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Determinants of adherence and consequences of the transition from adolescence to adulthood among young people with severe haemophilia (TRANSHEMO): A multicentric French national observational cross-sectional study based on the FranceCoag registry

Ngoc Anh Thu Nguyen, Pascal Auquier, Any Beltran Anzola, Annie Harroche, Sabine Castet, Yoann Huguenin, Sandrine Meunier, Yohann Repesse, Roseline d'Oiron, Antoine Rauch, et al.

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Determinants of adherence and consequences of the transition from adolescence to adulthood among young people with severe haemophilia (TRANSHEMO): A multicentric French national observational cross-sectional study based on the FranceCoag registry

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20 Marseille, July 25th, 2023

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24 Dear Dr Hermans,
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27 We thank you for giving us the opportunity to submit a revised version of our paper. We also
28 would like to warmly thank the reviewers for their valuable remarks and suggestions, which
29 allowed us to improve our work.
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32
33 We answered all questions raised by the reviewers and we altered the manuscript accordingly.
34 We hope that the manuscript will be accepted for publication in *Haemophilia* in its revised
35 form, and we thank you in advance for your time and consideration of the manuscript.
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41 Yours sincerely,
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For Peer Review

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3 1 **ABSTRACT**

4 2 **Introduction:** It is necessary to gain insights into adherence to healthcare in people with severe haemophilia
5 (PwSH), especially during the transition from pediatric to adult care, which is an important phase in lives
6 of young people with childhood chronic disease. This adherence can be considered as a marker of successful
7 transition.
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9 5
10 6 **Objectives:** The main objective of the quantitative phase of the TRANSEMO project was to compare the
11 adherence to healthcare between adolescents and young adults (YAs) with severe haemophilia. The
12 secondary objective was to identify the determinants (facilitators and barriers) of this adherence and
13 associations between these determinants.
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15 9
16 10 **Methods:** A multicenter, observational, cross-sectional study was conducted in 2017-2019 on PwSH aged
17 between 14 and 17 years (adolescents) or between 20 and 29 years (YAs), included in the FranceCoag
18 registry and having completed the questionnaires. The adherence to healthcare (treatment regimens and
19 clinical follow-up) was compared between adolescents and YAs using the chi-squared test. The
20 determinants of this adherence were analyzed by structural equation modeling.
21

22 15 **Results:** There were 277 participants, 107 adolescents and 170 YAs. The rate of adolescents adhering to
23 healthcare was 82.2%, while the rate of YAs was 61.2% ($p < 0.001$). The barriers to the adherence to
24 healthcare were being YA, having repeated at least one school grade and presenting mental health concerns.
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26 18 **Conclusion:** Adolescents had better adherence to healthcare than YAs. According to the determinants
27 enlightened in this project, targeted supportive strategies and adapted therapeutic education programs can
28 be developed for young PwSH to facilitate their adherence to healthcare.
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1 INTRODUCTION

2 Haemophilia is a rare and inherited bleeding disorder affecting mainly men due to deficiency in clotting
3 factors.¹ People with severe haemophilia (PwSH) have less than 1% blood clotting factors, which can cause
4 serious hemorrhagic events (e.g., intracranial hemorrhage, hemarthrosis) if insufficiently treated. It is
5 possible to avoid these events by haemophilia care, such as substitutive therapies and lifelong regular
6 clinical follow-up, whose major issue is adherence.

7 Non-adherence to healthcare might have serious consequences, such as hemarthrosis, which may lead to
8 impairment in physical functioning and quality of life (QoL).² A study on adherence to prophylaxis of people
9 with haemophilia (PwH) aged 12-25 years found a higher number of hemarthroses in people who were less
10 adherent to prophylaxis.³ It is necessary to gain insights into adherence to healthcare during the transition
11 from pediatric to adult care, since this is an important phase of young PwH.⁴⁻⁶ Previous studies assessed
12 adherence to the prescribed therapeutic regimen and found a decrease in the level of adherence when PwH
13 reached adulthood. In a study on practice patterns for the management of haemophilia A, the rates of high
14 adherence in people aged 13-18 years and those aged 19-28 years were 54% and 36%, respectively.⁷ In
15 another study, 83% of adolescents aged 13-17 years adhered to prophylaxis, while this rate was 53% in
16 young adults (YAs) aged 18-25 years.⁸ Similarly, a lower level of adherence in adults compared to children,
17 as well as in adolescents compared to children with haemophilia was found.^{9,10} As the decrease in adherence
18 to treatment regimens from adolescence to adulthood exists, maintaining the adherence to healthcare
19 remains one of the issues in the transition process.

20 In the context of transition to adult care in adolescents and YAs with serious pediatric illness conditions,
21 the SMART (Social-ecological Model of adolescents and young adults Readiness for Transition)¹¹
22 incorporates pre-existing objective factors (sociodemographics, medical status) and modifiable subjective
23 factors (knowledge, skills, beliefs, goals, relationships, psychosocial functioning).

24 In the general context of haemophilia outside the transition process, determinants of adherence to healthcare
25 were identified as barriers (absence of or infrequent symptoms, older age) and motivators (belief in necessity
26 of treatment, good relationship with healthcare provider, experience of symptoms).¹²⁻¹⁴ Regarding the
27 transition process in young PwH, younger age, positive emotions, high self-esteem, sufficient school
28 attendance, adequate disease management, family and social support were found to be positively associated
29 with adherence to treatment in quantitative studies.^{8,15,16}

30 However, the number of quantitative studies^{8,15,16} on determinants of adherence to healthcare in young PwH
31 is very limited. This adherence was only assessed by adherence to prophylaxis. People under on-demand
32 treatment were not included. Adherence to clinical follow-up was not assessed. The power of these studies
33 is rather small, with sample sizes below 100. The determinants explored in these studies are not based on

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1 the determinants proposed by SMART. Additionally, traditional regression and statistical tests may not be
2 sufficient to analyze complex associations between these determinants.
3 The main objective of the quantitative phase of the TRANSHEMO project was to compare the adherence
4 to healthcare, which was considered as a marker of the successful transition, between adolescents and YAs
5 with severe haemophilia. The secondary objective was to identify the determinants (facilitators and barriers)
6 of this adherence and associations between these determinants by structural equation modeling (SEM).
7

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1 MATERIALS AND METHODS

2 Study design and study population

3 The study protocol of the TRANSHAMO project was previously published.¹⁷

4 It was designed as a multicenter, observational, cross-sectional study involving 29 Haemophilia Treatment
5 Centers (HTCs) in France. The inclusion criteria were PwSH A or B, aged between 14 and 17 years
6 (adolescent group) or between 20 and 29 years (YA group), followed in one of the participating HTCs,
7 included in the national registry FranceCoag,¹⁸ affiliated with the French social security system and having
8 no reading or writing difficulties. Written consent was obtained from the YAs and the parents (or legal
9 representatives) of adolescents. Participants were those who met all the inclusion criteria, consented to
10 participate and sent back the questionnaires. The inclusion period started in February 2017 and ended in
11 February 2019.

