0.5)	1 (0.1)

*Each individual may have more than one recorded surgery.

95% CI: 1.7–17.8). Including all arthropathy surgeries, PWMH had almost a twofold increased hazard (SHR: 1.8, 95% CI: 0.9–3.5).

Examining specific types of joint surgeries, a greater diversity was observed among the comparison group than PWMH (Table 3). PWMH had only the following: 'other surgeries which refer to removal of joint structures' (839), 'hip plastic surgery' (NFB), 'arthrodesis of knee' (NGB), prosthesis for knee/patella (NGC) and 'arthrodesis of ankle or other foot joints' (NHG). Among the comparison group, the following were more common: 'reconstructive surgery of other joints' (843), 'operations on joints and joint structures – capsulotomy – ' (831) and 'hip plastic surgery' (NFB).

Hospital admissions due to arthropathy

Among those with at least one hospital admission for arthropathy, PWMH and the comparison group had a maximum of 13 and 10 admissions recorded. After adjusting for number of visits with a primary diagnosis of non-musculoskeletal diseases, PWMH from BC1 had about a twofold (IRR = 1.6, 95% CI: 1.0–2.4) and those from BC2 a ninefold (IRR = 9.4, 95% CI: 3.3–27.2) increased incidence rate of admissions for arthropathy diagnosis or surgery.

Discussion

To the best of our knowledge, this study is unique in that it examines a high proportion of a well ascertained and characterized national cohort of people with mild haemophilia with nearly three decades of follow-up. Moreover, it used a large random sample from the general population as the comparison group and a high-quality national patient register as a source of data on arthropathy diagnosis and surgery. These strengths may have addressed a number of the shortcomings of previous research on the burden of arthropathy in mild haemophilia.

People with mild haemophilia in their 20s already had a higher burden of arthropathy than their comparators in this study; a gap that became larger over the rest of their lives. The findings on arthropathy surgery showed that many of the arthropathy diagnoses did not necessarily result in surgical interventions. While surgery is an ultimate consequence of arthropathy diagnosis, many people suffer reduced mobility, joint pain and days lost from school or work due to frequent hospital admissions for arthropathy prior to that outcome. Such consequences have been shown

to have huge impacts on the health-related quality of life of people with haemophilia [18].

Although we covered a wider range of arthropathy diagnoses, our cohort with mild haemophilia seemed less affected by arthropathy than reported in the studies by Zhang *et al.* [12] (painful knees: 37.0%) and Ling *et al.* [10] (ankle arthropathy: 47.0%). However, our results were similar to a study conducted in Korea (chronic arthropathy: 16.1%) which also reported on a wide range of arthropathies [19]. Varied ages, treatment history and genetic factors [20] in the published literature make it difficult to compare findings across investigations. In addition, discrepancies in coagulation factor measurements from different laboratories and assays might have resulted in misdiagnosis of moderate vs. mild haemophilia in some settings. Finally, a wide range of CF levels and the numerous mutations resulting in mild haemophilia may explain its varying presentation and outcomes [21].

Having haemophilia almost always results in more comprehensive joint evaluations especially during the early years after diagnosis. Concerns of parents/guardians and clinicians regarding arthropathy risk may contribute to more intensive investigations for arthropathy-related symptoms among PWMH than in the general population. Additionally, hospital visits for reasons other than musculoskeletal diseases might result in an increased possibility of receiving a arthropathy diagnosis. Among the general population, on the other hand, having a chronic disease can increase the contact with the healthcare system and, as a result, the likelihood of being examined for other health issues. To address this possible source of bias, we adjusted our estimates for the number of hospital admissions with a primary non-musculoskeletal diagnosis.

We did not have primary healthcare (PHC) data in this study. PHC is the first level of contact of people with the healthcare system in Sweden. Some milder arthropathy diagnoses discovered in these centres may not be captured in the NPR. However, serious joint diagnoses in PHCs will eventually be referred to specialists for more detailed assessment and potentially needed interventions in hospitals, and consequently be included in the NPR. In a recent cohort study that analysed data collected from PHCs, 22.4% of men aged ≥45 from the general population had physician-diagnosed osteoarthritis [9]. PHC is an important complementary source of data on arthropathy diagnosis. At the time of this research, there was no national register for primary health data in the country.

Haemarthroses, especially spontaneous events, are considered to be rare in mild haemophilia [22]. Given the lack of clinically visible bleeding, subclinical bleeds have been suggested as a potential cause for development of chronic arthropathy in mild haemophilia [23]. On the other hand, the under reporting of bleeds, a common and serious issue among those with moderate and severe haemophilia, might be even more common in PWMH. In a study from the Netherlands, 11.0% of PWMH reported joint bleeds in the prior year [17]. Soucie *et al.* [24] found contradictory results obtained from bleeding history and clinical and radiologic evidence of arthritis in their study. Occurrence of haemarthroses and the impact of their treatment on preventing arthropathy in mild haemophilia remains to be investigated in future research.

Compared to PWMH, individuals in the general population are more likely to participate in joint destructive activities and rough sports (such as football) as well as perform heavy lifting, thereby increasing the risk of joint damage and bleeding. Fear of joint bleeding in PWMH likely reduces such activities. That being said, PWMH with lifestyles similar to the general population might expect more joint manifestations or their occurrence at earlier ages. Nevertheless, further research is needed to investigate the extent to which PWMH restrict work, life and leisure to compensate for their increased vulnerability to joint bleeds and arthropathy.

This study had several limitations. First, the definitions of the selected codes, as well as the quality of the registration of codes in the NPR, have evolved over time. Use of ICD codes might have resulted in under estimation of frequency of diagnoses. Although we had data prior to 1984, to minimize probable differences in quality and coverage of registrations between PWMH and comparisons in the NPR, we limited the study observation period to after 1983. Second, those PWMH who emigrated or died before 1984 were not included in this study. The same, of course, was true among the comparison group. Thus, the enrolled cohort of PWMH and comparisons born prior to 1984 may not be fully representative of their original birth cohorts. Third, in analysing time to first joint diagnosis or surgery, arthropathy diagnoses/surgeries occurred prior to the observation period were ignored because valid data were not available for that period. For example, there was one recorded knee prosthesis while six participants underwent knee arthrodesis. Arthrodesis is performed if knee prosthesis fails. Fourth, immigrants were not excluded from the study. They are an estimated 10% of the population of Sweden. Arthropathy diagnoses or surgeries occurring prior to registration in the population would not be captured through the NPR. By controlling for the number of hospitalizations, we have substantially reduced the impact of this issue on the results. Fifth, the possibility of misdiagnosis of moderate haemophilia as mild – especially around cut off levels due to discrepant assays – cannot be ruled out.

Finally, while we controlled for age, sex and frequency of hospital admissions, we did not have data to control for other determinants of joint health including physical activity, joint trauma, body mass index and genetic factors.

Conclusion

Our findings indicate that arthropathy imposes a burden on people with mild haemophilia early in life through frequent hospitalizations and, later on, because of higher risk of surgery for the index joints. Further research is needed to investigate whether targeted screening programmes are needed and how they should be defined for those with mild haemophilia. Such screening programmes need to be evaluated with reference to preventive actions and the options available for treatment of damaged joints in mild haemophilia.

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Authorship: F.B., M.H., J.A. and E.B. contributed with inclusion of PWMH; K.K. and E.B. designed the study; M.O., S.L. and K.S.C. designed the statistical analysis; M.O. contributed in designing the study, carried out the statistical analysis and drafted the manuscript; all authors contributed in process of writing the manuscript and have read and approved its final version.

Disclosures

K.K. and S.L. were employees of Novo Nordisk during the time of this research. F.B. has received honoraria as member of advisory board and speaker from Shire, NovoNordisk and Pfizer. All authors declared that they had no conflict of interest in relation to the findings of this study. The authors received funding from Bayer, NovoNordisk, ALF, Region Skåne and Lund University for this study.

