

# Categorizing factors of adherence to parenteral treatment in growth hormone deficiencies and hemophilia: What should be the targets for future research?

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**Abstract:** Adherence to treatment regimens in growth hormone dysregulations and hemophilia is related to better outcome and fewer complications over time. Subcutaneous growth hormone injection and intravenous blood factor replacement therapies are parenteral treatments with a comparable regimen calling for similar behavioral processes. Although we have lists of possible factors influencing adherence in these conditions, the evidence is scattered. The objective of this study was to systematically review empirical studies linking factors of adherence with measures of adherence. To categorize the factors, we used a taxonomy from the diabetes literature. We used four major electronic databases to identify articles. We synthesized 27 articles dated 2011–2017 corresponding to inclusion criteria. Results showed a consistent proportion of 20%–25% participants with adherent issues. Strong arguments pointed to the transition to self-care in pediatrics as a vulnerability period (7/27 reports). We found the domains of individual factors (<30% reports), relational factors (<13%), health care (<30%), to be understudied in comparison with that of demographic or clinical context (>74%), and practical issues (>37%). The results suggest that future research should focus on modifiable factors of adherence, with appropriate measurement and intervention strategies. One central methodological limitation of reviewed reports was the lack of longitudinal designs, and the quasi absence of behavioral trial targeting modifiable factors of adherence. A new research agenda should be set in these rare diseases as higher adherence should translate into improved outcome and better quality of life for patients and their families.

**Keywords:** adherence, factors, predictors, classification, growth hormone, hemophilia

## Introduction

Growth hormone (GH) dysregulations including growth hormone deficiencies (GHDs) and hemophilia are rare diseases affecting children and adults (prevalence 1–25/100,000 in childhood). They are non-curable diseases, generally diagnosed early and treated through the life span with replacement therapy designed to provide long-term benefits and avoid important health complications. In GHD for instance, poor adherence can undermine important health outcomes such as stature and height velocity.<sup>1,2</sup> Two-year follow-ups showed that children who missed more than half of their monthly dose had lower annual growth (6 cm/year) than those who missed less than half of their doses (9 cm/year).<sup>3</sup> In severe hemophilia, prophylactic replacement therapy has been the most effective treatment approach to prevent bleeding and maintain joint function. In this condition, recent studies demonstrate that adherence is associated with

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reduced chronic pain, improved physical functioning, and less orthopedic surgery.<sup>4,5</sup> However, adherent treatment behaviors have rarely been studied systematically, and factors of adherence are still unclear in these clinical contexts. The common characteristics of timeline, and the consistent role of treatment behaviors involving injection/infusion including a third party in childhood, suggest that behaviors may be approached similarly in these conditions. In addition, comparisons may be drawn with a far more prevalent condition (type 1 diabetes 300/100,000), where behavioral research is advanced.

GH therapy is indicated in a variety of conditions such as GHD. In this case, the treatment regimen typically includes daily injections of recombinant human GH (rhGH) until completion of linear growth. In this field, studies have mainly used indirect methods to assess treatment behavior.<sup>6</sup> The prevalence of non-adherence in pediatric populations was found to vary greatly from 5% to 82%, depending on the methods and definitions used. The most frequently used cut-off point to define non-adherence is one or more injections missed/week.<sup>6</sup> Estimates based on prescription data indicate that, of 75 children followed for 12 months, 39% and 23% missed more than one and two injections/week, respectively.<sup>7,8</sup> Similarly, prophylaxis regimen is essential in severe hemophilia. Although prophylaxis may be personalized, the regimen refers typically to two protocols (Malmö and Utrecht) requiring that factors be infused 3×/week for hemophilia A and 2×/week for hemophilia B. Reported levels of adherence to prophylaxis in severe hemophilia have ranged from 44% to 87% and non-adherence or suboptimal adherence from 13% to 56%.<sup>9</sup> A recent method based on expert consensus has helped define adherence, suboptimal adherence, and non-adherence to prophylaxis in relation to missed infusions, dose changes, and timing changes.<sup>10</sup> With this algorithm, adherence to prophylaxis treatment was defined as a maximum 15% infusions missed, maximum 10% deviation in dose (IU), and maximum 30% deviation in timing (hour). In contrast, non-adherence was defined as more than 25% infusion missed or >25% deviation in dose, or a combination of both. In both the conditions, non-adherence is thus mainly operationalized through an estimate of missed injections, although other aspects such as dosage are also considered. Frequencies of non-adherence vary greatly according to sample, study, and measures taken.

