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ORIGINAL ARTICLE

Socioeconomic participation of persons with hemophilia: Results from the sixth hemophilia in the Netherlands study

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Abstract

Background and objectives: Treatment availability and comprehensive care have resulted in improved clinical outcomes for persons with hemophilia. Recent data on socioeconomic participation in the Netherlands are lacking. This study assessed participation in education, in the labor market, and social participation for persons with hemophilia compared with the general male population.

Methods: Dutch adults and children (5–75 years) of all hemophilia severities ($n = 1009$) participated in a questionnaire study that included sociodemographic, occupational, and educational variables. Clinical characteristics were extracted from electronic medical records. General population data were extracted from Statistics Netherlands. Social participation was assessed with the PROMIS Ability to Participate in Social Roles and Activities short form, with a minimal important difference set at 1.0.

Results: Data from 906 adults and children were analyzed. Participation in education of 20 to 24 year olds was 68% (general male population: 53%). Educational attainment was higher compared with Dutch males, especially for severe hemophilia. Absenteeism from school was more common than in the general population. The employment-to-population ratio and occupational disability were worse for severe hemophilia than in the general population (64.3% vs. 73.2% and 14.7% vs. 4.8%, respectively), but similar for nonsevere hemophilia. Unemployment was 5.4% (general male population: 3.4%). Absenteeism from work was less common (38% vs. 45.2%). Mean PROMIS score was similar to or higher than in the general population (54.2; SD 8.9 vs. 50; SD 10).
Conclusion: Socioeconomic participation of persons with nonsevere hemophilia was similar to the general male population. Some participation outcomes for persons with severe hemophilia were reduced.

KEYWORDS
absenteeism, career choice, disability evaluation, educational status, employment, hemophilia A, hemophilia B

Essentials

- Current socio-economic participation of Dutch persons with hemophilia is unknown.
- Participation in education and in the labor market, and social participation were assessed.
- Educational outcomes were similar to or better than in the general population.
- Labor market outcomes were similar to the general population for non-severe hemophilia.

1 | INTRODUCTION

The X-linked congenital bleeding disorder hemophilia is characterized by an increased bleeding tendency because of a deficiency of functional coagulation factor VIII (hemophilia A) or IX (hemophilia B). It is classified into severe (<0.01 IU/ml FVIII or FIX), moderate (0.01–0.05 IU/ml FVIII or FIX) or mild (0.05–0.40 IU/ml FVIII or FIX) hemophilia. Bleeding occurs spontaneously in joints and muscles in persons with severe hemophilia, or when triggered by major trauma or surgery in persons with mild or moderate hemophilia.[1] In the long term, recurrent bleeding causes irreversible joint damage, which may lead to disability.[1]

Treatment first became available in high-income countries in the late 1960s. Modern treatment mostly consists of intravenous infusion of factor VIII or IX replacement products: 2–3 times a week as prophylaxis for severe hemophilia, or as treatment of bleeds in mild and moderate hemophilia ("on-demand"). The majority of persons with severe hemophilia have received prophylaxis since the mid-1980s.[2] A potential side effect of these products is the development of neutralizing antibodies ("inhibitors"). Also, bloodborne pathogens were transmitted through plasma-derived treatment products, such as HIV between 1980–1985 and hepatitis C until the early 1990s.[3] Nonfactor replacement hemostatic agents have been marketed in the past few years as alternative prophylactic treatment.[1]

Hemophilia care in the Netherlands is organized in six comprehensive hemophilia treatment centers distributed over nine locations across the country according to the European principles of Hemophilia Care.[4-6] Bleeding rates, joint impairment, consequences of comorbidities, life expectancy, and several aspects of health-related quality of life have improved tremendously in the Netherlands since the 1970s.[2,7] No recent data are available for socioeconomic participation in the Netherlands, even though the ability to participate in daily life is among the most important health outcomes for persons with hemophilia.[8,9] Insight into socioeconomic participation will help to evaluate the effects of comprehensive care over time.[9]

Several recent studies from other high-income countries suggested negative impacts of hemophilia on employment and disability rates,[10-13] absenteeism from work or school,[10,14,15] perceived impact on education or career,[12,13] and social functioning.[11] Dutch young adults with nonsevere hemophilia were more likely to have paid employment than those with severe hemophilia.[16] Among persons with severe hemophilia A in five European countries, lifelong prophylaxis and high therapy adherence led to reduced activity impairment and work productivity loss, whereas frequent bleeds and pain were associated with increased activity impairment and work productivity loss.[17]

Few studies have examined the "gap" in socioeconomic participation between persons with different severities of hemophilia and the general population. Furthermore, participation outcomes are often not reported in a standardized manner (i.e.,

using internationally recognized indicators that allow for comparison across settings). For example, the most important indicators labor market participation are the unemployment rate and the employment-to-population ratio.[18] Absenteeism from work and occupational disability are indicators of temporary and (semi-)permanent limitations on the labor market, and as such reflect the health status of a population.[19]

The aim of the current study was to assess participation of the Dutch hemophilia population, focused on participation in education and the labor market, and social participation, and to compare these outcomes with the general male population using standardized indicators.