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Appendix 1. List of arthropathy diagnoses and surgeries included in this study.

	ICD X	Description	ICD VIII/IX	Description
Arthropathy diagnosis	M13	Other arthritis	713	Arthropathy associated with other disorders classified elsewhere*
	M14	Arthropathy due to other diseases classified elsewhere	715	Osteo-arthrosis and allied disorders
	M16	Coxarthrosis (arthrosis of hip)	716	Other and unspecified arthropathies
	M17	Gonarthrosis (arthrosis of knee)	717	Internal derangement of knee
	M19	Other arthrosis	718	Other derangement of joint
	M20	Acquired deformities of fingers and toes	719	Other and unspecified disorder of joint
	M22	Disorders of patella	724	Internal derangement of joint
	M23	Internal derangement of knee	729	Other diseases of joint
	M24	Other specific joint derangements	731	Synovitis, bursitis and tenosynovitis
	M25	Other joint disorders, not elsewhere classified	733	Diffuse diseases of connective tissue or other diseases of bone
	M36	Systemic disorders of connective tissue in diseases classified elsewhere*	738	Other diseases of joint
Arthropathy surgery	NCK	Surgeries of elbow or forearm	830	Operations on joints and joint structures (arthrotomy, arthroscopy)
	NFB	Hip plastic surgery	831	Operations on joints and joint structures (capsulotomy)
	NFC	Secondary hip prosthesis/procedures	839	Other operations which refer to removal of joint structures
	NGB	Arthrodesis of knee	840	Arthroplasty of hip without using extrinsic material
	NGC	Prosthesis for knee/patella	841	Arthroplasty of hip with using extrinsic material
	NHB	Prosthesis for ankle	842	Reconstructive surgery of the ankle and knee joints
	NHC	Secondary prosthesis for ankle or other foot joints	843	Reconstructive surgery of other joints
	NHG	Arthrodesis of ankle or other foot joints	845	Arthrodesis

*Includes: haemophilic arthropathy diagnosis.

Paper IV

Joint disease among carriers of hemophilia

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Key points

1. Carriers of hemophilia experience a higher burden of joint disease than the female general population in Sweden
2. Further investigation of bleeding as a potential determinant of joint disease among carriers of hemophilia is recommended

Abstract

Introduction

Carriers of hemophilia A or B are women with one impaired clotting factor VIII/IX gene that potentially increases their risk of bleeding. Evidence describing long-term outcomes including joint disease among this group is scarce.

Aim

To assess the burden of joint disease among carriers of hemophilia compared to the general female population in Sweden (comparisons).

Methods

In this register-based study, participants were carriers of hemophilia and an age and sex-matched sample from the general population. We identified carriers through hemophilia treatment centers and the National Patient Register. Comparisons were identified through the Swedish population register. Data on joint diagnoses and surgeries were retrieved from the National Patient Register. The period of observation began in 1987 and ended in 2008. We analyzed the data using Kaplan-Meier curves, and Mantel-Cox regression.

Results

The study included 561 carriers of hemophilia and a comparison group of 2,684. Overall, carriers had an approximate 2.0-fold (95% CI: 1.3, 2.7) and 1.5-fold (95% CI: 1.1, 2.0) greater incidence of diagnoses in index joints and non-index joints, respectively, compared to comparisons. Carriers underwent surgery for the index joints at earlier ages than comparisons. The rates of in-patient and out-patient hospitalizations for joint disease were 2.1-fold (95% CI: 1.5, 2.8) and 1.6-fold (95% CI: 1.4, 1.9) higher among carriers than comparisons, respectively.

Conclusion

This study suggests that carriers of hemophilia experience a higher burden of joint disease than the general population. Screening of carriers for early symptoms can aid in prompt diagnosis and prevention of progressive joint damage.

Introduction

Carriers of hemophilia A or B (carriers) are women heterozygous for a defect in a clotting factor (CF) VIII/IX gene. The CF level in this group is likely 50% of that in the normal population, provided that the healthy chromosome is fully active [1], and it may vary between normal and low levels due to lyonization, in which a random suppression occurs in one of the two X chromosomes [2]. Many carriers are identified through their link to a person with hemophilia, while some are diagnosed due to their symptoms such as prolonged bleeding during menstruation or following abnormal coagulation lab studies. Today, many haemophilia treatment centers (HTCs) across the world provide carrier testing and genetic counselling for families of people with haemophilia.

Despite the traditional belief that carriers bleed rarely because they have normal hemostasis, there is evidence suggesting that carriers have increased risk of bleeding compared to non-carriers [3,4] which is weakly correlated with their clotting factor level [5]. Notably, even carriers with CF levels within normal ranges may have a high risk of bleeding. Serious bleeding symptoms often emerge at the start of menstruation or later in pregnancy and delivery. Bleeding and corresponding symptoms are associated with reduced health related quality of life (HRQL) [6] even among those carriers with normal CF levels [7]. Evidence is scarce regarding treatment practices, bleeding events and their consequences on the health and HRQL of carriers.

In Sweden, three HTCs provide specialized healthcare services to persons with bleeding disorders including carriers. The ascertainment of hemophilia is reasonably high [8] and the family investigation and genetic testing provided for persons with hemophilia increases the likelihood of early and more extensive coverage for diagnosis of carriers in Sweden. Carriers with new mutation/s may be diagnosed through CF assay testing following prolonged bleeding episodes or

prior/during invasive medical procedures. In general, very few carriers visit HTCs for treatment or follow-up in Sweden. Consequently, data on treatment and bleeding symptoms for this cohort is not fully available from that source.

The availability of high-quality national registers and a long tradition of national-level data collection on topics and disciplines including health care have made it possible to investigate rare health conditions and long-term outcomes in Sweden [9]. Using the available register infrastructures and data, we conducted this study to compare the burden of joint disease between carriers (of hemophilia) and women without bleeding disorders (comparisons) of the same age from the general population.

Methods

Participants and registers

In this retrospective longitudinal study, eligible participants were carriers of hemophilia A or B, born between 1941 and 2008, and living in Sweden. Carriers in this study were identified through their registered diagnosis in one of the HTCs or in the national patient register (NPR). Data on their diagnostic procedures, hemostasis laboratory test results or verification of genetic defect were not available for evaluation in this study. For each included carrier, we randomly selected up to five birthdate and sex-matched individuals from the Swedish population register to serve as the comparison group, referred herein as comparisons. We excluded carriers and their matches that emigrated or died prior to the start of observation.

We used the NPR as the source of data for joint diagnoses, surgeries and hospitalizations. The NPR contains records for all in-patient and out-patient hospital admissions in Sweden [10]. The registration of in-patient hospitalizations in

the NPR began in 1964 and reached full coverage in 1987, while out-patient registration began in 2001 and was completed in 2004. The NPR allows registration of up to six diagnoses and 11 surgical procedures for each admission. Additional information about registers used in this study are available on the web page of NBHW [10] and have been published previously [8,11].

The observation period began at the participants' date of birth, but earliest January 1987, and continued until they emigrated, died or the end of study (December 2008). This manuscript was prepared as part of a large register-based project to assess outcomes of the entire cohort of people with bleeding disorders in Sweden, for which approval from the ethical review board of Lund University, Sweden (reg. number: 706/2008) was received. As required by the ethical review board, we used the opt-out method to inform participants through advertising the study in mass media in Sweden.