A review of factor of adherence to GH therapy<sup>6</sup> concluded that there was conflicting evidence from different studies, which demonstrated an association or lack thereof between adherence and age, socioeconomic status, duration of treatment, level of understanding, injection giver, practical

difficulty with injections, type of device used, and choice of device. The reasons for these discrepancies remain unclear. These may be due to differences in methodology, sample size, and the population assessed. The factors associated with poor adherence to GH therapy in pediatric patients include heterogeneous aspects such as being adolescent, discomfort with injections, low level of understanding of treatment, and ethnicity. Another review in hemophilia identified the motivators and barriers of adherence.<sup>11</sup> Motivators for a high adherence were experiencing symptoms, holding a positive belief of necessity of treatment, and a good relationship with the health care provider. Barriers were infrequent or absence of symptoms and older age. The authors concluded to the importance of developing an age-specific approach to adherence and adherence factors. Both the reviews were thus exclusively empirically driven and did not provide a taxonomy of factors, an aspect which is essential for future research recommendation and intervention. This contrasts with the results obtained in type 1 diabetes where the authors have proposed classifications of factors that help comparisons of adherence determinants and intervention.

Two reviews of real-world studies in diabetes suggest that the main factor domains of adherence to insulin injection may be summarized in demographic and clinical context, individual, social environment, practical, and health care issues.<sup>12,13</sup> Examples for demographic and clinical context are sex or older age.<sup>12</sup> For individual factors, an example is perceived treatment efficacy: patients are more likely to adhere if they have a tangible sense that the injection will contribute to some positive and not too remote outcome.<sup>14</sup> For social environment, normative pressure and social influence are examples.<sup>12,13</sup> An example of practical factor refers to the type of delivery device, with the use of pens consistently yielding higher levels of adherence than syringe in all reviewed studies.<sup>12</sup> This is also underlined by several large-scale surveys suggesting that practical barriers are central.<sup>14,15</sup> As for health care issues, studies demonstrate the role of health care provider trust, a sense of concordance with the physician and a perception of a good quality of communication as perceived by patients and families.<sup>13</sup> These broad categories are further defined in Table 1. They may constitute a simple comparator to evaluate the current state of research in GH and hemophilia prophylaxis treatment.

## Objective

The purpose of this work was to identify the categories of factors of adherent treatment behavior in patients treated with GH or those with severe hemophilia treated with prophylaxis.

**Table 1** Taxonomy of factors of adherence identified in diabetes research and expected to be found in growth hormone–treated conditions and hemophilia

Domains	Factors or predictors
Demographic and clinical context (non-modifiable)	Diagnosis, illness severity, symptoms, treatment outcomes Illness duration Age, maturity, pubertal status, or adolescent phase Injector/infuser (parent vs child, confounded with age)
Injector or infuser (patients or parents)	Knowledge, understanding (disease, treatment) Know-how (treatment skills) Feeling capable, controllability, self-efficacy Positive beliefs: treatment necessity, expected benefits Negative beliefs: treatment concern, expected side effects, negative consequences Psychological barriers: psychological issues, negative effects, distress
Social environment	Child–parent relationship quality Parental monitoring and supervision Parental involvement Promoting transition to self-care Social norms Social and peer support Social stigma
Practical issues	Barriers such as issues in treatment availability, tight schedule, etc. Delivery device: burden, complexity, convenience Financial cost to the family
Health care	Trust with health care provider Good relationship with provider Transition program Type of care: rural vs urban, country specificities