12 Ethical approval

13 The study was approved by the French Ethical Research Committees, by the French National Agency for
14 the Safety of Medicines and Health Products (reference number ID RCB: 2016-A01034-47), and by French
15 Data Protection Authority, whose principles are in line with those of the General Data Protection Regulation.
16 The protocol was registered in ClinicalTrials.gov (NCT02866526).

19 Data collection

20 Sociodemographic and psycho-behavioral data were collected by a self-administered questionnaire sent by
21 post. There were two versions of the questionnaire: one for adolescents and one for YAs. The questionnaires
22 for adolescents were completed by the adolescents themselves. People who agreed to participate completed
23 it at home and sent it back in a prepaid envelope. Clinical data were extracted from FranceCoag's database
24 and filled in a short questionnaire by the referring physician of each participant. Organizational data were
25 collected by an ad hoc questionnaire completed by the physician in charge of each HTC.

27 Measurements

28 *Main evaluation criterion*

29 The adherence to healthcare was assessed using the seven dichotomized criteria described in Table 1.

30 A composite quantitative endpoint was created by adding these criteria (7 for people under prophylaxis, 5
31 for people under on-demand treatment). Adherent people were defined as those having 4 to 7 points if under
32 prophylaxis, and as those having 3 to 5 points if under on-demand treatment.

1 **Other measurements**

2 The measurements are presented in Table 1. International validated scales and ad hoc items were used to
3 assess sociodemographic, clinical, psycho-behavioral and organizational (HTC-related) aspects. They were
4 completed by the referring physicians of the participants and/or by the participants themselves.

5 **Statistical analyses**

6 **Descriptive analysis.** Categorical variables were described by counts and percentages. Quantitative
7 variables were described by mean values and standard deviations (SD).

8 **Comparison between participants and non-participants.** Sociodemographic and clinical data were
9 compared using the chi-squared test or Fisher's test for categorical variables, and Student's t test or
10 Mann–Whitney U test for quantitative variables.

11 **Comparison of the adherence to healthcare between adolescents and YAs.** The evaluation criteria were
12 compared between adolescents and YAs using the chi-squared test.

13 **Analyses of determinants of adherence to healthcare**

14 **Univariate analysis.** The characteristics of participants were compared between adherent and non-
15 adherent people by using the chi-squared test or Fisher's test for categorical variables, and Student's t test
16 or Mann–Whitney U test for quantitative variables. The univariate logistic regression was performed to
17 analyze the association of each characteristic with the adherence to healthcare. Odds ratios (ORs) and 95%
18 confidence intervals (CIs) were calculated for this analysis.

19 **Structural equation modeling** (Figure 1). Based on the results from previous studies presented in
20 Table 2 and results of the univariate analysis, a theoretical model was built consistently with SMART. The
21 model specification is shown in Figure 1.

22 Confirmatory factor analysis (CFA) and mediation analysis were carried out to estimate the effects of the
23 determinants on adherence to healthcare. As the main evaluation criterion was a binary variable, logistic
24 regression in SEM was performed. There were two mediators (mental health concerns and haemophilia-
25 specific QoL) for the effects on the outcome. “Mental health concerns” was a latent variable manifested by
26 past-negative perspective,^{19,20} avoidance coping strategy^{21–23} and mental health-related quality of life
27 (HRQoL).²⁴ “Haemophilia-specific QoL” was a latent variable manifested by six items in the Haemo-QoL
28 Index^{25,26} (Item 2-feeling, Item 3-view, Item 4-family, Item 5-friends, Item 6-others, Item 7-sports).
29 “Autonomy” was a latent variable manifested by functional, emotional, and attitudinal autonomy.²⁷ All
30 latent variables were verified by CFA.

31 The total indirect effect via two mediators was obtained by adding two indirect effects. To estimate the total
32 effect, the direct effect was added to the total indirect effect. The model was built using diagonally weighted
33 least squares estimation with robust standard errors. ORs and 95% CIs were calculated for the direct, indirect
34

1 and total effects. Standardized coefficients (β) were calculated for the association between the two mediators
2 and the other determinants.

3 *Model fit.* Indicators to assess the model fit were Comparative Fit Index (CFI), Tucker Lewis Index
4 (TLI), Root Mean Square Error of Approximation (RMSEA), Standardized Root Mean Square Residual
5 (SRMR). Recommended cutoffs for good fit are $CFI \geq 0.90$; $TLI \geq 0.95$; $RMSEA$ and $SRMR < 0.08$.²⁸

6 All statistical tests were two-sided with p-value < 0.05 as statistically significant and performed with
7 RStudio version 3.4.1 (RStudio, Boston, MA). The Rstudio “lavaan” package was used to conduct the SEM.
8

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1 RESULTS

2 Participants

3 According to FranceCoag's database and considering the inclusion criteria, 543 questionnaires were sent.
4 There were 266 non-participants who did not send back the questionnaires and 277 participants (107
5 adolescents and 170 YAs).

6 Regarding sociodemographic and clinical characteristics, the non-participants were more frequently YAs
7 and had a history of major orthopedic interventions more often than the participants. Regarding
8 organizational factors, the non-participants more often stayed in the same hospital and service from
9 adolescence to adulthood. The non-participants came from the HTCs without education activities for
10 transition more often than the participants. The remaining sociodemographic and clinical characteristics did
11 not significantly differ between the participants and non-participants (Table 3).

13 Adherence to healthcare

14 The results concerning the main objective are presented in Table 4.

15 The adherence to healthcare in adolescents was 21% higher than in YAs (82.2% vs. 61.2%, $p < 0.001$).

16 The adolescents also had better results than the YAs in all subcriteria. Wider differences between
17 adolescents and YAs were found in the physician-reported adherence to clinical follow-up (+22.9%,
18 $p < 0.001$) and in the adherence to prophylaxis if under this treatment (+26.6%, $p < 0.001$).