Data preparation and variable definitions

Statistics of Sweden provided pseudo anonymized data for this study. A unique study ID was used to link data across registers. We used international classification of diseases (ICD) codes to extract data from the NPR for joint diagnoses and surgeries. A list of the included ICD codes and their definitions is presented in the Table S1. Three main outcome variables were defined: 1. age at first joint diagnosis/surgery, 2. incidence of joint disease diagnoses/surgeries, and 3. incidence of hospitalizations due to joint problems. Based on the affected joint, we categorized diagnoses and surgeries into those related to 1. an index joint, or 2. a non-index joint. Index joints included knees, elbows and ankles. The remaining joints including those of shoulders, wrists, fingers and toes were categorized as non-index joints. In estimating the incidence of joint disease and the age at first diagnosis, we included eligible ICD codes regardless of whether they were the primary or accompanying reason for that hospital visit. However, in estimating the

incidence of hospitalizations, only visits with a joint disease as the primary reason were included. For estimating incidence of diagnosis and surgery, participants were removed from the risk set upon receipt of the first registered joint diagnosis or surgery. The hospitalization was considered as a recurrent event and therefore participants remained in the risk set until they were lost to follow-up or the end of study. We used the following age categories for reporting age-specific estimates of burden of joint disease: 0-19, 20-39 and ≥40 years.

Statistical analysis

We used observed and relative frequencies to describe the categorical variables. To present quantitative variables, we used medians and inter quartile ranges (IQR). Using Kaplan-Meier estimates curves we presented and compared age at first joint disease/surgery between carriers and comparisons. The Wilcoxon-Breslow-Gehan test was used to evaluate the independence of the Kaplan-Meier estimates curves. We estimated the overall and age-specific incidence rate ratios (IRR) for mortality, emigration, joint diagnosis and related surgery, and hospitalizations using Mantel-Cox regression. For quantitative estimates the 95% confidence intervals (CI) were reported and a *P*-value (*P*) <0.05 considered as statistically significant. STATA release 13.0 (StataCorp LP, College Station, TX) was used for data analysis.

Results

Characteristics of participants

Overall, 561 carriers and 2,684 comparisons were included in the analysis. As presented in Table 1, among carriers 90 (16%) were aged 40-48 years (oldest group) at enrollment and 240 (33%) were under 20 years. In the entire cohort, only one of the subjects, a woman in the comparison group, was positive for HIV. Twenty (3.6%) carriers and 16 (0.6%) comparisons were positive for viral

hepatitis (P<0.001). Over 22 years of observation, this study accrued 11,537 and 54,687 person years of follow-up for carriers and comparisons, respectively. Death and emigration were the only reasons for loss to follow up. During the observation period, 26 (4.6%) carriers and 84 (3.0%) comparisons were lost to follow-up due to death (IRR: 1.8; 95% CI: 0.9, 3.5). On the other hand, 230 (8.2%) comparisons and seven (1.2%) carriers were lost to follow-up because they emigrated from the country (IRR: 0.4; 95% CI: 0.2, 1.1).

Table 1. Characteristics of participants.

	Carriers, n(%)	**Comparisons, n(%)**	***P***
Age at inclusion			
0-19	240 (42.8)	1,178 (43.8)	-
20-39	131 (41.2)	1,084 (40.4)	-
≥40*	90 (16.0)	423 (15.8)	-
Accrued person years per age groups	240 (42.8)		
0-19	2,702 (24.1)	13,228 (24.8)	-
20-39	4,276 (38.2)	20,188 (37.8)	-
≥40†	4,218 (37.7)	20,007 (37.4)	-
Overall	11196	53423	-
Human immunodeficiency virus (HIV)	0	1 (0.01)	0.647‡
Viral hepatitis (type B or C)	20 (3.6)	16 (0.6)	0.000‡
Emigrated	6 (1.1)	138 (5.1)	0.07§
Deceased	25 (4.5)	57 (2.1)	0.007§

(Total No. of participants: 561 carriers / 2684 non-carrier comparisons)

* Maximum age at inclusion was 48 years.

† Maximum age at study end was 68 years.

‡ *P* from Chi-squared test

§ *P* estimated using Mantel-Cox regression

Incidence of joint diseases

Over the observation period, 87 (15.5%) carriers and 230 (8.6%) comparisons had at least one joint diagnosis. Numbers (proportions) of specific joint diagnoses are listed in Table S2. The most common joint diagnoses among both groups were "other joint disorders, not elsewhere classified" (ICD X: M25), "gonarthrosis or arthrosis of knee" (ICD X: M17), and "internal derangement of knee" (ICD 9: 717, ICD X: M23). "Acquired deformities of fingers and toes" (ICD X: M20) was one of the top diagnoses among those in the comparison group (Table S2). There were five carriers with a diagnosis of "hemophilic arthropathy" or "systemic disorders of connective tissue in diseases classified elsewhere" (M36).

Overall, carriers had an approximate two-fold increased incidence of a diagnosis in an index joint (IRR: 1.9; 95% CI: 1.3, 2.7) and also increased risk in non-index joints (IRR: 1.5; 95% CI: 1.1, 2.0) compared to non-carriers (Table 2). Under age 20 years, carriers were more likely to have index joint diagnoses (IRR: 3.0; 95% CI: 1.0, 8.7). The incidence of non-index joint diagnosis, however, was similar among both groups in that age range (IRR: 1.1; 95% CI: 0.4, 3.0). Among those 20 and over, carriers showed a 50 to 80% increased incidence of index and non-index joint diagnoses than comparisons. The difference in the incidence of an index joint diagnosis was not statistically significant for age group 20-39 (IRR: 1.7; 95% CI: 0.8, 3.3). For all joints, carriers had a 1.6-fold increased risk of having a joint diagnosis than comparisons.

Table 2. Mantel-Cox based incidence rate ratio (IRR) of joint disease in carriers of hemophilia (carriers) in relation to comparison group (comparisons) stratified by age group.

Age (years)	Index joints, IRR (95% CI)	Non-index joints, IRR (95% CI)	All joints, IRR (95% CI)
0-19	**3.0** (1.0, 8.7)	1.1 (0.4, 3.0)	1.8 (0.9, 3.6)
20-39	1.7 (0.8, 3.3)	**1.6** (1.0, 2.7)	**1.7** (1.1, 2.6)
≥40*	**1.8** (1.1, 3.0)	**1.5** (1.0, 2.3)	**1.5** (1.0, 2.1)
Overall†	**1.9** (1.3, 2.7)	**1.5** (1.1, 2.0)	**1.6** (1.2, 2.1)

* Maximum age was 68 years.

† Pooled estimate across age groups adjusted for birthdate.

Incidence of joint surgeries

Over the observation period 18 carriers (3.2%) and 40 (1.5%) comparisons had a registered joint surgery. As shown in Table S3, "hip plastic surgery" (ICD X: NFB) was the most common procedure among both populations. In the entire non-carrier group, only one individual under the age of 40 had an index joint surgery. Among those under age 40, because of the rarity/lack of index joint surgery estimates of IRR could not be estimated. Consequently, the overall and all joints estimates in relation to these groups were skipped. Among those ≥40 years, carriers had 3.3-fold (95% CI: 1.4, 8.0) greater incidence of index joint surgeries than comparisons (Table 3). The rates of non-index joint surgery were not statistically different between carriers and comparisons aged 20-39 years (IRR: 2.1; 95% CI: 0.2, 22.9) and ≥40 years 1.6 (95% CI: 0.7, 3.8). For all joints, carriers 40 years and older had approximately twice (95% CI: 1.1, 3.9) the rate of surgical procedures than those in the comparison group.

Table 3. Mantel-Cox based incidence rate ratio (IRR) of joint surgery in carriers of hemophilia (carriers) in relation to comparison group (comparisons) stratified by age group.

Age (years)	Index joints, IRR (95% CI)	Non-index joints, IRR (95% CI)	All joints IRR (95% CI)
0-19	NE	0.8 (0.1, 6.9)	-
20-39	NE	2.1 (0.2, 22.9)	-
≥40*	**3.3** (1.4, 8.0)	1.6 (0.7, 3.8)	**2.1** (1.1, 3.9)
Overall†	-	1.5 (0.7, 3.2)	-

(Not estimated due to too few or no observations)

* Maximum age was 68 years.

† Pooled estimate across age groups adjusted for birthdate.