We wished to identify extant empirical data and coherently group the factors of adherence according to categories emerging from the diabetes literature (Table 1). The specifications of this literature review are the following. Patients: children, adolescents, and adults. Conditions: any condition treated by rhGH, or hemophilia A or B treated with prophylaxis blood factor replacement therapy. Adherence measure: any explicit measure of adherence. Association: any estimate of association or difference, such as *r*, *d*, *t*, or *beta* for quantitative and frequency or presence for qualitative reports. Factors: any aspect for which an estimate of association, difference, frequency, or presence was mentioned and that was interpreted as an explanatory factor of adherence.

## Method

### Search strategy

For both the domains, we used a similar systematic search strategy applied to common electronic databases. The electronic databases PubMed, Embase, CINAHL, and PsycINFO were searched for eligible studies. Given that previous reviews examined adherence factors up to 2011, we focused on the time period January 2011 to December 2017. The keywords applied to title and abstract included both 1) terms concerning GH treatment (or hemophilia)

and 2) terms concerning adherence. For GH-treated conditions, the syntax was: (growth hormone) AND (adherence OR compliance OR nonadherence OR noncompliance OR non-adherence OR non-compliance OR persistence OR concordance). For hemophilia, the first term was replaced by (hemophil\* OR haemophil\*). Limits were set in all searches to human studies and English language full-texts. To ensure inclusion of gray literature, we set no limits on the type of document retrieved (congress abstracts, theses, etc). We tracked references and related articles to minimize the risks of false negatives. A preliminary selection was performed by two reviewers (SS and MEH) on the basis of the abstract in order to screen for irrelevant items. In case of doubt of one reviewer, full-texts were retrieved and examined. Following this preliminary selection, full-text were read, selected for relevance, and information was extracted for relevant items. The inter-rater agreement for full-text relevance was 90% and in the rare cases where reviewers disagreed the full-text was discussed until a consensus was reached.

### Assessment of methodological quality

To avoid an excessive rate of exclusion on the basis of strict quality criteria, we did not use a formal inventory such as Cochrane or STROBE statements.<sup>16,17</sup> However, retrieved

studies were discussed on ad hoc criteria, particularly whether modifiable factors preceded the outcome (see “Discussion” section).

### Data extraction and management

The following data items were extracted in an Excel spreadsheet: author, year of publication, sample origin/country, clinical condition, sample demographics and clinical features, primary/secondary objective, data collection design (eg, quasi-experimental trial, cross-sectional survey), statistical design, adherence measure, factors of adherence significant, factors of adherence nonsignificant, factors of adherence suggested by authors, and funding source. The same two reviewers (SS and MEH) extracted data independently, and discrepancies were resolved based on the contents of the articles.

### Summary measures

To summarize findings on factors, we compared the number of studies addressing each group of adherence factors from Table 1. We also produced a narrative synthesis on unstudied factors suggested by authors as explanatory factors in the discussion sections of the reports.

## Results: GH-treated conditions

### Study selection

The selection process is presented in a flow diagram (Figure S1). The initial search resulted in 423 hits (PubMed: 99, Embase: 268, CINAHL: 52, PsycINFO: 4). After removing 131 duplicates, 292 items were screened on the basis of their abstract. In case of the absence of abstract, full-text was retrieved; 264 were excluded following this pass (eg, adherence was not studied in 123, factors were not investigated in 39). Then, 28 were thus selected for full-text analysis and six of these were excluded for various reasons (eg, four did not inquire factors). Finally, 22 reports were matched to the inclusion criteria and relevant to the research question. Eleven reports were full research articles published in peer-reviewed journals and eleven were conference abstracts. However, due to limited details, we could not include abstracts in the full review. The final set of eleven full research articles is summarized in Table 2.<sup>18–28</sup>

### Study description

Nine of the eleven studies were from one country and two included more than one country. Most studies were performed in Europe (6/11) and only two samples were partly from the USA.