2 | METHODS

2.1 | Study design

The Hemophilia in the Netherlands (HiN) studies are a series of cross-sectional studies that provide a comprehensive evaluation of the medical, psychosocial, and socioeconomic situation of the Dutch hemophilia population since 1972.[15,20-22] The sixth edition, HiN-6, was conducted during 2018–2019. Approval was obtained from the Medical Ethics Committee at Leiden University Medical Center, the Netherlands.

2.2 | Participants and procedures

All Dutch male adults and children with mild, moderate, or severe congenital hemophilia A or B (<40 IU/ml coagulation factor VIII/IX) receiving treatment from one of six Dutch hemophilia treatment centers were invited by letter to participate between June 2018 and July 2019. Excluded were females with hemophilia, persons with acquired hemophilia, and nonhemophilic individuals with reduced FVIII levels resulting from von Willebrand disease. Individuals between 5 and 75 years were included in the analyses.

Individuals who agreed to participate received a comprehensive questionnaire (hard copy or electronic; captured with the Castor Electronic Data Capture system.[23]). Participants were reminded during their regular outpatient clinic appointment and two reminders were sent by email. Three questionnaire versions were available: children aged 0–11 years (completed by parents), teenagers aged 12–17 years, and adults of 18 years and older. Clinical characteristics were extracted from medical records if the participant (or parents) had signed written informed consent. If the participant did not consent, only self-reported data from the questionnaire were used. Hemophilia severity was known for all responders and nonresponders.

2.3 | Data collected

The questionnaire contained clinical and sociodemographic questions: chronic joint problems due to hemophilia (defined as "do you have any chronic joint problems due to hemophilia" [yes/no]), current and highest completed education level, work status, time missed from work or school in the past year, and the perceived impact of hemophilia on education and career (yes/no and an open-ended question). Social participation was assessed with the PROMIS-29 Profile v2.01 Ability to Participate in Social Roles and Activities.[24] In brief, PROMIS short forms are based on Item Response Theory, which provides valid and reliable results that can be compared across populations.[25] The ability to participate is measured with four items, each scored from 1 to 5; a higher score indicates better social participation.[26]

The following clinical characteristics were collected: date of birth, type of hemophilia (A or B), severity of hemophilia based on factor VIII or factor IX activity (severe: <0.01 IU/ml; moderate: 0.01–0.05 IU/ml; or mild >0.05–0.40 IU/ml), prophylaxis use (yes/no), inhibitor status (current/past/never), HIV infection (yes/no), and hepatitis C virus status (currently/past/never infected).

2.4 | Outcomes and definitions

Three types of outcomes were assessed in partially overlapping populations: educational outcomes, labor market participation, and the ability to participate in social roles and activities.

Educational outcomes were assessed according to the International Standard Classification of Education (ISCED).[27,28] The following educational outcomes were assessed: (1) participation in education, defined as the proportions of 15 to 19 and 20 to 24 year olds enrolled in formal education; (2) educational attainment, defined as the percentage of the population aged 15–75 years that completed at least upper secondary education (ISCED level 3), which is the Dutch minimally required qualification considered sufficient to enter the labor market[29]; (3) absenteeism from school because of hemophilia, defined as the number of days missed from school in the past 12 months from hemophilia (bleeds or outpatient clinic visits) for individuals aged 5 years and older enrolled in formal education.

Labor market participation was assessed using internationally recognized labor market indicators.[18,19] The study population for labor market outcomes consisted of individuals aged 15–75 years. Participants were either part of the labor force (individuals with paid employment and individuals without paid employment but actively looking for work) or the nonlabor force (full-time students, retirees, individuals with an occupational disability, unpaid employment).[30] The following outcomes were reported: (1) the employment-to-population ratio, defined as the proportion with paid employment for at least 1 hour a week (including self-employed persons)[18,30] relative to the study population; (2) unemployment, defined as the proportion of the labor force without paid employment who were available for the labor market and actively looking for work[30]; (3) occupational disability, defined as the proportion of the study population being unable to obtain or maintain paid employment from an illness or disability (with ≥80% disability considered fully occupationally disabled according to Dutch law[19,30];) (4) the proportion of individuals working full-time (i.e., ≥36 h a week)

among employed persons; (5) absenteeism from work, defined as the total number of days missed from work, and the number of days missed from work due to hemophilia (bleeds or outpatient clinic visits) in the past 12 months for individuals with paid employment; and (6) perceived impact of hemophilia on education or career.

The ability to participate in social roles and activities was assessed for adults (≥18 years) by calculating T-scores for the PROMIS-29 Ability to Participate in Social Roles and Activities domain using the Health Measures Scoring Service.[31] T-scores are a normalized score with a population mean of 50 and a standard deviation (SD) on 10 in the reference population (the US general population).

2.5 | Data analysis and comparisons

Educational outcomes and labor market indicators were compared with aggregate-level data from the Dutch general male population when possible, as specified in the following section.

Descriptive statistics (*N*, %, median, interquartile range [IQR]) were mainly used, categorized according to disease severity. Educational outcomes and labor market participation were presented as percentages with 95% confidence intervals (CI) and stratified by hemophilia severity, type, and inhibitor status. If confidence intervals for our estimates did not include the estimate for the general population, we consider our estimate to be different from the general male population. The employment-to-population ratio was also stratified by 10-year age groups. The number of days of absenteeism was reported as medians with the IQR. The ability to participate in social roles and activities was presented as mean and median T-scores with IQR, stratified by hemophilia severity.