Age at first joint diagnosis and surgery

Using Kaplan-Meier estimates, Figure 1 presents the age at first joint diagnosis among carriers and comparisons from birth to 68 years. Overall, carriers were diagnosed with joint diseases at earlier ages (P<0.001). The graph shows an increasing gap beginning around age 15 and by age 60, 35% of carriers compared to 21% of comparisons had a joint diagnosis. Figure 2 presents the age at first joint surgery. Until the age of 40, surgery was rare in both groups. By the age of 60, approximately 8% of carriers compared to 4% in the non-carrier group underwent surgery. Overall, carriers were more likely to undergo joint surgery, and at earlier ages, than comparisons (P<0.01).

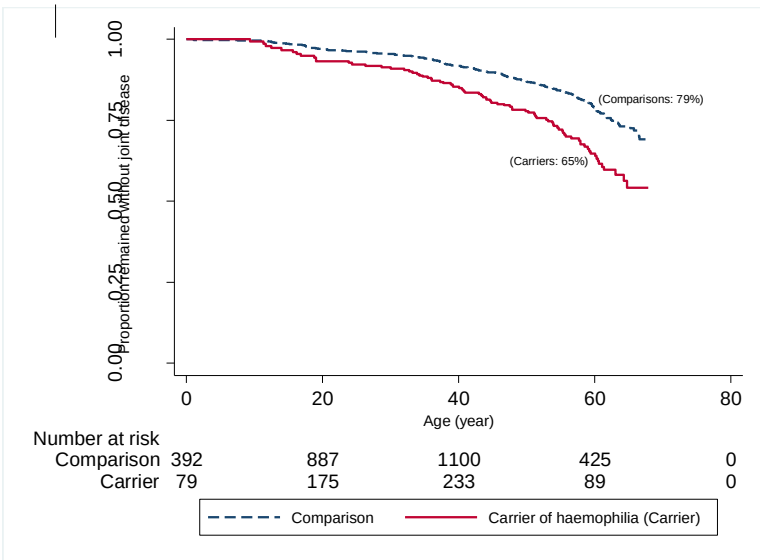

Figure 1. Kaplan-Meier curves for age at first joint disease diagnosis among carriers of hemophilia (carrier) and the comparison group born between 1941-2008.

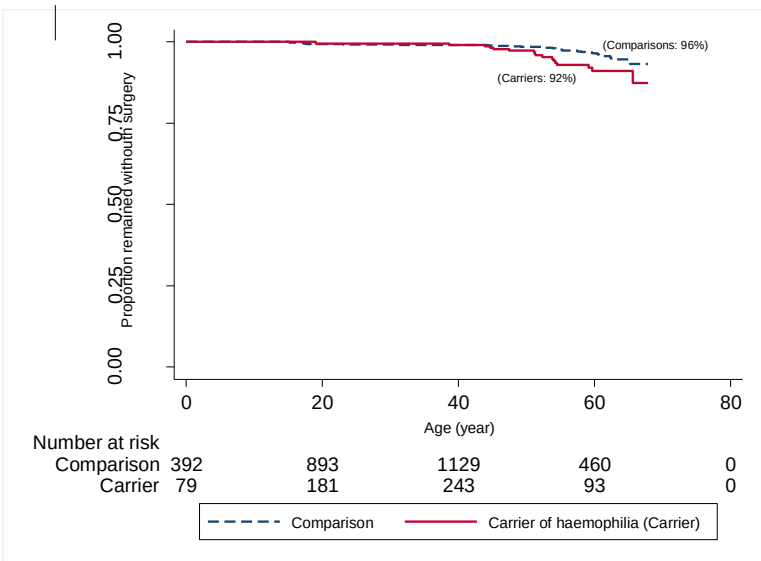

Figure 2. Kaplan-Meier curves for age at first joint surgery among carriers of hemophilia carriers (carriers) and the comparison group born between 1941-2008.

Hospitalizations due to joint diseases

Overall, carriers experienced higher inpatient (IRR: 2.1; 95% CI: 1.5, 2.8) and outpatient (IRR: 1.6; 95% CI: 1.4, 1.9) hospitalizations due to joint disease or surgeries than comparisons (Table 4). Under age 20 years, the incidence of hospitalizations due to joint problems was similar in both groups. Among those aged 20-39 and ≥40, however, carriers had statistically significant higher rates of hospitalizations.

Table 4. Mantel-Cox based incidence rate ratio (IRR) of hospitalization due to joint disease in carriers of hemophilia (carriers) in relation to comparison group (comparisons) stratified by age group.

Age (years)	Inpatient, IRR (95% CI)	Outpatient, IRR (95% CI)
0-19	1.1 (0.4, 3.3)	1.1 (0.5, 2.4)
20-39	**2.3** (1.4, 3.7)	**1.6** (1.1, 2.3)
40-68[†]	**2.1** (1.4, 3.2)	**1.7** (1.4, 2.1)
Overall*	**2.1** (1.5, 2.8)	**1.6** (1.4, 1.9)

[*] Pooled estimate across age groups adjusted for birthdate.

[†] Maximum age was 68 years.

Discussion

This investigation demonstrated that carriers of hemophilia experience a greater burden of joint diseases than a general population comparison group of women who were non-carriers. More specifically, carriers were more likely to get diagnosed with joint disease and undergo joint surgery at earlier ages. Our study had several unique features: it had a longitudinal design with an observation period of 22 years, it included a national cohort of carriers and a large random sample of women free from bleeding disorders as comparisons and, finally, it used the NPR as the source of data for occurrence of joint diseases, surgery and

hospitalizations. These unique features increase the validity and reliability of the results as well as the caliber of the evidence obtained by this analysis.

Evidence on bleeding events among carriers of hemophilia is scarce. We found five peer-reviewed original articles that reported on joint complications and bleeding among carriers [3,4,12-14]. In 2006, Plug *et al.* conducted a national survey and demonstrated a two-fold (95% CI: 0.9–3.7) increased risk of joint bleeds among carriers compared to comparisons [4]. In their paper, Plug *et al.* reported that carriers had increased risk of bleeding, especially following medical interventions. However, the authors hypothesized that the observed excess risk could be an effect of misclassification of superficial bleeding of tissue in the joint region.

Several years after the Plug *et al.* report, researchers from Vanderbilt University investigated joint range of motion (ROM) and magnetic resonance imaging (MRI) changes among carriers [12,13]. Sidonio *et al.*, using the Universal Data Collection (UDC) database [12], conducted a cross-sectional study comparing the joint range of motion (ROM) of 148 carriers with a historical sample of 303 comparisons. They reported that carriers from all age groups, including those under age 20, had reduced ROM compared to their healthy comparisons. In addition, the ROM gap between groups increased with decreasing clotting factor activity among carriers as their age increased. In the same year, Gilbert *et al.* also from Vanderbilt University reported that carriers with factor levels within normal ranges (0.41 IU/mL to 0.60 IU/mL) have MRI-detectable joint abnormalities [13]. The authors suggested that sub-clinical joint bleeding might explain the observed joint abnormalities. Finally, in 2015, Paroskie *et al.* compared the prevalence of clinically relevant bleeding between obligate carriers of hemophilia A and comparisons aged 18-60 years [3]. The study showed that the carriers had higher numbers of bleeding events than comparisons. Further, they reported a positive history of hemarthrosis for approximately 20% of carriers compared to 0% among comparisons.

Our study demonstrated that carriers are diagnosed with joint disorders at earlier ages than comparisons and those 20 years and older experience higher inpatient and outpatient hospitalizations for joint disorders than comparisons. Finally, our results showed that carriers aged 40-68 years had an approximate 3-fold increased incidence of surgery in their knees, elbows or ankles. Compared to the previous studies, our investigation was unique in that it included a national cohort with over two decades of follow up, a large random sample of comparisons drawn from the general population and, because of the use of the NPR, full population ascertainment of joint outcomes. These features greatly strengthen the level of evidence derived. Our results confirmed the findings of the previous studies with regard to increased risk of joint bleeds [3,4], reduced ROM and structural joint changes [12,13] among carriers.