Table 2 Data extraction from eleven studies on factors of adherence to rhGH treatment (2011–2017)

Reference	Sample	Objectives	Data collection and analysis design	Adherence measure and level	Factors of higher adherence	Factors unrelated
Bagnasco et al (2017) <sup>18</sup> <i>Endocrine Practice</i> Italy (support: Novo Nordisk)	1,007 children 6–16 years Mixed conditions treated with rhGH % GHD: NA Mean age (estimated): 11–12 years % pubertal: NA % male: NA % self-injection: 22%	1. Evaluate the prevalence of non-adherence to rhGH therapy 2. Assess treatment and patient-level correlates of poor adherence using a questionnaire	Cross-sectional survey (self-reported) Multivariate logistic regression to predict adherence	Injection missed over a typical week in the last 12 months of rhGH treatment (self-report, parents, and child) High: No injection missed (72.1%) Low: $\approx$   injection missed (24.4%)	Level of education (parents). Very low level associated with lower adherence Shorter duration of therapy, using current device Parent injected. Adolescence period associated with lower adherence Easy parent–child relations over treatment Injection less painful. High reported pain associated with lower adherence Understanding the consequences of non-adherence	Who prepares injection Device that covers the needle during injection Degree of knowledge of the disease

<p>Gau and Takasawa (2017)<sup>19</sup> <i>Journal of Pediatric Endocrinology and Metabolism</i> Japan (support: N/A)</p>	<p>46 children % GHD: 100% Mean age: 7.6 years % pubertal: NA % male: 52% % self-injection: 74%–80%</p>	<p>1. Examine the influence of PC on adherence to GH therapy 2. Examine therapeutic effects of GH therapy</p>	<p>Retrospective, single-center, comparative study Associations with adherence tested with 2x2 Fisher test</p>	<p>Number of missed injections per week (charts) Low: <math>\geq 1</math> injection missed per week (33% in non-PC, 7% in PC)</p>	<p>Treatment satisfaction, convenience of the device, satisfaction with the device Satisfaction with the health care team</p>	<p>Age Sex Device type</p>
<p>Auer et al (2016)<sup>20</sup> <i>Clinical Endocrinology</i> Germany (support: Pfizer)</p>	<p>179 adults % GHD: 100% % Adult onset: 79% Mean age: 35–64 years % male: 50%</p>	<p>1. Assess long-term adherence in adult patients with GHD 2. Identify markers of long-term adherence</p>	<p>Retrospective, single-center, cohort study Associations with adherence tested in bivariate analyses (ANOVA, t-tests, correlations) and multivariate regression for selected variables</p>	<p>Prescription filled/recommended dose • Prescription filled: prescribed GH dose filled by patients during period • Recommended GH dose: calculated retrospectively according to patient files Mean overall adherence: 74%±28.2% High: 81%–100% (53%) Low: 0%–60% (29%)</p>	<p>Shorter duration of therapy, especially at the start of therapy Adult-onset higher adherent than child-onset, higher age associated with adherence</p>	<p>Sex Device type</p>
<p>de Pedro et al (2016)<sup>21</sup> <i>Growth Hormone &amp; IGF Research</i> Spain (support: Pfizer)</p>	<p>158 children 4–16 years Mixed conditions treated with rhGH % GHD: 77% Mean age: 11 years % pubertal: 52% % male: 64% % self-injection: NA</p>	<p>1. Identify patients non-adherent to GH therapy 2. Assess the effect that adherence has on treatment outcome 3. Analyze serum IGF-I measurements as a biomarker for adherence 4. Analyze the possible influence of socioeconomic factors on therapeutic adherence</p>	<p>Retrospective, single-cohort, study-chart, and patient survey Associations with adherence tested in bivariate analyses (t-tests, chi-squared, 2x2 Fisher test). Multivariate logistic model to predict adherence levels</p>	<p>Prescription filled/recommended dose • Prescription filled: doses annually picked up by the patient • Recommended doses: available from the pharmacist High: not missing at least 92% of the prescribed doses (66.5%) Medium: &lt;92% and <math>\geq 85%</math> (at least 2 doses missed in 1 month) (12.5%) Low: &lt;85% (at least 1 dose missed per week) (21%)</p>	<p>Younger age Shorter duration of treatment Higher education level of mothers</p>	<p>Pubertal status Ethnicity Education level of fathers</p>