Participation in education was compared to Organization for Economic Co-operation and Development aggregate data in 2018 (combined for males and females because data for males are not available).[32] Educational attainment was compared with data at the aggregate level from Statistics Netherlands in 2019.[33] Children aged 5–18 years were assumed to be in compulsory education. The only data available for comparisons of school absenteeism was the proportion of Dutch boys in grades 8 (13–14 years old) and 10 (15–16 years old) who reported at least 1 day of school absenteeism in 2015.[34]

The employment-to-population ratio and occupational disability were compared with aggregate data of the general male population aged 15–75 years in 2018, stratified by age group, extracted from Statistics Netherlands.[35] Absenteeism from work was compared with data from Statistics Netherlands in 2018.[36]

The impact of hemophilia on career or education and the Ability to Participate in Social Roles and Activities were assessed for adults in three age groups: those born before the introduction of coagulation factor products (born before 1971), those born before the introduction of pathogen inactivation and removal techniques (1971–1992), and those born after the introduction of such techniques (1993 or later). T-scores were plotted by age group and hemophilia severity. The minimal important difference was 1; a difference of ≥1 was considered clinically relevant.[37]

Analyses were performed in IBM SPSS Statistics for Windows, version 25.0.

3 | RESULTS

3.1 | Study population

In total, 2192 adults and children with hemophilia were invited to participate; 1009 of them completed the questionnaire in part or in full (response 46%). Of these 1009 individuals, 906 were between 5 and 75 years (84 children 5–11 years old, 57 adolescents 12–17 years old, and 765 adults) and included in the current analysis. Medical record data were available for 665 of 906 individuals (73.4%). Of all participants, 86.4% had hemophilia A and 339 participants had severe hemophilia (37.4%). Individuals with severe hemophilia were younger (median age 36 years, IQR 20–54) than individuals with moderate (median age 40 years, IQR 25–57.5) and mild hemophilia (median age 48 years, IQR 27–61, Table 1).

3.2 | Educational outcomes

Educational outcomes are summarized in Table 2. Participation in education was 96% (CI 92–100) for 15–19 year olds and 68.1% (CI 57–79) for 20 to 24 year olds, compared with 92% and 53% in the general population, respectively. One-third (33.8%) of individuals enrolled in education also had full-time or part-time work or was self-employed, and another 3.8% was actively looking for work.

Information on educational attainment was missing for 63 individuals. Of 731 remaining participants, 557 (76.2%; CI 73.1–79.3), had completed at least upper secondary education (ISCED level 3), compared with 72.8% in the general male population. Educational attainment was similar across severities and types of hemophilia (Table 2 and Table S1a and b).

Data for school absenteeism because of hemophilia were available for 154 of 263 persons aged 5–75 years who were enrolled in formal education; part of the absenteeism data were missing because of a routing error in the first electronic version of the questionnaire, which was corrected after 6 months. Overall, 69.5% (CI 63.6–75.3) reported absenteeism from hemophilia in the past 12 months (Table 2), compared with 37.8% of Dutch boys in grades 8 and 10. The number of days of absenteeism from hemophilia was higher among individuals with severe hemophilia (median 2 days, IQR 0.9–4.8) than among those with moderate (median 1 day, IQR 0.2–3) and mild hemophilia (median 0.8, IQR 0–2).

3.3 | Labor market participation

The analysis population consisted of 794 individuals aged 15–75 years. Information on labor market status was missing for 24

TABLE 1 Characteristics of persons with hemophilia aged 5–75 years

Characteristic, N (%) or median (IQR)	Total (n = 906)	Severe (n = 339)	Moderate (n = 133)	Mild (n = 434)
Age	43.0 (21–59)	36 (20–54)	40 (25–57.5)	48 (27–61)
Type of hemophilia				
Hemophilia A	783 (86.4)	294 (86.7)	113 (85.0)	376 (87.2)
Hemophilia B	113 (12.5)	45 (13.3)	19 (14.3)	49 (11.4)
Missing	10 (1.1)	-	1 (0.8)	9 (2.5)
Treatment modality				
Prophylaxis	327 (36.0)	303 (89.4)	21 (15.8)	2 (0.5)
No prophylaxis	553 (61.0)	28 (8.3)	111 (83.5)	414 (95.4)
Missing	27 (3.0)	8 (2.4)	1 (0.8)	18 (4.2)
Hepatitis C infection[a]				
Never infected	557 (61.5)	166 (49.0)	81 (60.9)	310 (71.4)
Past infection	226 (24.9)	142 (41.9)	38 (28.6)	46 (10.6)
Current infection	7 (0.8)	5 (1.5)	0 (0)	2 (0.5)
Missing	116 (12.8)	26 (7.7)	14 (10.5)	76 (17.5)
HIV positive				
No	853 (94.2)	314 (92.6)	129 (97.0)	410 (94.5)
Yes	21 (2.3)	21 (6.2)	0 (0)	0 (0)
Missing	32 (3.5)	4 (1.2)	4 (3.0)	24 (5.5)
Inhibitor status[b]				
Never	732 (80.8)	269 (79.4)	113 (85.0)	350 (80.6)
Past	85 (9.4)	51 (15.0)	14 (10.5)	20 (4.6)
Current	14 (1.5)	4 (1.2)	2 (1.5)	8 (1.8)
Missing	73 (8.1)	13 (3.8)	4 (3.0)	56 (12.9)
Joint impairment[c]				
No	478 (52.8)	102 (30.1)	67 (50.4)	309 (71.2)
Yes	327 (36.1)	205 (60.5)	54 (40.6)	68 (15.7)
Missing	101 (11.1)	32 (9.4)	12 (9.0)	57 (13.1)

Note: Information on ethnicity was not collected because this is not allowed under Dutch law.