19 In the univariate analysis (Table 5), people having repeated at least one school grade (OR 0.31; 95% CI
20 0.18-0.53) and people having history of major orthopedic interventions (OR 0.40; 95% CI 0.18-0.92) were
21 less likely to adhere to healthcare, while members of the French association for people with haemophilia
22 (OR 1.74; 95% CI 1.04-2.97) and people under prophylaxis (OR 2.51; 95% CI 1.27-4.94) were more likely
23 to adhere to healthcare. No significant differences were found in comorbidities, psycho-behavioral and
24 organizational factors.

25 The results of SEM are presented in Figure 2, Table 6 and Table 7. Being YA (OR 0.64; 95% CI 0.41-0.99),
26 having repeated at least one school grade (OR 0.47; 95% CI 0.31-0.71) and presenting mental health
27 concerns (OR 0.37; 95% CI 0.15-0.94) had negative effects on adherence to healthcare. No significant direct
28 effects of the remaining factors on the adherence, neither indirect effects were found.

29 Regarding the association between the determinants, higher level of autonomy was associated with fewer
30 mental health concerns ($\beta = -0.10$, $p < 0.001$) and better haemophilia-specific QoL ($\beta = -0.09$, $p < 0.001$).
31 Higher frequency of using social support coping strategies was associated with more mental health concerns
32 ($\beta = 0.09$, $p = 0.022$).

33 Indicators verifying good fit of the model were CFI=0.919, TLI=0.964, RMSEA=0.031, SRMR=0.054.

1 DISCUSSION

2 Comparison of the adherence to healthcare between adolescents and YAs

3 In this study, the adherence to healthcare in adolescents was 21% higher than in YAs. The adolescents also
4 had better results than the YAs in all subcriteria. This result is consistent with the findings of previous
5 studies on adherence to prophylaxis of young PwH. Geraghty et al. showed that 54% of their participants
6 aged 13 to 18 years had high adherence, while this rate was 36% in the 19-28 age group.⁷ Witktop et al. also
7 reported a higher percentage of adherence to prophylaxis in adolescents (13-17 years) compared to YAs
8 (18-25 years) (83% vs. 53%, $p=0.01$).⁸ Van Os et al. used VERITAS-Pro (Validated Hemophilia Regimen
9 Treatment Adherence Scale-Prophylaxis) and found better adherence in adolescents (12-17 years) than in
10 YAs (18-25 years).¹⁵ These studies focused on adherence to prophylaxis, without including adherence to
11 on-demand treatment and to clinical follow-up.

12 Determinants of the adherence to healthcare

13 Being YA and having repeated at least one school grade had negative direct effects on adherence. Presenting
14 mental health concerns was considered simultaneously as a determinant and a mediator in this model. Its
15 direct effect on the outcome was found, whereas the indirect effects through this mediator were not
16 significant.

17 Being YA had a negative direct effect on the adherence to healthcare. During the transition from adolescence
18 to adulthood, like other people, young PwSH may have pressures and changes in their life when they move
19 out of their parents' house, adapt to lifestyle changes, have new relationships and make a career.^{4-6,29,30}
20 However, they have an additional difficulty, which is disease management. It seems that the shift in
21 responsibilities for disease management from parents is the most common reason for the non-adherence of
22 YAs.⁸ They need to take responsibility for building a relationship with a new medical team when transferring
23 from pediatric to adult services, communicating with caregivers, managing to attend clinic appointments,
24 adapting to a complex treatment plan, performing self-injection and reordering medicine.^{5,6,31} These
25 healthcare-related challenges can make them feel uncomfortable following treatment plans and avoid
26 regular medical visits.

27 The negative effect of having repeated at least one school grade on adherence to healthcare has not been
28 analyzed previously, and school-related problems have been rarely studied. A positive association between
29 sufficient school attendance and adherence to prophylaxis was found in a study on QoL in children and
30 adolescents with haemophilia A.¹⁶ Concerning childhood chronic disease like haemophilia, academic
31 difficulty may be a potential marker for the difficulties in seeking and applying health information.
32 Knowledge about the disease, sufficient abilities and skills in treatment management have been considered
33 to be important for adequate adherence to healthcare and successful transition to adult care.^{12,15,31,32} This
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1 finding on academic achievement emphasizes the essential role of adapted and targeted education programs,
2 during transition process.^{5,6}

3 Mental health concerns (avoidance coping strategies, past negative perceptions, mental HRQoL) directly
4 impaired the adherence to healthcare. Avoidance coping strategies can be considered as a lack of disease
5 acceptance. Previous studies^{6,15,31,32} found that struggling with haemophilia acceptance was associated with
6 a lower level of adherence to healthcare, since this adherence was perceived as a burden. PwSH may avoid
7 coping with difficulties in disease management since they think that prophylaxis and clinical follow-up
8 would interfere in daily activities, preventing them from integrating into life with other people.^{4-6,31,33}
9 Avoidance, which is less adaptive for long-term psychological well-being,³⁴ may not be a suitable way to
10 eliminate psychological distress in a complex phase like the transition process from adolescence and
11 adulthood. Certain concerns, such as stress, worries about understanding health information, fear of lifestyle
12 changes and fear of the unknown, are very common in young PwSH during the transition process and may
13 have negative impacts on the adherence to healthcare.^{5,15,16,30,31,35} These concerns stem from their negative
14 experiences with the disease, which may constrain social-emotional functioning, making it difficult for them
15 to prepare for taking responsibility, to maintain a healthy mental state and good QoL. Acquiring autonomy,
16 for example by gradually assuming responsibility, and appropriate social support, such as therapeutic
17 education programs, accompaniment of medical team, support from family, friends and peers, can be
18 effective to enhance mental health and QoL.⁶

19 Autonomy was not significantly associated with adherence to healthcare. However, it was associated with
20 improvement in mental health and QoL, which may help young people adapt better to the condition.
21 Autonomy during the transition from adolescence to adulthood can be developed by adjusting life (i.e.,
22 taking new opportunities and responsibilities) for self-regulation and independent decision-making.^{36,37}
23 Helping young PwSH to acquire autonomy may be a good way to calm their worries about treatment
24 management and gain confidence in making decisions and assuming responsibility.