(Continued)

Table 2 (Continued)

Reference	Sample	Objectives	Data collection and analysis design	Adherence measure and level	Factors of higher adherence	Factors unrelated
Kappelgaard et al (2015) <sup>22</sup> <i>Expert Review of Medical Devices</i> France, Germany, Italy, USA (support: Novo Nordisk)	103 children 3–13 years 48 self-described, others Caregivers Mixed conditions treated with rhGH % GHD: 76% Mean age (estimated): 8–9 years % pubertal: NA % male: 61% % self-injection: NA	1. Examine the functional and emotional impact (including adherence) of storage-flexible GH products in young patients compared with refrigeration-only products	Cross-sectional patient survey (online) Differences between adherence groups tested by t-test	Injections missed each month (self-reported) Storage-flexible: 76% missed 0 injection, 22% missed 1–3 injections, 0.58 missed/month Refrigeration-only: 57% missed 0, 38% missed 1–3 injections, 0.88 missed/month	Storage-flexible product (as compared to a refrigeration-only product) is positively associated with high adherence and negatively associated with low adherence	
Lass and Reinehr (2015) <sup>23</sup> <i>Hormone Research in Paediatrics</i> Germany (support: Merck Serono)	103 children 8–12 years Mixed conditions treated with rhGH % GHD: 72% Mean age: 10 years % prepubertal: 64% % pubertal: NA % male: 65% % self-injection: 35%	1. Identify factors that influence treatment adherence	Retrospective chart review Associations with adherence tested in bivariate analyses (chi-squared, t-tests, correlations) and multivariate regression for selected variables	Prescription refill rates during last year (charts) High: < 1 missed dose per week (>85.7% adherence) =51% Medium: 1–3 missed doses per week (57.1%–85.7% adherence) =23% Low: > 3 missed doses per week (<57.1% adherence) =26%	Prepubertal children (as compared to pubertal children) Younger age Parent-injected Shorter treatment duration in younger children	Device type (easypod vs other) Treatment success (height gain during observation period)
Spoudeas et al (2014) <sup>24</sup> <i>Patient Preference and Adherence</i> UK (support: Ferring Pharma)	4,093 children Mixed conditions treated with rhGH % GHD: NA Mean age: 10 years % male: 58% % self-injection: NA	1. Investigate how the use of a jet-delivery device (ZomaJet) impacts persistence and adherence compared to needle-based devices	Retrospective cohort study (charts from UK nationwide database of GH home-delivery schedules) Comparison of persistence between ZomaJet and needle-based devices: Mantel-Cox log-rank and chi-squared tests Association with adherence tested with independent t-tests	PDC = number of days with access to viable heads/number of days receiving treatment PDC score >0.8: highly adherent (58% using ZomaJet) Persistence (data not shown): time interval between a patient's first and last delivery of GH for each GH brand		Sex Age (children vs teenage) Service type (full health care at home vs stores only)