The etiology of the greater frequency of joint diseases and the lower ages at their occurrence among carriers should continue to be investigated. It is very unlikely that trauma-related injuries could have biased our results towards observing increased risk. Rather, we believe that if carriers have similar lifestyles and activities as comparisons their rates of joint disease/surgery would increase due to more frequent hemarthrosis. In this study, we were unable to differentiate symptomatic from asymptomatic carriers, however, as the observed burden of joint disease was significantly greater among the overall carrier population compared to the general population comparison group of non-carriers, the effect size and clinical importance of preventable joint disorders is expected to be even higher among symptomatic carriers.

In a recent publication, our group demonstrated that males with mild hemophilia are at higher risk of arthropathy than the general population [11]. Persons with mild hemophilia <25 years age had a nine-fold (IRR: 9.4; 95% CI: 3.3, 27.2) increased incidence of hospitalizations due to joint disorders compared to the general population. In this study, carriers <20 years showed no increase in hospitalizations

for joint disorders. However over the age of 40, carriers demonstrated a higher risk of joint disorders and surgery than the general population similar to those with mild hemophilia. This may reflect missed opportunities in early assessment of joint status among carriers despite their vulnerability. Research is needed to understand the pathophysiology of structural joint changes and their determinants among carriers.

While evidence suggests that some carriers have an increased bleeding risk [3-5,12-14], as of this moment treatment and outcome monitoring of this group do not conform to modern hemophilia care in many settings. Carriers of hemophilia have a wide range of CF levels which overlap those of persons with mild as well as moderate to severe hemophilia. Likely due to factors such as insurance coverage, physicians' perceptions, the lack of evidence on clinical severity, and the carriers' own perception of their bleeding disorder, carriers have not been regularly followed up in HTCs. We did not have data on treatment among carriers in this study to allow us to investigate how it might have determined their risk of developing joint disease. Data are scarce with respect to treatment practices, type and frequency of bleeding events, and the long term outcomes of bleeding in this group. However, this practice is likely changing in some settings. As reported by Baker *et al*., the absolute number of carriers treated in HTCs across the US increased by 62% between 2002 and 2010 [15]. Similar to persons with hemophilia, carriers benefit from follow-up at HTCs for their bleeding and joint evaluation. Use of sensitive and available techniques, e.g. ultrasound [16], can help in early detection of soft tissue changes in the joints of carriers allowing the provision of treatment when needed.

Our study had some limitations. First, we could not investigate the difference in joint outcomes between carriers with lower and higher CF levels due to the lack of those data. Second, our study, like many other longitudinal observational studies, suffered from truncation. It was necessary to set the start of the investigation

period to the year that national patient register in Sweden reached full coverage (1987). Thus, it was not possible to investigate the occurrence of joint disease or surgeries since birth for those born before 1987. Third, about 10% of the population of Sweden are immigrants whose records of healthcare prior to immigration would not be included in the Swedish population register. Nor did we have the data to permit an adjustment of our analysis for their omission. Finally, we did not have information on other potential correlates/determinants of joint disorders including level of physical activity, participation in sports, or trauma. Symptomatic carriers, hypothetically, are likely to reduce their physical activity and participation in sports due to fear of bleeding which, in turn, may gradually affect joints by the development of osteoporosis, as has been observed among persons with hemophilia [17].

Conclusion

This study showed that carriers of hemophilia experience a higher burden of joint disease than the general female population in Sweden. Our results support and urge further investigation of joint comorbidities and bleeding risk among carriers. Research is needed to optimize treatment of carriers to ensure the maintenance of healthy joints throughout life. Screening to identify those at higher risk can help in providing early treatment where needed. The integration of such screening activities with ongoing hemophilia care programs may improve their feasibility.

Author contributions

E.B. proposed the research idea; E.B., M.O. and S.D. designed the study; F.B., M.H., J.A., and E.B. contributed with inclusion of carriers; M.O. performed the statistical analysis and drafted the manuscript; K.S.C. assisted with the statistical analysis; S.D., K.S.C., F.B., M.H., J.A., and E.B critically reviewed the paper and contributed to finalization of the manuscript; all authors have read and approved the final version of the manuscript prior to submission.

Conflict of interest

M.O. has received speaker/consultant fees from NovoNordisk, Shire and Bayer AG. F.B. has received honoraria as a member of an advisory board and/or speaker from Shire, NovoNordisk, Sobi, Pfizer, Bayer AG. E.B. has acted as a paid consultant to Bayer AG and has received funding for research carried out in this work. All authors declared that they had no conflict of interest in relation to the findings of this study.

Acknowledgement

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Appendix 1. List of arthropathy diagnoses and surgeries included in this study

	ICD X	Description	ICD VIII/IX	Description
Joint diagnosis	M13	Other arthritis	713	Arthropathy associated with other disorders classified elsewhere [a]
	M14	Arthropathy due to other diseases classified elsewhere	715	Osteo-arthrosis and allied disorders
	M16	Coxarthrosis (arthrosis of hip)	716	Other and unspecified arthropathies
	M17	Gonarthrosis (arthrosis of knee)	717	Internal derangement of knee
	M19	Other arthrosis	718	Other derangement of joint
	M20	Acquired deformities of fingers and toes	719	Other and unspecified disorder of joint
	M22	Disorders of patella	724	Internal derangement of joint
	M23	Internal derangement of knee	729	Other diseases of joint
	M24	Other specific joint derangements	731	Synovitis, bursitis and tenosynovitis
	M25	Other joint disorders, not elsewhere classified	733	Diffuse diseases of connective tissue or other diseases of bone
	M36	Systemic disorders of connective tissue in diseases classified elsewhere*	738	Other diseases of joint
Joint surgery	NCK	Surgeries of elbow or forearm	830	Operations on joints and joint structures (arthrotomy, arthroscopy)
	NFB	Hip plastic surgery	831	Operations on joints and joint structures (capsulotomy)
	NFC	Secondary hip prosthesis/procedures	839	Other operations which refer to removal of joint structures
	NGB	Arthrodesis of knee	840	Arthroplasty of hip without using extrinsic material
	NGC	Prosthesis for knee/patella	841	Arthroplasty of hip with using extrinsic material
	NHB	Prosthesis for ankle	842	Reconstructive surgery of the ankle and knee joints
	NHC	Secondary prosthesis for ankle or other foot joints	843	Reconstructive surgery of other joints
	NHG	Arthrodesis of ankle or other foot joints	845	Arthrodesis

* Includes: hemophilic arthropathy diagnosis

Appendix 2. Observed frequency (%) of arthropathy diagnoses among carriers of hemophilia (carriers) born between 1941-2008 and a sex and birthdate-matched comparison group (comparisons)

ICD code*	Description	Carriers (N= 561), n (%)	Comparisons (N= 2,684), n (%)
713	Arthropathy associated with other disorders classified elsewhere †	1 (0.2)	1 (0.1)
715	Osteo-arthrosis and allied disorders	2 (0.4)	8 (0.3)
716	Other and unspecified arthropathies	0	1 (0.1)
717	Internal derangement of knee	5 (0.9)	5 (0.2)
718	Other derangement of joint	0	2 (0.1)
719	Other and unspecified disorder of joint	3 (0.5)	5 (0.2)
724	Internal derangement of joint	6 (1.1)	19 (0.7)
729	Other diseases of joint	3 (0.5)	8 (0.3)
731	Synovitis, bursitis and tenosynovitis	0	0
733	Diffuse diseases of connective tissue or other diseases of bone	1 (0.2)	1 (0.1)
738	Other diseases of joint	1 (0.2)	1 (0.1)
M13	Other arthritis	8 (1.4)	17 (0.6)
M14	Arthropathy due to other diseases classified elsewhere	0	0
M16	Coxarthrosis (arthrosis of hip)	8 (1.4)	19 (0.7)
M17	Gonarthrosis (arthrosis of knee)	20 (3.6)	49 (1.8)
M19	Other arthrosis	5 (0.9)	15 (0.6)
M20	Acquired deformities of fingers and toes	10 (1.8)	36 (1.3)
M22	Disorders of patella	7 (1.2)	21 (0.8)
M23	Internal derangement of knee	19 (3.4)	34 (1.3)
M24	Other specific joint derangements	2 (0.4)	11 (0.4)
M25	Other joint disorders, not elsewhere classified	21 (3.7)	50 (1.9)
M36	Systemic disorders of connective tissue in diseases classified elsewhere†	5 (0.9)	0