25 Use of social support coping strategies was positively associated with the presence of mental health concerns.
26 This result showed that people with mental health concerns needed more social support from others (e.g.,
27 help, comfort, understanding, advice), probably because they do not have enough personal resources to
28 lighten the burden. Although they are frequently supported by others, this support may not be sufficient for
29 them. These findings may suggest the essential role of family and social support in enhancing mental health
30 for young PwSH during their transition process.

31 Although we assumed that comorbidities and complications of severe haemophilia might have impacts on
32 the adherence to healthcare, significant associations between these clinical factors and the adherence were
33 not found.

34

1 **Strengths and limitations**

2 Certain limitations need to be acknowledged. This study was designed as a cross-sectional study to provide
3 a general understanding of the adherence to healthcare in young PwSH. Future longitudinal study allowing
4 to follow PwSH from adolescence to adulthood could be proposed to evaluate changes during the transition
5 process and shed light on the findings of our study.

6 The validity of the results might be affected by the non-inclusion of some eligible people, especially those
7 who did not return the questionnaire. The non-participants were more often followed by the HTC's in the
8 same hospital and same medical service from adolescence to adulthood. This might suggest that they were
9 less interested in the transition issue.

10 Although the main outcome of this study is still debatable as a measure of the successful transition, it allows
11 to assess the adherence to healthcare more completely than previous studies, as it combines physician- and
12 patient-reported adherence to treatment regimens and to clinical follow-up, as well as the number of
13 prophylactic injections, number of follow-up visits and number of hemorrhagic events collected in the
14 FranceCoag registry database. Moreover, the level of adherence to healthcare is in the top five of healthcare
15 transition outcomes identified by the Delphi process with an interdisciplinary group of medical and
16 psychosocial professionals.³⁸ It can apply for adolescents and YAs, allowing for a more specific assessment
17 of the potential impact on the transition from adolescence to adulthood. Since the distance between Likert-
18 type response options might not be equal, ³⁹ and since some of the subcriteria assessing the adherence in
19 our study were binary criteria and some others were based on 5-point Likert-scales, the Likert-type
20 responses were dichotomized to make all the subcriteria similar in order to create a composite endpoint .

21 To the best of our knowledge, the sample size of this study is larger than that of previous studies on
22 adherence to healthcare in young PwSH. The participants were included from the exhaustive national cohort
23 of PwSH in France (FranceCoag registry).

24 Although not all the associations between the potential determinants and the adherence to healthcare
25 hypothesized in the theoretical model were significant, this model suited to explore the determinants of the
26 adherence to healthcare, as recommended indicators for goodness of fit were acquired. Moreover, the SEM
27 had higher statistical power than that of traditional regressions and allowed to analyze associations between
28 the determinants.⁴⁰ Additionally, the determinants were chosen based on data from the literature and
29 consistent with SMART, which can be considered as an ideal framework to identify the determinants of
30 transition for people with serious pediatric illness conditions.¹¹

31 **CONCLUSION**

32 Adolescents with severe haemophilia adhere better to healthcare than YAs. The barriers to the adherence to
33 healthcare were being YA, having repeated at least one school grade and presenting mental health concerns.
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1 Based on these barriers, healthcare professionals can develop targeted supportive strategies and adapted
2 therapeutic education programs, which will be proposed to young PwSH according to their profiles. The
3 TRANSHAMO project is based on a mixed methods design with quantitative and qualitative phases. The
4 qualitative phase will shed light on the results from the quantitative phase and will be published later.
5

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13 The authors have no competing interests.

14 **Data sharing statement**

15 The data that support the findings of this study are available on request from the corresponding author.

16 The data are not publicly available due to privacy or ethical restrictions.

17 **Appendix: TRANSHEMO Study Group**

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Table 1. Measurements

| Dichotomized criteria assessing the adherence to healthcare | | |
|--|--|---|
| | Original | Dichotomized |
| Number of follow-up visits over the last two years (FranceCoag registry) | Quantitative variable | In agreement / Not in agreement with the recommended number |
| Physician-reported adherence to clinical follow-up | - Very high - High - Average - Low - Very low | Very high / High to very low |
| Patient-reported adherence to clinical follow-up | Visiting Haemophilia Treatment Centre (HTC) at least once a year / Not visiting HTC every year | |
| If under prophylaxis, number of prophylactic injections over the last three months (FranceCoag registry) | Quantitative variable | In agreement / Not in agreement with the recommended number |
| If under prophylaxis, physician-reported adherence to prophylaxis | - Very high - High - Average - Low - Very low | Very high / High to very low |
| Patient-reported adherence to treatment | <p>If under prophylaxis:</p> <p>- Having no difficulties in adherence to prophylaxis or having difficulties but missing treatment less than once a week / Having difficulties and missing treatment once a week or more</p> <p>If under on-demand treatment:</p> <p>- Having no difficulties in recognizing early signs of hemorrhage / Having difficulties in recognizing early signs of hemorrhage</p> | |
| Physician-reported number of hemorrhagic events over the last two years | Quantitative variable | None / At least one |
| Sociodemographics | | |
| Age, sex | | |
| Living near the HTC | Yes (under 30 km) / No (more than 30 km) | |
| Socioeconomic status (SES) of family measured by Family Affluence Scale (FAS) | 4-item questionnaire measuring family material wealth Scores ranging from 0 to 5 indicating "low or medium" SES Scores ranging from 6 to 9 indicating "high" SES | |
| Academic difficulty | At least one grade repetition at school | |
| Member of French association for people with haemophilia (AFH) | Yes / No | |