Abbreviation: IQR, interquartile range.

[a]Two individuals with severe hemophilia had a past or current hepatitis C virus infection, but current status could not be established.

[b]Two individuals with severe hemophilia had a past or current inhibitor, but current status could not be established.

[c]Joint impairment is self-reported joint impairment in any joint (yes/no).

individuals. Of the remaining 770 individuals, 379 had mild hemophilia, 119 had moderate hemophilia, and 272 had severe hemophilia (Table S2a); 555 were in the labor force (of whom 30 were unemployed) and 215 were not in the labor force (Figure 1); Of 525 individuals with paid employment, 89 were also enrolled in education.

The employment-to-population ratio of the hemophilia population was 525/770 = 68.2% (CI 64.9–71.5), compared with 73.2% in the general male population (Table 3 and Figures 1 and 2). Persons with severe hemophilia had the lowest employment-to-population ratio: 64.3% (CI 58.6–70.0). For moderate and mild hemophilia, the employment-to-population ratio was similar to that of the general population (70.6%, CI 62.4–78.8 and 70.2%, CI 65.6–74.8, respectively, Table S2a and Figure S1). For most 10-year age groups, the employment-to-population ratio followed the same pattern as the general population; however, it was consistently lower for persons with severe hemophilia than for mild and moderate hemophilia and the general population, except for the 15–25 year age group (Figure 3). The employment-to-population ratio for hemophilia A and B was 68.1% and 67%, respectively (Table S2b). Finally, the employment-to-population ratio for individuals with a current inhibitor was 41.7% (5 of 12).

Unemployment was 5.4% (CI 3.5–7.3; 30 of 555), compared with 3.4% among the general male population. Unemployment was higher for severe hemophilia (6.9%) than for mild hemophilia (4.3%) (Table 3 and Table S2a), but estimates are imprecise because of low numbers. Unemployment was 5.6% and 4.5% for hemophilia A and B, respectively (Table S2b).

TABLE 2 Educational outcomes for persons with hemophilia and the general male population

	Participation in education, % (95% CI)[a]			Absenteeism from school[c]	
	15–19 years	20–24 years	Educational attainment (% with ISCED ≥3 (95% CI))[b]	% with absenteeism	Median days (IQR)
General male population	92	53	72.8	37.8	n.a.
HiN-6	96 (90–100)[d]	**68.1 (57–79)**[e]	**76.2 (73.1–79.3)**	**69.5 (63.6–75.3)**	1.0 (0–3.3)
Severe	–	–	**78.7 (73.6–83.7)**	**80 (70–90)**	2.0 (0.9–4.8)
Moderate	–	–	72.2 (64.0–80.4)	77 (22–140)	1.0 (0.2–3)
Mild	–	–	75.8 (71.3–80.2)	**54 (38–70)**	0.8 (0–2)

Note: Outcomes that are different from the general population are indicated in bold.

Abbreviations: CI, confidence interval; ISCED, International Standard Classification of Education; n.a., not available.

[a]263 individuals were enrolled in formal education (i.e., ISCED level 1 and higher); 151 of them were between 5 and 18 years old and in compulsory education. One-third (33.8%) of individuals enrolled in education also had full-time or part-time work or was self-employed, and another 3.8% was actively looking for work. General population data are from the Organization for Economic Co-operation and Development (OECD) for males and females combined.[32]

[b]Highest completed education level of the hemophilia population and general male population aged 15–75 years. Educational attainment was missing for 63 individuals (8%) with hemophilia and for 1.6% of individuals in the general population. General population data are from Statistics Netherlands.[33]

[c]Because of hemophilia for all individuals aged 15–75 years and enrolled in formal education of any type or level, or absenteeism from school for any illness for Dutch boys in grades 8 and 10 without hemophilia.[34]

[d]Education status was unknown for 2 of 46 individuals. Participation in education was not stratified by severity because of low numbers ($n = 18$ for mild hemophilia, $n = 4$ for moderate hemophilia, and $n = 24$ for severe hemophilia).

[e]Education status was unknown for 1 of 72 individuals. Participation in education was not stratified by severity because of low numbers ($n = 28$ for mild hemophilia, $n = 12$ for moderate hemophilia, and $n = 32$ for severe hemophilia).