* Each individual may have more than one diagnosis across rows.
† Includes hemophilic arthropathy diagnosis (M36.2)

Appendix 3. Observed frequency (%) of arthropathy surgeries among carriers of hemophilia (carriers) born between 1941-2008 and a sex and birthdate-matched comparison group (comparisons)

ICD code*	Description	Carriers (N=561), n (%)	Comparisons (N=2,684), n (%)
830	Operations on joints and joint structures (arthrotomy, arthroscopy)	1 (0.2)	1 (0.1)
831	Operations on joints and joint structures (capsulotomy)	0	0
839	Other surgeries which refer to removal of joint structures	0	2 (0.1)
840	Arthroplasty of hip without using extrinsic material	0	0
841	Arthroplasty of hip with using extrinsic material	2 (0.4)	3 (0.1)
842	Reconstructive surgery of the ankle and knee joints	1 (0.2)	0
843	Reconstructive surgery of other joints	0	6 (0.2)
845	Arthrodesis	0	2 (0.1)
NCK	Surgeries of elbow or forearm	0	0
NFB	Hip plastic surgery	9 (1.6)	17 (0.6)
NFC	Secondary hip prosthesis/procedures	0	0
NGB	Arthrodesis of knee	5 (0.9)	9 (0.3)
NGC	Prosthesis for knee/patella	2 (0.4)	1 (0.1)
NHB	Prosthesis for ankle	2 (0.4)	0
NHC	Secondary prosthesis for ankle or other foot joints	0	0
NHG	Arthrodesis of ankle or other foot joints	3 (0.5)	5 (0.2)

* Each individual may have more than one recorded surgery across rows.

Paper V

Surgery and survival in birth cohorts with severe haemophilia and differences in access to replacement therapy: the Malmö experience

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Running title

Joint surgery and survival in haemophilia

Keywords: haemophilia, factor VIII/IX deficiency, replacement therapy, treatment outcomes, joint surgery, survival, register-based study

Word count: 2266

Abstract: 248

References: 17

Table: 1

Figures: 4

Abstract

Background Persons with severe haemophilia require life-long replacement therapy, prophylaxis, to prevent bleeding. Data describing long term outcomes of prophylactic treatment are scarce. The aim of this study was to investigate joint surgery and survival among persons with severe haemophilia with special attention to access to prophylaxis in the early years of life.

Methods Eligible participants had severe haemophilia A or B and were treated at the Malmö centre from the 1960s onward. Time from birth until joint surgery was analysed for participants alive in 2000. We compared survival among the entire cohort with severe haemophilia treated at the Malmö centre with the general male population of Sweden and a sample of subjects with severe haemophilia from the United Kingdom (UK).

Results Overall, 167 participants were included, 106 (63.5%) of whom were also assessed for the occurrence of joint surgery. Among those born before 1970, 1970-79 and ≥1980 approximately 37%, 21% and 0% had their first joint surgery by age 30, respectively. There were no second joint surgeries reported in cohorts born ≥1970. Persons with severe haemophilia and negative for HIV treated in Malmö have attained approximately similar survival to that of the general male population in Sweden and live slightly longer than persons with severe haemophilia from the UK.

Discussion and conclusion Prophylaxis in Sweden, although costly, has markedly improved survival and joint outcomes for persons with severe haemophilia. This study highlights the importance of early start of replacement therapy to prevent or postpone serious joint damage.

Introduction

Haemophilia is an X-chromosome linked recessive bleeding disorder. Haemophilia A and haemophilia B refer to factor VIII and IX deficiencies, respectively. Persons with severe haemophilia have a clotting factor (CF) level <0.01 kIU/l^{-1} [1]. Spontaneous or trauma related bleeding can occur in the absence of efficient treatment resulting in pain, limits in mobility and reduced health related quality of life. Treatment consists of replacing the missing CF following bleeding (on-demand) or on a regular basis to prevent bleeding (prophylaxis). Prophylaxis was first introduced during the late 1950s in Sweden [2]. The aim was to prevent spontaneous haemorrhages by maintaining a CF level above 0.01 IU L^{-1}. The availability of clotting factor replacement product was a limitation during the first two decades following the implementation of prophylaxis – infusion frequency and dosing began at a low level and gradually increased to those recommended in modern haemophilia treatment. Since its inception, prophylaxis has evolved not only in Sweden but in other countries as well. Today there are a number of prophylaxis regimens varying in dose, injection frequency and/or age at initiation [3-5].

Recent generations of persons with haemophilia treated in the Malmö centre have received greater amounts of factor due to increased dose, frequency of infusions and a reduction in age at start of prophylaxis. Those who were born prior to the 1950s did not have access to prophylaxis during the early years of life, starting later in life and after experiencing multiple bleeding episodes. Their overall treatment, however, was superior to those treated on-demand for their entire lives. The majority of people with severe haemophilia born after the 1960s have had access to lifelong prophylaxis from early childhood. Between 1956 and 1976 for example, 10-20 IU/kg body weight of factor VIII was given at intervals of 4-10 days [6]. The same dose of factor IX was recommended for those with haemophilia B and was given every third day or twice weekly. Today, those with

haemophilia A infuse 20-40 IU/kg factor VIII every second day or three times weekly [5]. Persons with haemophilia B are treated with the same dose but with lower frequency. The current prophylaxis regimen has been available since early childhood only to those born in 1980 and onwards. Though the dose and injection frequency in prophylaxis have been modified (intensified and/or tailored) over the years, once started, the majority of persons with severe haemophilia in the Malmö centre have been maintained on "high-dose" prophylaxis for life. Age at the onset of prophylaxis has gradually decreased and is now generally around one year and before the occurrence of any joint bleed.

The method of prophylaxis in Sweden has clearly shown better results than the on-demand regimen used in Norway [7], however, it had limited advantages when compared with the intermediate-dose method employed in The Netherlands [5]. In a recent publication, our team reported cause specific mortality rates for the Swedish national haemophilia cohort [8]. The aim of the current study is to examine the impact of access to prophylaxis on occurrence of joint surgery among persons with severe haemophilia treated in the Malmö haemophilia treatment centre (HTC). In addition, we compared the survival of the Malmö cohort with that of the general male population of Sweden and a cohort of persons with severe haemophilia from the UK.

Methods

Study design and participants

This was a register-based longitudinal study. Eligible participants were living with severe haemophilia A or B (<0.01 kIU/l^{-1}) and had been treated in the Malmö centre between 1960 and 2008. We used the general male population of Sweden and a cohort of persons with severe haemophilia in the UK [9] as external comparison groups to investigate survival of participants in relation to access to treatment (different birth cohorts).

Registers

The Malmö register includes data for persons with bleeding disorders treated at the centre since 1980 [10]. The information has been collected by nurses, physiotherapists and physicians during routine visits and encompasses general health, socioeconomic status, treatment and clinical outcomes. Definitions of variables, coverage and the frequency and quality of registration have evolved over time. The register has been used for clinical decision making and research purposes.

The register of the UK Haemophilia Centre Director Organisation (UKHCDO) is one of the largest, and the oldest, haemophilia databases worldwide. We extracted data on the survival of persons with severe haemophilia from the database through a publication by Darby *et al.* [9]. That study included all persons with haemophilia who were registered in the UKHCDO from 1977 to 1998. Vital status was retrieved in 2000.