| | |
|---|--|
| Clinical characteristics | |
| Type of haemophilia | Severe haemophilia A or B |
| Comorbidity | Human immunodeficiency virus (HIV) infection Hepatitis B virus (HBV) infection Hepatitis C virus (HCV) infection Cancer Other chronic pathology |
| Complication | History of inhibitors Current inhibitor status (if having history of inhibitors) History of intracranial hemorrhage History of major orthopedic interventions |
| Current treatment regimen | On-demand treatment Prophylaxis |
| Self-injection (if under prophylaxis) | Yes / No (by family members and/or healthcare professionals) |
| Number of injections per week (if under prophylaxis) | 1 injection 2 or more than 2 injections |
| Emicizumab | Yes / No |
| Psycho-behavioral factors | |
| Family functioning measured by Family Assessment Device (FAD) | 6-item questionnaire Scores range from 1 to 4 with lower score indicating better general family functioning |
| Generic quality of life (QoL) measured by Short form 12 Health Survey (SF- 12) | Two subscores: Physical component score (PCS) for physical health-related quality of life (HRQoL), mental component score (MCS) for mental HRQoL. Scores range from 0 to 100 with higher scores indicating better HRQoL |
| Haemophilia-specific QoL measured by Haemo-QoL Index | 8-item questionnaire Each item represents for one dimension of QoL: Physical well- being, emotional well-being, perceived support, relationship with friends, view, relationship with others, sports, treatment management Scores range from 0 to 100 with lower scores indicating better haemophilia-specific QoL |
| Coping strategies measured by Brief Coping Orientation to Problems Experienced Scale (Brief COPE) | 28-item questionnaire evaluating 14 coping strategies, which are grouped into four main strategies: Social support, problem solving, avoidance, and positive thinking Higher scores indicate a more frequent use of the assessed coping strategy |
| Autonomy measured by Noom questionnaire | 15-item questionnaire classified into three dimensions: Attitudinal autonomy, Functional autonomy, Emotional autonomy Scores range from 5 to 25 with higher scores indicating higher level of autonomy |

| | |
|---|---|
| Time perspective measured by Zimbardo Time Perspective Inventory (ZTPI) | Two subscales “Negative past” (9 items) and “Future” (12 items) were retained from the original 56-item questionnaire, measuring tendency to focus on different aspects of the past and future Higher scores indicate stronger projection in the assessed time perspective |
| Satisfaction with the clinical follow-up of the HTC | Yes / No |
| Organizational (HTC-related) factors | |
| Type of healthcare transition in the HTC | Same hospital and service for adolescents and adults Same hospital, two different services (pediatric/adult) |
| Pediatrician in the medical team of the HTC | Yes / No |
| Setup of therapeutic education activities for transition in the HTC | Yes / No |

Table 2. Previous findings on adherence to treatment regimens of PwH

| | Findings | References |
|---|---|-------------------------------|
| Comparison between adolescents and young adults | Adolescents have better adherence to healthcare compared to young adults | 7, 8, 15, 33 |
| Factors positively associated with adherence | <ul style="list-style-type: none"> - Younger age - Lower level of chronic pain, fewer orthopedic interventions, better physical functioning associated with better adherence to prescribed treatment regimen - Good quality of life | 5, 6, 7, 8, 9, 10, 15, 16, 33 |
| Factors negatively associated with adherence | <ul style="list-style-type: none"> - Negative emotions, inadequate emotional management, low self-esteem - Struggling with stress of disease acceptance, concerns about treatment - Overprotection of family - Limitations in sport practices | 5, 15, 16, 35 |
| Challenges during the transition from adolescence to adulthood | <ul style="list-style-type: none"> - Education - Finances - Career - New relationships - Communication and collaboration with medical team | 6, 8, 30 |

Table 3. Characteristics of the participants and non-participants

| | Participants (n=277) | Non- participants (n=266) | p-value |
|---|-------------------------|---------------------------------|---------|
| <i>Sociodemographics</i> | | | |
| Group | | | <0.001 |
| Adolescents | 107 (38.6) | 62 (23.3) | |
| Young adults | 170 (61.4) | 204 (76.7) | |
| Age, mean (SD) | 21.3 (5.1) | 21.8 (4.6) | 0.201 |
| Sex: male, n (%) | 273 (98.6) | 266 (100.0) | 0.124 |
| <i>Clinical characteristics</i> | | | |
| Type of haemophilia, n (%) | | | 0.634 |
| Haemophilia A | 241(87.0) | 235 (88.3) | |
| Haemophilia B | 36 (13.0) | 31 (11.7) | |
| At least one comorbidity: yes, n (%) | 35 (12.6) | 36 (13.5) | 0.756 |
| Comorbidity: yes, n (%) | | | |
| HIV infection | 0 | 0 | |
| HBV infection | 7 (2.5) | 2 (0.8) | 0.177 |
| HCV infection | 3 (1.1) | 3 (1.1) | 0.999 |
| Cancer | 2 (0.7) | 1 (0.4) | 0.999 |
| Other chronic pathology | 16 (5.8) | 20 (7.5) | 0.415 |
| Complication: n (%) | | | |
| History of inhibitors | | | 0.286 |
| No | 215 (77.6) | 196 (73.7) | |
| Yes | 62 (22.4) | 70 (26.3) | |
| Current inhibitor status (if having history of inhibitors) | | | 0.092 |
| Disappeared | 47 (75.8) | 61 (87.1) | |
| Always present | 15 (24.2) | 9 (12.9) | |
| History of intracranial hemorrhage | | | 0.604 |
| No | 266 (96.0) | 253 (95.1) | |
| Yes | 11 (4.0) | 13 (4.9) | |
| History of major orthopedic interventions | | | <0.001 |
| No | 251 (90.6) | 198 (74.4) | |
| Yes | 26 (9.4) | 68 (25.6) | |
| Current treatment regimen, n (%) | | | 0.307 |
| On-demand treatment | 41(14.8) | 48 (18.0) | |
| Prophylaxis | 236 (85.2) | 218 (82.0) | |
| Emicizumab, n (%) | | | 0.240 |
| No | 277 (100) | 264 (99.2) | |
| Yes | 0 | 2 (0.08) | |
| <i>Organizational (HTC-related) factors: yes, n (%)</i> | | | |
| Type of healthcare transition in the HTC | | | <0.001 |
| Same hospital and service for adolescents and adults | 177 (63.9) | 227 (85.3) | |
| Same hospital, two different services (pediatric/adult) | 100 (36.1) | 39 (14.7) | |

| | | | |
|--|------------|------------|-------|
| Pediatrician in the medical team of HTC | 208 (75.1) | 210 (79.0) | 0.286 |
| Setup of therapeutic patient education activities for transition by the HTC | 60 (21.7) | 40 (15.0) | 0.047 |

Abbreviations: HIV, human immunodeficiency virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HTC, haemophilia treatment center.