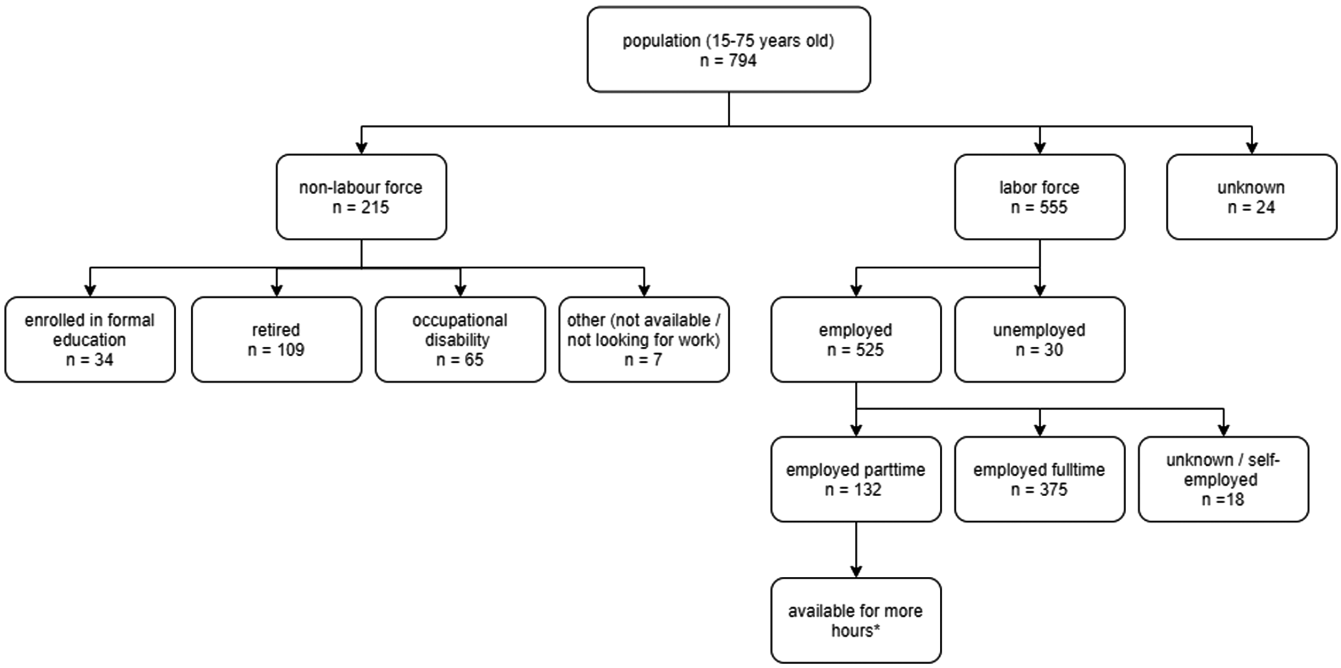

FIGURE 1 Distribution of the hemophilia population aged 15–75 years in the labor force and the nonlabor force. The labor force consists of individuals with paid employment >1 hour/week and individuals who are legally unemployed. Persons in the nonlabor force are not able to work or available for work because they are enrolled in (full-time) education, retired, have an occupational disability, or have unpaid employment. *No data were available for the work availability of persons with a parttime job

Occupational disability was reported by 8.4% (CI 6.5–10.4) of the population aged 15–75 years, higher than among the general male population (4.8%). This was mainly attributable to those with severe hemophilia, in which 14.7% (CI 10.5–18.9) reported an occupational disability (Table 3). Of 12 individuals with a current inhibitor, two had an occupational disability (17%). The majority

TABLE 3 Comparison of labor market participation for persons with hemophilia and the general male population aged 15–75 years

	Labor market indicators			Limitations labor market			
	Employment-to-population ratio[a]	Unemployment[b]	% working full-time[c]	Occupational disability (%)[d]	% with work absenteeism (any reason)	% with work absenteeism (hemophilia)	Median days (IQR)
General male population[d]	73.2	3.4	72	4.8	45.2	–	n.a.
HiN-6	**68.2 (64.9–71.5)**	**5.4 (3.5–7.3)**	71.4 (67.6–75.3)	**8.4 (6.5–10.4)**	**37.7 (31.4–43.9)**	19.7 (14.5–24.8)	0 (0–5)
Severe	**64.3 (58.6–70.0)**	6.9 (3.3–10.5)	66.9 (59.9–73.8)	**14.7 (10.5–18.9)**	42.6 (30.9–54.4)	25.0 (14.7–35.3)	0 (0–5)
Moderate	70.6 (62.4–78.8)	5.6 (0.8–10.4)	75 (65.7–84.3)	4.2 (0.6–7.8)	34.4 (17.9–50.8)	21.9 (7.6–36.2)	0 (0–4)
Mild	70.2 (65.6–74.8)	4.3 (1.9–6.7)	73.3 (68.0–78.6)	5.3 (3.0–7.5)	**35.9 (27.7–44.1)**	16.3 (9.9–22.6)	0 (0–4)

Note: Outcomes that are different from the general population are indicated in bold.

Abbreviations: HiN, Hemophilia in the Netherlands; IQR, interquartile range; n.a., not available.

[a]Defined as the proportion of the (male) population aged 15–75 years with paid employment for at least 1 hour a week.[18,30]

[b]Proportion of the labor force (aged 15–75 years) without paid employment who were available for the labor market and actively looking for work.

[c]For another 18 individuals (3.4% of individuals with paid employment), full-time/part-time status was unknown. Most of them were self-employed.

[d]Defined as the proportion of the population aged 15–75 years being unable to obtain or maintain paid employment because of an illness or disability.[30]

[d]Aggregate-level data from the general male population from Statistics Netherlands.[35]

of persons with an occupational disability (89%) were considered ≥80% occupationally disabled. Hemophilia was the cause of occupational disability for 34 of 65 individuals (52%). For another 10, a combination of hemophilia and hemophilia-related comorbidities (such as hepatitis C virus and/or HIV infection) was the cause of occupational disability. Sixteen individuals had an occupational disability not related to hemophilia and for five the cause was not reported. Individuals with self-reported joint impairment were more likely to have an occupational disability than those without joint damage (14.3% with joint impairment vs. 3.4% without joint impairment).