<p>Aydim et al (2014)<sup>25</sup> <i>Endocrine Practice</i> Turkey (support: Pfizer)</p>	<p>217 children Mixed conditions treated with rhGHD % GHD: 85% Mean age: 11 years &gt;10 years: 67% % pubertal: NA % male: 53% % self-injection: 28%</p>	<p>1. Evaluate the adherence to GH therapy 2. Identify influencing factors and outcomes</p>	<p>Prospective follow-up (4 time points, survey, and charts) Association with adherence tested with Mann-Whitney U test, chi-squared test, Fisher's exact test, and correlations</p>	<p>Percent of doses omitted at each evaluation period (M3–M6–M12 of therapy, charts) Excellent: 0 doses missed (87.6%, 84.8%, and 77.9%) Good: 5% of doses missed (8.3%, 7.4%, and 12.9%) Fair: 5%–10% of doses missed (1.4%, 2.8%, and 1.8%) Poor: &gt; 10% of doses missed (2.8%, 5.1%, and 7.4%)</p>	<p>Shorter duration of treatment Boys (vs girls) had higher adherence rates</p>	<p>Age Diagnostic type Socioeconomic status Who injects treatment Injection device GH product used</p>
<p>Hartmann et al (2013)<sup>26</sup> <i>Hormone Research in Paediatrics</i> Germany (support: Merck Serono)</p>	<p>75 children Mixed conditions treated with rhGH % GHD: 64% Mean age: 12 years % pubertal: 55% % male: 61% % self-injection: NA</p>	<p>1. Evaluate rhGH therapy adherence in children and adolescents with different growth disorders</p>	<p>Cross-sectional online survey with electronic device recording Associations with adherence explored with t-tests</p>	<p>Actual injection/prescribed dose Actual injection = injected rhGH recorded by electronic device (easypod) High: missed <math>\leq</math> 1 dose a week on average (85.7%–100% proportion injected) (78.7%) Medium: missed 1–3 doses/week (57.1%–85.7% proportion injected) (18.7%) Low: missed <math>\geq</math> 3 doses/week (&lt;57.1% proportion injected) (2.7%)</p>	<p>Prepubertal age (vs pubertal)</p>	<p>Sex Diagnosis</p>
<p>Bozzola et al (2011)<sup>27</sup> <i>BMC Endocrine Disorders</i> 15 countries including Argentina, France, Italy (support: Merck Serono)</p>	<p>824 children 1–18 years Mixed conditions treated with rhGH % GHD: 66% Mean age: 11 years % pubertal: NA % male: 56% % self-injection: 39%</p>	<p>1. Assess adherence to rhGH treatment as a function of use of electronic auto-injector 2. Compare adherence patterns in treatment-naïve and treatment-experienced children 3. Assess the acceptability of the device</p>	<p>Cross-sectional online survey with electronic device recording Association with adherence tested with Fisher's exact test</p>	<p>Actual injection/prescribed dose (recorded by electronic device) (measure 1) Injection missed each month (self-reported)/injection prescribed (measure 2)</p>	<p>Shorter duration of treatment (treatment naïve vs treatment experienced). In almost all countries was related to higher adherence Living in Spain (vs living in Argentina)</p>	<p>Who injects the treatment</p>

(Continued)

Table 2 (Continued)

Reference	Sample	Objectives	Data collection and analysis design	Adherence measure and level	Factors of higher adherence	Factors unrelated
Cutfield et al (2011) <sup>28</sup> PLoS ONE New Zealand (support: NZ ministry of health)	150 children Mixed conditions treated with rhGH % GHD: 57% Mean age: 12 years % pubertal: NA % male: 48% % self-injection: NA	1. Assess adherence to GH treatment 2. Examine the effects of age, sex, ethnicity, area of residence, and diagnosis on GH treatment adherence	Cross-sectional survey and chart review (nationwide New Zealand) Association with adherence assessed with binary logistic linear regression	High: if >92% (missed a maximum of 2 daily injections per month or 6 daily injections for the 3-month period) Self-reported % of GH vials required/number of vials prescribed (Measure 1) and chart-recorded % GH returned/number of vials prescribed (Measure 2) High: $\leq 1$ dose a week on average (27.3%) Medium: missed 2 doses/week (46.4%) Low: missed $\geq 3$ doses/week (26.4%)	Self-report measure GHreq yields higher adherence rates Other ethnicity than Maori associated with higher adherence	Age Sex Diagnosis Area of residence

Abbreviations: GH, growth hormone; GHD, growth hormone deficiency; PC, patient choice; PDC, proportion of days covered; GHreq, required GH treatment; rhGH, recombinant human GH; NA, not available.