For Peer Review

Table 4. Comparison of the adherence to healthcare between adolescents and young adults

| | All participants (n=277) | Adolescents (n=107) | Young adults (n=170) | p-value |
|--|---|--------------------------------|-------------------------------------|----------------|
| Composite main evaluation criterion, adherence to healthcare: yes, n (%) | 192 (69.3) | 88 (82.2) | 104 (61.2) | <0.001 |
| Evaluation criteria: yes, n (%) | | | | |
| Adherence to recommended number of follow-up visits | 144 (52.0) | 61 (57.0) | 83 (48.8) | 0.184 |
| Physician-reported adherence to clinical follow-up | 145 (52.4) | 71 (66.4) | 74 (43.5) | <0.001 |
| Patient-reported adherence to clinical follow-up | 231 (83.4) | 97 (90.7) | 134 (78.8) | 0.010 |
| If under prophylaxis, adherence to recommended prophylactic treatment injections | 184 (78.0) | 89 (84.8) | 95 (72.5) | 0.024 |
| If under prophylaxis, physician-reported adherence to the prophylaxis | 145 (61.4) | 80 (76.2) | 65 (49.6) | <0.001 |
| Patient-reported adherence to treatment | 248 (89.5) | 98 (91.6) | 150 (88.2) | 0.375 |
| At least one hemorrhagic event | 216 (78.0) | 82 (76.6) | 134 (78.8) | 0.669 |

Table 5. Characteristics of the adherent and non-adherent people

| | Non-adherent people (n=85) n/mean (%/SD) | Adherent people (n=192) n/mean (%/SD) | p-value | OR (95% CI) |
|--|---|--|----------------|--------------------|
| <i>Sociodemographics</i> | | | | |
| Group | | | <0.001 | |
| Adolescents | 19 (17.8) | 88 (82.2) | | |
| Young adults | 66 (38.8) | 104 (61.2) | | 0.34 (0.19-0.60) |
| Age, years | 22.9 (4.4) | 20.6 (5.2) | <0.001 | 0.91 (0.86-0.96) |
| Age group (if adolescent) | | | 0.073 | |
| 14-15 | 5 (10.4) | 43 (89.6) | | |
| 16-17 | 14 (23.7) | 45 (76.3) | | 0.37 (0.11-1.07) |
| Age group (if young adult) | | | 0.888 | |
| 20-24 | 31 (38.3) | 50 (61.7) | | |
| 25-29 | 35 (39.3) | 54 (60.7) | | 0.96 (0.51-1.77) |
| Sex | | | >0.999 | |
| Male | 84 (30.8) | 189 (69.2) | | |
| Female | 1 (25.0) | 3 (75.0) | | 1.33 (0.17-27.17) |
| Living near the HTC | | | 0.440 | |
| No | 44 (28.8) | 109 (71.2) | | |
| Yes | 41 (33.1) | 83 (66.9) | | 0.82 (0.49-1.37) |
| Socioeconomic status of the family | | | 0.059 | |
| Low or medium | 48 (35.8) | 86 (64.2) | | |
| High | 36 (25.4) | 106 (74.6) | | 1.64 (0.98-2.77) |
| Academic difficulty (at least one grade repetition at school) | | | <0.001 | |
| No | 29 (19.3) | 121 (80.7) | | |
| Yes | 55 (43.7) | 71 (56.3) | | 0.31 (0.18-0.53) |
| Member of AFH | | | 0.037 | |
| No | 54 (36.0) | 96 (64.0) | | |
| Yes | 31 (24.4) | 96 (75.6) | | 1.74 (1.04-2.97) |
| <i>Clinical characteristics</i> | | | | |
| Type of haemophilia | | | 0.712 | |
| Haemophilia A | 73 (30.3) | 168 (69.7) | | |
| Haemophilia B | 12 (33.3) | 24 (66.7) | | 0.87 (0.42-1.89) |
| At least one comorbidity | | | 0.546 | |
| No | 76 (30.2) | 176 (69.8) | | |
| Yes | 9 (36.0) | 16 (64.0) | | 0.77 (0.33-1.89) |
| HIV infection | | | - | |
| No | 85 (30.7) | 192 (69.3) | | |
| Yes | 0 | 0 | | - |
| HBV infection | | | 0.442 | |
| No | 82 (30.4) | 188 (69.6) | | |
| Yes | 3 (42.9) | 4 (57.1) | | 0.58 (0.13-3.01) |
| HCV infection | | | 0.555 | |
| No | 85 (30.7) | 189 (69.3) | | |
| Yes | 0 | 3 (100.0) | | 3.16 (0.30-426.43) |

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|---|-------------|-------------|-------|-------------------|
| Cancer | | | 0.520 | |
| No | 84 (30.6) | 191 (69.4) | | |
| Yes | 1 (50.0) | 1 (50.0) | | 0.44 (0.02-11.2) |
| Other chronic pathology | | | 0.999 | |
| No | 80 (30.7) | 181 (69.3) | | |
| Yes | 5 (31.3) | 11 (68.7) | | 0.97 (0.34-3.17) |
| Complication | | | | |
| At least one complication | | | 0.696 | |
| No | 60 (31.4) | 131 (68.6) | | |
| Yes | 25 (29.1) | 61 (70.9) | | 1.12 (0.65-1.97) |
| History of inhibitors | | | 0.344 | |
| No | 69 (32.1) | 146 (67.9) | | |
| Yes | 16 (25.8) | 46 (74.2) | | 1.36 (0.73-2.63) |
| Current inhibitor status (if having history of inhibitors) | | | 0.505 | |
| Disappeared | 11 (23.4) | 36 (76.6) | | |
| Always present | 5 (33.3) | 10 (66.7) | | 0.61 (0.17-2.30) |
| History of intracranial hemorrhage | | | 0.181 | |
| No | 84 (31.6) | 182 (68.4) | | |
| Yes | 1 (9.1) | 10 (90.9) | | 4.62 (0.86-85.39) |
| History of major orthopedic interventions | | | 0.025 | |
| No | 72 (28.7) | 179 (71.3) | | |
| Yes | 13 (50.0) | 13 (50.0) | | 0.40 (0.18-0.92) |
| Current treatment regimen | | | 0.007 | |
| On-demand treatment | 20 (48.8) | 21 (51.2) | | |
| Prophylaxis | 65 (27.5) | 171 (72.5) | | 2.51 (1.27-4.94) |
| Self-injection (if under prophylaxis) | | | 0.429 | |
| No (by family members and/or healthcare professionals) | 20 (24.4) | 62 (75.6) | | |
| Yes | 45 (29.2) | 109 (70.8) | | 0.78 (0.42-1.43) |
| Number of injections per week (if under prophylaxis) | | | 0.438 | |
| 1 injection | 5 (20.8) | 19 (79.2) | | |
| 2 or more than 2 injections | 60 (28.3) | 152 (71.7) | | 0.67 (0.21-1.74) |
| Psycho-behavioral factors | | | | |
| Family functioning (score of FAD) | 1.87 (0.6) | 1.78 (0.6) | 0.248 | 0.78 (0.51-1.19) |
| Participation in therapeutic education activities | | | 0.949 | |
| No | 28 (30.4) | 64 (69.6) | | |
| Yes | 57 (30.8) | 128 (69.2) | | 0.98 (0.57-1.68) |
| Quality of life | | | | |
| Physical health (PCS) | 46.3 (10.7) | 48.2 (10.2) | 0.154 | 1.02 (0.99-1.04) |
| Mental health (MCS) | 47.8 (10.7) | 49.0 (9.2) | 0.344 | 1.01 (0.99-1.04) |
| Haemophilia-specific quality of life (Haemo-QoL Index) | 33.4 (24.9) | 32.9 (21.9) | 0.889 | 1.00 (0.99-1.01) |
| Coping strategies (scores of Brief COPE) | | | | |