Most persons with paid employment worked full-time (71.4%; CI 67.6–75.3), which is similar to the general male population (72%).

Data on absenteeism from work were available for 231 of 525 individuals with paid employment; data from the remaining individuals were missing because of a routing error in the electronic version of the questionnaire. Persons with hemophilia less often reported work absenteeism than the general male population (37.7%, CI 31.4–43.9, general male population: 45.2%, Table 3). Almost 20% of persons with paid employment reported absenteeism from work because of hemophilia.

The number of days of absenteeism was skewed and ranged from 0 to 250 days (Figure S2). The median number of days of absenteeism was zero for all severities (IQR severe hemophilia: IQR 0–5 days, IQR mild/moderate hemophilia: 0–4 days; Table 3).

3.4 | Perceived impact of hemophilia on career and education

Of 273 participants aged 15–75 years with severe hemophilia, 129 (47.3%) reported that hemophilia had affected their choice of education or career to some or to a large extent. This proportion was 35.6% for moderate hemophilia and 17.6% for mild hemophilia (Table S3). Among participants born in 1993 or later, 16.5% reported that hemophilia had affected this decision. For participants born between 1971 and 1992, this was 28.6% and for the group born in 1970 or earlier this was 36.1%. Frequently mentioned impacts in the open-ended question were choosing jobs that required little physical activity or that had a low injury risk.

3.5 | Social participation

Persons with hemophilia had similar or better scores on the PROMIS Ability to Participate in Social Roles and Activities than the general population mean of 50, with differences larger than the minimal important difference (set at 1.0). The overall mean score was 54.2 (median 53.8; IQR 48.0–64.2); for severe hemophilia the mean was 51.2 (median 51.8, IQR 44.2–58.2), for moderate hemophilia it was 56.4 (median 58.1; IQR 51.7–64.2) and for mild hemophilia it was 55.5 (median 55.9; IQR 50.1–64.2). The Ability to Participate in Social Roles and Activities declined with age in all severity groups;

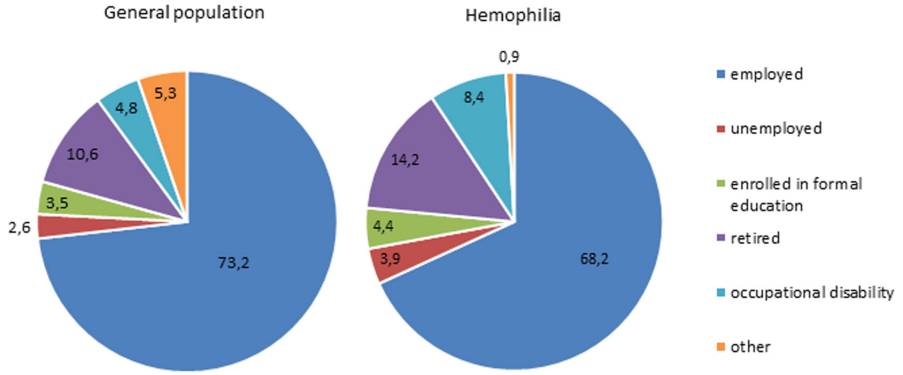

FIGURE 2 Labor market participation for the general population (left) and for persons with hemophilia (right)

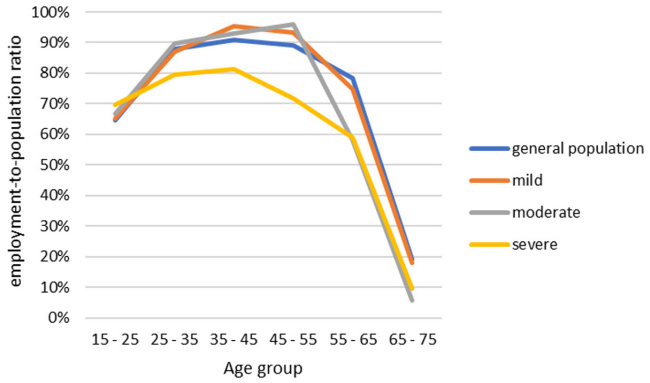

FIGURE 3 Employment-to-population ratio by hemophilia severity and 10-year age group

the negative association was more pronounced among those with severe hemophilia (Figure 4).

4 | DISCUSSION

This study assessed socioeconomic participation in Dutch persons with hemophilia. To our knowledge, this is the first comprehensive report of nationwide participation in education, labor market participation, and social participation of persons with hemophilia using internationally recognized socioeconomic standards.

Participation in education and educational attainment of Dutch persons with hemophilia were similar to or higher than among the general population. Absenteeism from school was increased. The most important labor market indicators (i.e. the employment-to-population ratio, unemployment, and occupational disability) were worse than in the general population, especially for individuals with severe hemophilia. Absenteeism from work and the ability to participate in social roles and activities were similar to or better than in the general population. However, the latter was worse for the oldest age group with severe hemophilia.