Variables and data extraction

Longitudinal clinical data on joint surgery available from the Malmö register for persons with severe haemophilia A and B with at least one registration between January 2000 and December 2009 were used for this study. For these persons we explored the association between availability of prophylaxis early in life and need for haemophilia related joint surgery later in life. Outcome was measured as number of years from birth to first and second joint surgery where the event was any of the following: knee plastic, arthrodesis, shoulder plastic surgery, hip replacement, and capitulum radii resection. The history of joint surgery was identified for persons with severe haemophilia without a history of inhibitor and who were alive in 2000.

Survival was defined as the time from birth to death observed between 1980 and 2000 for the Malmö cohort and between 1977 and 2000 for the UK cohort. We extracted data on survival of the general male population of Sweden from life

tables produced by Statistics of Sweden for the years 1951-1955 [11] and 2009 [12]. To examine long-term effects on survival of haemophilia treatment available at different points in time and at different stages of life for different birth cohorts, we also extracted and present data from a publication by Larsson *et al.* [13] on survival of persons with severe haemophilia in Sweden born before and after the introduction of prophylaxis.

Statistical analysis

Absolute and relative frequencies were reported. We used Kaplan Meier estimates curve to analyse age at joint surgery. The log-rank test was used for assessing equality of survival functions. We compared the occurrence of joint surgery between the following birth cohorts from the Malmö register: 1. <1970, 2. 1970-1979 and 3. ≥1980. We used Stata 13.0 (StataCorp LP, College Station, TX) for data analysis. P <0.05 was considered as statistically significant.

Ethics and patient permissions

The Ethical Review Board of Lund University (ERBLU) approved the study protocol. As endorsed by ERBLU, researchers published an opt-out announcement about the study in the newspapers.

Results

In total, 167 participants were included in the study. Of these, 106 (63.5%) were included in the assessment of joint surgery (Table 1). Within the observation period, 29 (17.4%) and 250 (18.9%) deaths were registered in the Malmö cohort and the UK cohort, respectively. The number of surgeries ranged from 0-4 with 74 (69.8 %) and 4 (3.8%) participants having zero and four joint surgeries, respectively. As shown in Figure 1, the age at first surgery differed substantially across birth cohorts (P < 0.05).

Table 1. Characteristics of persons with severe haemophilia from the Malmö register and the UKHCDO register *

	Malmö register, n (%)	**The UKHCDO register, n (%)**
Alive and residing in the country †	138 (82.6)	1013 (76.7)
Inhibitor	26 (21.5)	-
Undergone joint surgery	32 (30.2)	-
Died	29 (17.4)	250 (18.9)
Emigrated	0	14 (1.1)
Lost to follow-up	0	43 (3.2)
Total number of participants	167	1320

Joint surgery

Joint surgery was evaluated among 106 participants including 41 (38.7%), 14 (13.2%) and 51 (48.1%) born <1970, 1970-1979 and ≥1980, respectively. As shown in Figure 1, age at first procedure differed in the three cohorts (*P*=0.017). Among those born prior to 1970 and 1970-1979, about 37% and 21% had their first surgery by the age of 30, respectively. No participant born ≥1980 had had a joint surgery by the end of the study period.

None of the participants born after 1970 had a second surgery (Figure 2), in contrast to 18 (16.7%) of those born prior to 1970. By the age of 52, half of those born before 1970 had surgery on one or more joints. The differences between the three age cohorts did not reach statistical significance (*P*=0.214).

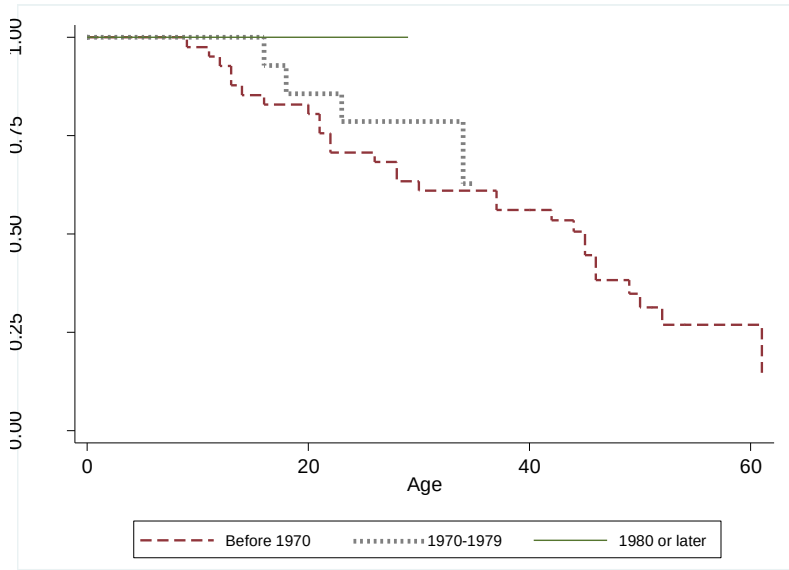

Figure 1. Kaplan-Meier survival function for age at first joint surgery among persons with severe haemophilia and negative for an inhibitor treated in the Malmö centre between 1980-2009.

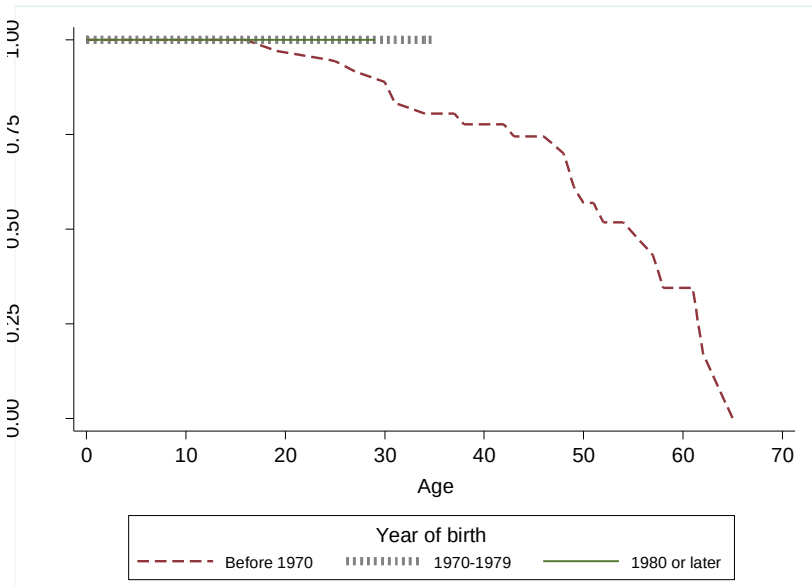

Figure 2. Kaplan-Meier survival function for age at second joint surgery among persons with severe haemophilia and negative for an inhibitor treated in the Malmö centre between 1980-2009.

Survival

Using data from a publication by Larsson *et al*. [13] survival of the population with haemophilia in Sweden 1941-1960 and 1961-80 and that of the general male population for the period 1951-1955 have been plotted (Figure 3). Before the introduction of factor replacement therapy, 35% of those with severe haemophilia died prior to age 20. This decreased to approximately 15% for those born between1960 and1980. In almost the same time period (1951-55), 5% of the general male population were younger than 20 years at time of death. In Figure 4, survival of persons with severe haemophilia registered in Malmö has been compared with that of the general male population of Sweden and the UK cohort with severe haemophilia.