| | | | | | |
|----|---|------------|------------|-------|------------------|
| 1 | | | | | |
| 2 | | | | | |
| 3 | Social support | 3.8 (1.1) | 3.7 (0.9) | 0.251 | 0.86 (0.66-1.11) |
| 4 | Problem solving | 5.1 (1.3) | 5.0 (1.4) | 0.803 | 0.98 (0.81-1.18) |
| 5 | Avoidance | 3.6 (0.8) | 3.4 (0.7) | 0.147 | 0.77 (0.53-1.10) |
| 6 | Positive thinking | 5.2 (1.1) | 5.4 (1.2) | 0.190 | 1.16 (0.93-1.44) |
| 7 | | | | | |
| 8 | Autonomy | | | | |
| 9 | (scores of Noom questionnaire) | | | | |
| 10 | Attitudinal autonomy | 17.3 (4.0) | 17.4 (4.4) | 0.883 | 1.00 (0.94-1.07) |
| 11 | Functional autonomy | 18.5 (3.8) | 18.2 (4.1) | 0.550 | 0.98 (0.92-1.05) |
| 12 | Emotional autonomy | 18.1 (2.9) | 18.0 (3.9) | 0.910 | 1.00 (0.93-1.07) |
| 13 | | | | | |
| 14 | Time perspective (scores of ZTPI) | | | | |
| 15 | Negative past | 2.75 (0.7) | 2.68 (0.7) | 0.426 | 0.86 (0.59-1.24) |
| 16 | Future | 3.29 (0.5) | 3.29 (0.6) | 0.973 | 0.99 (0.62-1.58) |
| 17 | | | | | |
| 18 | Satisfaction with the clinical follow- | | | | |
| 19 | up of the HTC | | | 0.228 | |
| 20 | No | 6 (46.2) | 7 (53.8) | | |
| 21 | Yes | 79 (29.9) | 185 (70.1) | | 2.01 (0.63-6.23) |
| 22 | | | | | |
| 23 | Organizational (HTC-related) factors | | | | |
| 24 | Type of healthcare transition in the | | | | |
| 25 | HTC | | | 0.317 | |
| 26 | Same hospital, two different | | | | |
| 27 | services (pediatric/adult) | 27 (27.0) | 73 (73.0) | | |
| 28 | Same hospital and service for | | | | |
| 29 | adolescent and adults | 58 (32.8) | 119 (67.2) | | 0.76 (0.44-1.03) |
| 30 | | | | | |
| 31 | Pediatrician in the medical team of | | | | |
| 32 | the HTC | | | 0.395 | |
| 33 | No | 24 (34.8) | 45 (65.2) | | |
| 34 | Yes | 61 (29.3) | 147 (70.7) | | 1.29 (0.71-2.28) |
| 35 | | | | | |
| 36 | Setup of therapeutic education | | | | |
| 37 | activities for transition by the HTC | | | 0.896 | |
| 38 | No | 67 (30.9) | 150 (69.1) | | |
| 39 | Yes | 18 (30.0) | 42 (70.0) | | 1.04 (0.57-1.98) |

Abbreviations: OR, odds ratio; CI, confidence interval; HTC, haemophilia treatment center; HIV, human immunodeficiency virus; HBV, hepatitis B virus; HCV, hepatitis C virus; FAD, Family Assessment Device; AFH, French association for people with haemophilia; HRQoL, health-related quality of life; PCS, physical component summary; MCS, mental component summary; Brief COPE, Brief Coping Orientation to Problems Experienced; ZTPI, Zimbardo Time Perspective Inventory.

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Table 6. Association of the determinants with two mediators of the structural equation model

| | Standardized coefficient (β) | p-value |
|--|---|---------|
| <i>Mental health concerns</i>[†] | | |
| Sociodemographics | | |
| High socioeconomic status of family | -0.04 | 0.608 |
| At least one grade repetition at school | -0.08 | 0.337 |
| Member of AFH | -0.07 | 0.397 |
| Clinical characteristics | | |
| Being young adult | 0.13 | 0.153 |
| At least one comorbidity | 0.23 | 0.099 |
| At least one complication | 0.09 | 0.287 |
| Current treatment: Prophylaxis | -0.01 | 0.925 |
| Psycho-behavioral factors | | |
| Social support | 0.09 | 0.022 |
| Autonomy [‡] | -0.10 | <0.001 |
| <i>Haemophilia-specific quality of life</i>[§] | | |
| Sociodemographics | | |
| High socioeconomic status of family | -0.14 | 0.295 |
| At least one grade repetition at school | 0.19 | 0.119 |
| Member of AFH | -0.06 | 0.653 |
| Clinical characteristics | | |
| Being young adult | 0.04 | 0.628 |
| At least one comorbidity | 0.41 | 0.062 |
| At least one complication | 0.21 | 0.098 |
| Current treatment: Prophylaxis | 0.24 | 0.216 |
| Psycho-behavioral factors | | |
| Social support | 0.12 | 0.051 |
| Autonomy [‡] | -0.09 | <0.001 |

Abbreviations: AFH, French association for people with haemophilia.