Most of our results corroborate those of previous reports. However, in contrast with other studies,[12,13] occupational disability in HiN-6 was lower than reported in other studies,[12,15] and fewer participants perceived a negative impact of hemophilia on their career or education.[12,13] These differences may be explained by differences in population and study settings. For example, lower and upper-middle income countries may have higher disability rates than high-income countries such as the Netherlands because of suboptimal availability of treatment products.[12,13] On the other hand, unemployment was higher in HiN-6 than in other studies and the general population.[10,11] The reason for this is unknown, but unemployment rates are known to vary seasonally and according to economic developments.[38] Finally, school absenteeism was much higher than among Dutch boys, which may in part be due to regular hospital visits. However, data may not be comparable because of differences in age groups and reference year.

Occupational disability was almost twice as common. The employment-to-population ratio was 5 percentage points lower than in the general population, especially for severe hemophilia. This does not necessarily imply worse participation because it depends to a large degree on the size of the nonlabor force.[18] Persons in the nonlabor force are not necessarily inactive because of disease, but they may be enrolled in education or be retired. Our study showed large proportions of students and retirees, resulting in a larger nonlabor force and thus a lower employment-to-population ratio.[18] Still, men with hemophilia have a better employment-to-population ratio than 45- to 75-year-old men with a chronic disease (14%).[39]

Our findings of lower absenteeism from work may be explained by a healthy worker effect[40]: working individuals with hemophilia may be relatively healthy and therefore have low absenteeism.

The PROMIS T-scores for Ability to Participate was lower for individuals born before the introduction of prophylaxis, especially for severe hemophilia. This is consistent with PROMIS short form scores of a recent Spanish study among patients with rheumatoid arthritis, spondyloarthritis, and systemic lupus erythematosus.[41] However, we found higher participation rates than for rheumatic disease patients, who had mean scores of 26.2 (SD 7.79). In our study, scores of younger persons with nonsevere hemophilia were higher than in the general population. We cannot explain this finding. Further research is needed to study the determinants of the ability to participate. The differences in participation outcomes with the general population appear to be of the same order of magnitude as those reported in the HiN-5 survey conducted in 2001.[11] However, historic comparisons should be interpreted with caution because of changes in legislation (e.g., for occupational disability),[42] decreasing trends

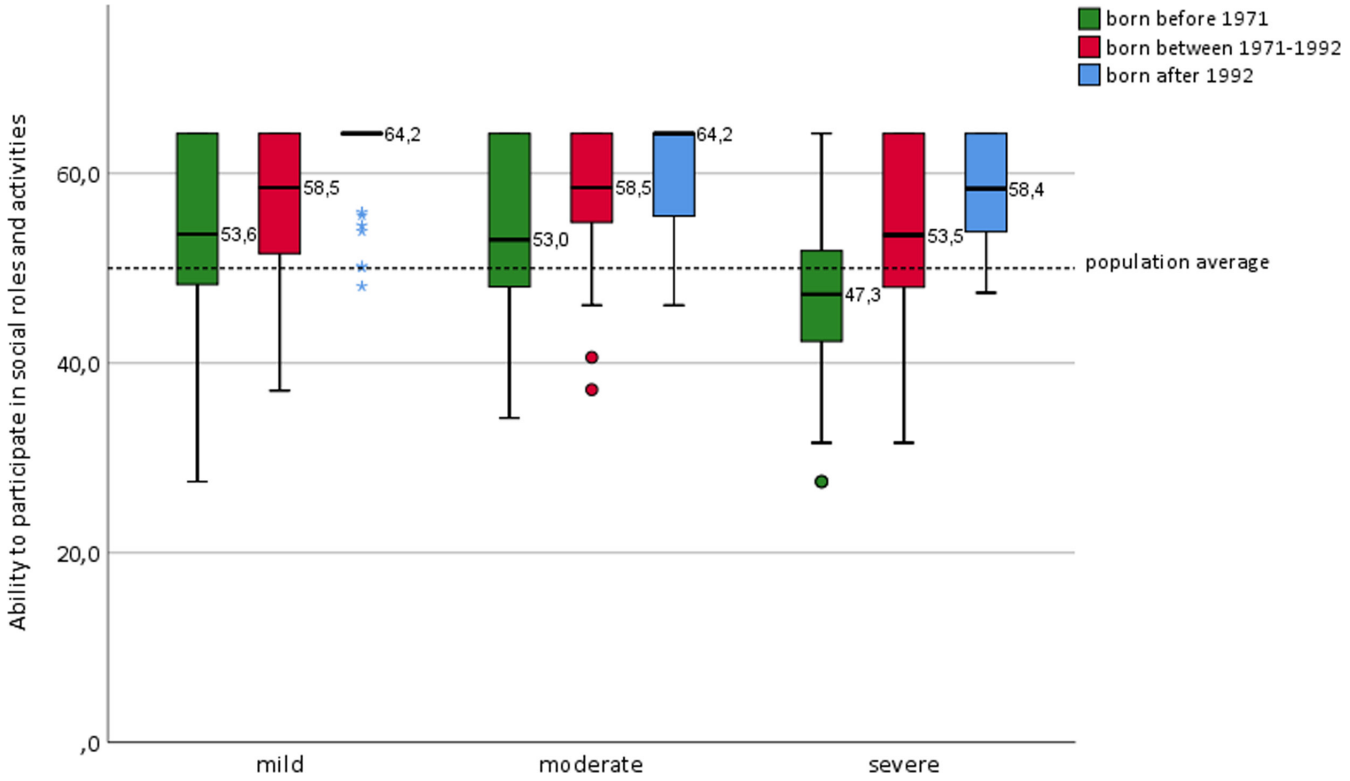

FIGURE 4 Median T-scores on PROMIS Profile-29 Ability to participate in social roles and activities, by hemophilia severity and age group (≥18 years old). Medians are shown as horizontal bars. Boxes indicate interquartile range and whiskers indicate range of T-scores.