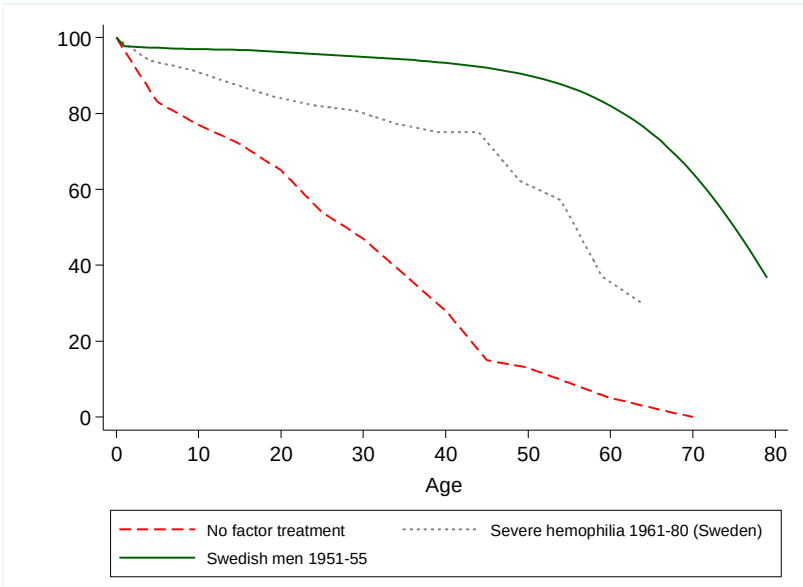

Figure 3. Trend of survival among persons with severe haemophilia born before factor replacement therapy (<1960), during the early years that factor replacement became available (1960-1980) *[13]* and for men from the general population of Sweden (1951-1955).

The Malmö cohort, including those with HIV, had similar survival compared to the UK cohort with those with HIV excluded. When only subjects with

haemophilia and negative for HIV are compared, the Malmö cohort demonstrates a better survival than the UK cohort. Among those negative for HIV, the median survival in the Malmö cohort and the UK cohort were 75 and 63 years, respectively. The median survival of the general male population of Sweden was 80 years.

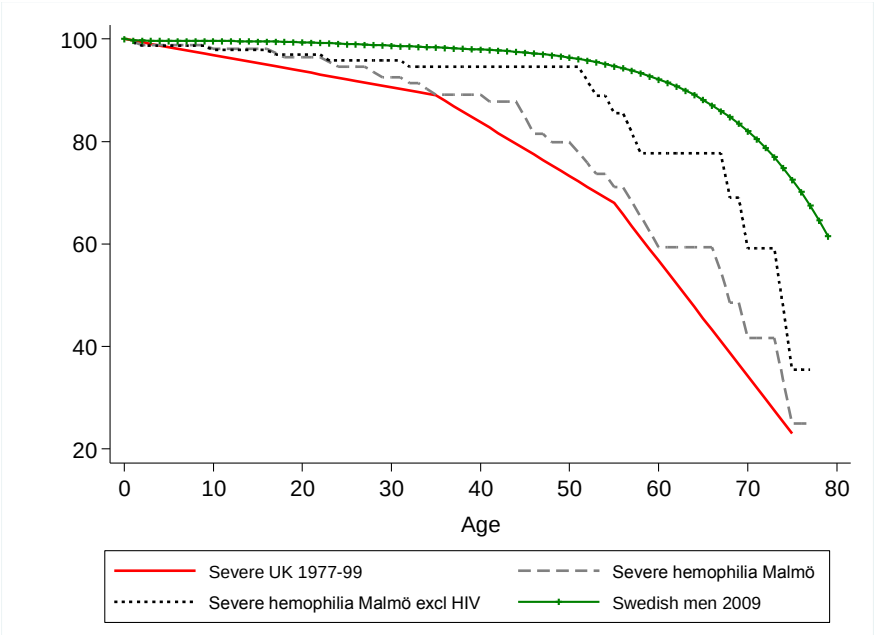

Figure 4. Comparison of survival between persons with severe haemophilia from Malmö (with and without HIV), persons with severe haemophilia and negative HIV status from the UK, and the general male population from Sweden (estimate from 2009).

Discussion

This study used the natural history of the introduction of prophylactic treatment at the Malmö haemophilia centre to describe the long-term effect of initiating and continuing prophylaxis at different stages in life. It showed that early access to

prophylaxis has protected joints against surgery for the first two decades of life in the Malmö cohort. In addition, this investigation revealed that persons with severe haemophilia and negative HIV status treated in this centre are approaching the life expectancy of the general population.

Maintaining musculoskeletal health, especially for the joints, has been one of the highest priorities in haemophilia treatment. Different levels of success in preserving joint health have been achieved through prophylaxis. Tailored prophylaxis in Canada, for example, is efficiently protecting joints for about four years [14].

Maintaining musculoskeletal health, especially for the joints, has been one of the highest priorities in haemophilia treatment. Different levels of success in preserving joint health have been achieved through prophylaxis. Tailored prophylaxis in Canada, for example, is efficiently protecting joints for about four years [14]. However, after eight years of treatment the probability of having intact joints among patients will be reduced by 20%. Adult patients on intermediate-dose — a method of prophylaxis practiced in The Netherlands — were reported to have seven to eight additional bleeding events compared to patients in Sweden [5]. Those in The Netherlands have also experienced more limitations in their daily activities compared to subjects in the Swedish cohort. While prophylaxis may not completely prevent orthopaedic surgery [3], it can postpone it, resulting in higher health related quality of life.

Having a second joint surgery was rare in the Malmö cohort. None of the participants born after 1970 had a second joint operated on by the age 30. These findings, when compared to those observed in the cohort born before 1970, and individuals born 1970-1980 with less likely or delayed access to prophylaxis,

reveals the outstanding effects of early start of this preventive measure. Oldenburg, *et al.,* conducted a longitudinal study with 28 years of follow-up and concluded that prophylaxis may not prevent joint damage in the long term [15]. We could not reject their hypothesis with data from this study. However, it should be noted that participants in the study by Oldenburg, *et al.*, started prophylaxis between the ages of one and 16 years. Established joint damage cannot be reversed by using prophylaxis in the later years of life.

Performing joint surgery today, with access to high quality factor concentrates, likely presents fewer difficulties compared to those encountered in the 1960s and 1970s. People may have waited longer for surgery than in current times. That being the case, the data shown in Figure 2 is not likely exaggerating the differences between birth cohorts. Based on the results observed in our oldest study group, the need for a second surgery began to increase between the age of 25 and 30. The youngest cohort, born after 1980 and on the current prophylactic regimen, did not reach that age by the end of the observation period.

Persons with severe haemophilia in The Netherlands and Italy have been reported to reach similar life expectancy as that of the general population [16, 17]. The median survival of the persons cared for in Malmö before replacement therapy became available (1941-1960) was 28 years [13]. For the periods 1981-1990, 1991-2000 and 2001-2008 the median survival of the population with haemophilia (all severities) in Sweden was reported as 45.6, 40.5 and 56.0 years, respectively [8]. While the Malmö cohort had a slightly better survival than the UK cohort, it has not yet reached similar life expectancy of the general male population of Sweden.

We cannot attribute all the achievements in increased survival solely to the success of prophylactic treatment. Other factors, such as improvement of social welfare,

better monitoring and evaluation, modern diagnostic tools, and additional support for patients may have contributed to these improvements as well.

This study had some limitations. In analysing joint surgery, we did not have access to high quality data for those who died prior to 2000 and, therefore, excluded them from the study. This might introduce a healthy survivor bias, however, we did not find any evidence that younger age at death, per se, could be associated with poorer joint outcomes. We did not directly control for each individual's history of treatment, but it is likely that the overall differences between levels of prophylaxis available during childhood and adolescence are more important than within cohort variation between individuals.

Despite its high costs, the prophylaxis provided in Sweden has demonstrated progressive improvements in survival and joint surgery for persons with severe haemophilia. This study highlights the importance of starting prophylaxis as early as possible in order to prevent or postpone serious joint damage along with a gradual movement towards equalizing life expectancy with the general population.

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Author contributions

EB and KSC proposed the research idea. KSC performed the statistical analysis. MO contributed in the analysis, interpreted the results and drafted the paper. JA,

EB and KSC read and commented on the drafted manuscript and contributed in developing the final version. All authors read and approved the final version of the manuscript prior to submission.

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Declaration of conflict of interest

Authors declare that they had no conflict of interest in relation to the findings and their interpretations in this paper.

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