[†]Latent variable manifested by Past-negative perspective of ZTPI, Avoidance of Brief COPE, Mental component summary (MCS) of SF-12.

[‡]Latent variable manifested by attitudinal, functional and emotional autonomy of the Noom questionnaire.

[§]Latent variable manifested by item 2-feeling, item 3-view, item 4-family, item 5- friends, item 6-others, item 7-sports of the Haemo-QoL Index.

Table 7. Determinants of the adherence to healthcare

| | Direct Effect | Total Indirect Effect[†] | Total Effect |
|---|----------------------|--|---------------------|
| | OR (95% CI) | OR (95% CI) | OR (95% CI) |
| Sociodemographics | | | |
| High socioeconomic status of family | 1.10 (0.73–1.67) | 0.99 (0.85–1.14) | 1.09 (0.73–1.61) |
| At least one grade repetition at school | 0.47 (0.31–0.71) | 1.16 (0.96–1.41) | 0.56 (0.38–0.81) |
| Member of AFH | 1.00 (0.68–1.48) | 1.05 (0.91–1.20) | 1.05 (0.71–1.54) |
| Clinical characteristics | | | |
| Being young adult | 0.64 (0.41–0.99) | 0.91 (0.76–1.10) | 0.55 (0.38–0.80) |
| At least one comorbidity | 1.06 (0.50–2.22) | 0.94 (0.71–1.23) | 1.01 (0.50–2.04) |
| At least one complication | 1.47 (0.94–2.31) | 1.00 (0.86–1.15) | 1.46 (0.95–2.25) |
| Current treatment: Prophylaxis | 1.58 (0.93–2.68) | 1.11 (0.90–1.38) | 1.75 (1.05–2.91) |
| Psycho-behavioral factors | | | |
| Mental health concerns [‡] | 0.37 (0.15–0.94) | - | - |
| Haemophilia-specific quality of life [§] | 1.49 (0.95–2.33) | - | - |
| Social support | 0.96 (0.78–1.17) | 0.96 (0.88–1.04) | 0.92 (0.75–1.12) |
| Autonomy [¶] | 0.94 (0.85–1.03) | 1.06 (0.99–1.14) | 0.99 (0.93–1.05) |
| Organizational (HTC-related) factors | | | |
| Same hospital and service for adolescents and adults | 0.76 (0.51–1.14) | - | - |
| Pediatrician in the medical team of the HTC | 0.86 (0.53–1.40) | - | - |
| Setup of therapeutic education activities for transition by the HTC | 0.81 (0.49–1.33) | - | - |

Abbreviations: OR, odds ratio; CI, confidence interval; AFH, French association for people with haemophilia; HTC, haemophilia treatment center.

[†]Indirect effect via Mental health concerns and Haemophilia-specific quality of life

[‡] Latent variable manifested by Past-negative perspective of ZTPI, Avoidance of Brief COPE, Mental component summary (MCS) of SF-12.

[§]Latent variable manifested by item 2-feeling, item 3-view, item 4-family, item 5-friends, item 6-others, item 7-sports of the Haemo-QoL Index.

[¶]Latent variable manifested by attitudinal, functional and emotional autonomy of the Noom questionnaire.

Figure 1. Model specification for the determinants of the adherence to healthcare.

Rectangles represent observed variables, ovals represent latent variables, single-headed arrows represent direct effects, and double-headed row represents correlation.

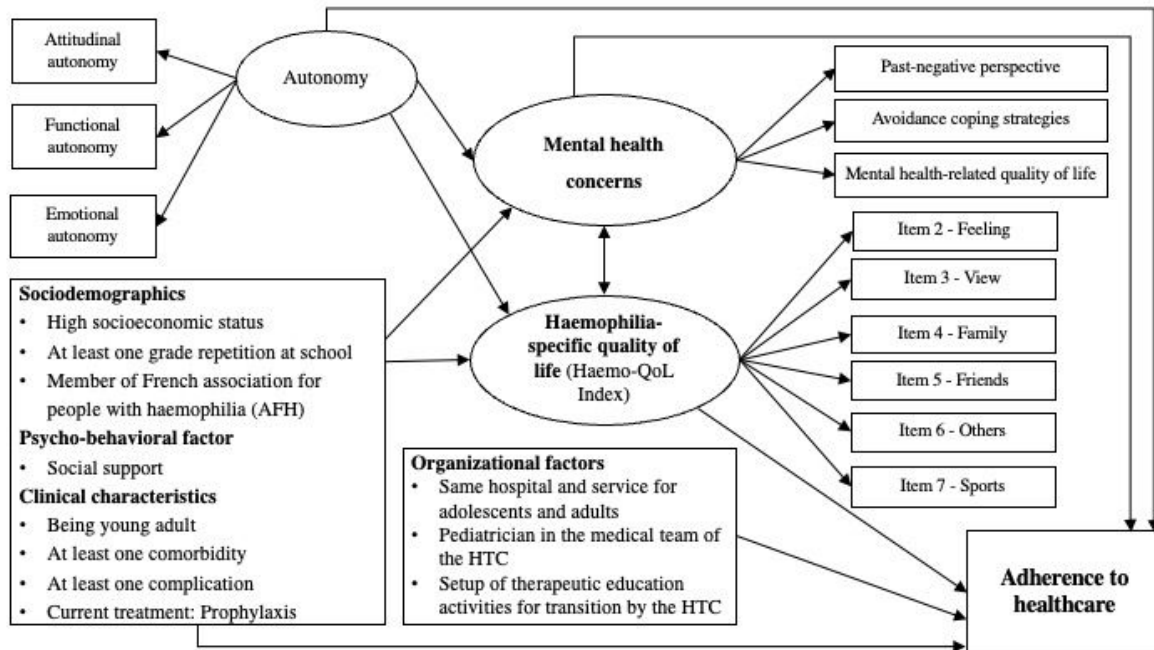


Figure 2. Results of the structural equation model.

Associations of the determinants with mental health concerns and haemophilia-specific quality of life are presented by standardized coefficients (β). Effects on adherence to healthcare are presented by odds ratios (ORs). Dashed arrows represent non-significance.

a: associations of the determinants with two mediators are presented in Table 6.

b: factor loadings of the latent variable “Autonomy” manifested by attitudinal, functional and emotional autonomy of the Noom questionnaire are 0.80; 0.74; 0.47, respectively.