in absenteeism,[19] increasing education level in the general population and other labor market developments.[43] Therefore, rather than comparing indicators over time, it is more meaningful to compare socioeconomic participation outcomes for persons with hemophilia with the general population in the same reference year.

This study has several limitations. First, the response rate was 46%. Despite this, the most important characteristics of responders were similar to those of nonresponders in terms of hemophilia severity and age distribution[2]: 48% of persons in our sample had mild hemophilia compared with 53.5% in the Dutch hemophilia population. We therefore consider our results generalizable to the full Dutch hemophilia population. Some selection based on education level or ethnicity is possible because completing a comprehensive questionnaire is a cognitive task that requires sufficient Dutch language skills; individuals with a lower education level or limited ability to understand Dutch (i.e., immigrants) may therefore have been less likely to respond. This may have resulted in possible underrepresentation of these groups and overestimation of educational attainment. Under Dutch law, we were not allowed to collect information on ethnicity. On the other hand, those with higher education levels may have busier jobs and schedules and less time to complete a questionnaire. This source of selection bias is inherent to questionnaire research and may be similar for the previous HiN survey as well as for the surveys conducted by Statistics Netherlands.

Second, we relied on self-reported clinical data for part of our sample because electronic medical record data were not available for 26.6% of participants. Self-reported clinical data may be less reliable, which may have resulted in some misclassification, for example for disease severity. However, low rates of misclassification were observed among those with complete data. Therefore, misclassification is unlikely to have affected our results.

Third, we were only able to compare outcomes with aggregate-level data from the general male population. This may have led to some confounding by age. To overcome this, we stratified our analyses by age groups when possible. However, within-stratum confounding cannot be ruled out completely.

Fourth, reliability of our estimates for unemployment may be limited because of low numbers, resulting in imprecise estimates. The same applies to the employment-to-population ratio and occupational disability for individuals with a current inhibitor. Comparisons with the general population should therefore be interpreted with caution.

Fifth, women with hemophilia were not included in HiN. Our results may therefore not be applicable to women with hemophilia. Finally, the data on work and school absenteeism are incomplete because of a routing error in the electronic version of the questionnaire that occurred until December 2018. This resulted in fewer participants responding to the questions about absenteeism, making our estimates of absenteeism less reliable. The missing data on absenteeism may be considered missing completely at random because missingness is not dependent on any other variable.[44]

The more favorable outcomes of younger compared with older participants and modest improvements since the previous nationwide study suggest beneficial effects of widespread prophylaxis.

Hemophilia treatment is costly. However, treatment has also brought direct and indirect gains for persons with hemophilia and for society because of near-normal participation. Monitoring such outcomes in a standardized manner will help evaluate the long-term effects of comprehensive hemophilia care, including innovations in treatment. Such novel treatments were not yet available at the time the survey was conducted and their effects on socioeconomic outcomes could not be taken into account in this study.

In conclusion, educational outcomes and social participation were similar to or better than in the general population. Some labor market indicators were worse for severe hemophilia. Further research is needed to establish whether comprehensive care contributed to better participation.

AUTHOR CONTRIBUTIONS

E.C. van Balen wrote the analysis plan, conducted the analyses, and wrote the manuscript. J.G. van der Bom and S.C. Gouw provided critical comments on design and analysis of the study and the manuscript. All authors provided written feedback and approved the final manuscript.

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RELATIONSHIP DISCLOSURE

E.C. van Balen, S. Hassan, C. Smit, M.H. Driessens, E.A.M. Beckers, H.L. Hooimeijer, E.P. Mauser-Bunschoten, and F.R. Rosendaal have no conflicts of interest to disclose. S.E.M. Schols has received travel grants from Bayer and Takeda, consultancy grants from Takeda and Novo Nordisk, and a research grant from Bayer. M. Coppens has received financial support for research from Bayer, CSL Behring, Daiichi Sankyo, Portola/Alexion, Roche, Sanquin Blood Supply, and UniQure and consultancy or lecturing fees from Bayer, CSL Behring, Medcon International, MEDtalks, NovoNordisk, Pfizer, and Sobi. J. Eikenboom received research support from CSL Behring and has been a teacher on educational activities of Roche. F.W.G. Leebeek received unrestricted research grants from CSL Behring, Takeda, UniQure, and Sobi and is a consultant for UniQure, Novo Nordisk, Biomarin, and Takeda, of which the fees go to the institution. He is also a DSMB member for a study by Roche. L.F.D. van Vulpen received research grants from CSL Behring and Grifols and is a consultant for Sobi and Tremeau. All fees go to the institution. J.G. van der Bom has been a teacher on the educational activities of Bayer and received unrestricted research grants from NovoNordisk. S.C. Gouw has received unrestricted research grants from Sobi.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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