Patients' conditions were mixed with all treatments being rhGH replacement therapy, and most frequent conditions being growth-related conditions. GHD was the most frequent condition in the studied samples (median %GHD =76%). Ten studies were performed in children or adolescents with a median age of 11 years and sex ratio of 57% males. Sample sizes varied greatly with median N=158 but three studies included 800+ participants and only two had <100 participants. Nine reports mentioned identifying the factors of adherence in their primary or secondary objectives. Most of the studies adopted a cross-sectional data collection with an association with historical data (9/11). In four of these cases, only charts were analyzed. Two were cross-sectional fully self-reported survey.<sup>18,22</sup> Only one was a prospective cohort follow-up.<sup>25</sup> This implies strong limitations on causal interpretations as, in most cases, factors did not precede the adherence outcome.

Adherence was measured in three different ways. Four studies used the number of missed injection with typically  $\geq 1$  missed injection being a threshold for lower adherence, five used prescriptions filled or medication possession ratios, and one study used both, from chart reviews or pharmacist reports. Finally, two studies used data recorded by an electronic device (easypod).<sup>26,27</sup> In addition, one study also reported on persistence, that is, the time interval between a patient's first and last delivery of GH.

### Adherence

The levels were difficult to synthesize given the variety of measures. Results of calculations on the basis of injection missed indicate a frequency of low adherence, that is, one or more injection missed/week, of median =25% in the studied samples. From the calculations on prescriptions filled, author-described low levels were observed in a median of 26% of patients. On the basis of electronic devices recording, the median proportion of those missing more than one dose is 21%. Overall, recent reports indicated that approximately one fourth of participants, children, adolescents, and adults had clear issues with adherence to rhGH treatment. This proportion is consistent across outcome measures.

### Factors of adherence

A wide range of factors have been studied since 2011, from parents' level of education<sup>18</sup> to being able to choose an injection device.<sup>19</sup> When classifying these factors in the categories from the diabetes literature (Table 1), we found a striking evidence that a large majority of studies (10/11) investigated non-modifiable sociodemographics and contextual factors



such as current age, diagnosis, or pubertal status. A majority of studies also explored practical issues such as the impact of device type or product (6/11). In sharp contrast, among the eleven studies, only one surveyed individual predictors (eg, understanding consequences, knowledge of the disease) and social aspects (quality of parent–child relations over treatment).<sup>18</sup> In addition, only two reports explored relationship issues (eg, satisfaction with the health care team<sup>18</sup> and type of health care, home vs stores).<sup>24</sup> Importantly, most studies explored one or two domains of factors of adherence (median number of domains =2), but modifiable domains were only investigated 50% of the time. This is probably related to the high frequency of chart-based studies among the reports. This observation shows that there is a great potential in the future for the investigation of modifiable factors within the individual, social, and health care domains, beside practical issues as device type in the GH-treatment literature.

When examining the factors whose relation was found significant with the measures of adherence, we found arguments suggesting that younger children treated by their parents have higher adherence rates than pubertal-adolescents caring for themselves<sup>18,21,23,26</sup> (but this relation was not significant in all reports).<sup>24,25</sup> Higher levels of education in

parents were also consistently related to higher adherence.<sup>18,21</sup> In contrast, studies tended to show no relation with sex, diagnosis type, or device/product used<sup>19,20,23,25</sup> except the fact that storage-flexible products were associated with higher adherence.<sup>22</sup>

Importantly, we collected comments or interpretations in the discussion sections on key factors that according to authors may explain treatment adherence and thus should be studied in the future (Table 3). This analysis revealed that at least six of eleven reports recommended to investigate modifiable explanatory factors. For instance, a strong case was made in favor of perceived barriers and benefits,<sup>20,23,28</sup> physician–patient relationship,<sup>20,23,27</sup> risk perception,<sup>23,27</sup> patient knowledge and skills,<sup>20,26</sup> controllability issues,<sup>22,24,27</sup> and emotional distress.<sup>23,24</sup> Notably, these factors can only be studied in real-world observational data collection strategies. It is very significant that so few studies collected evidence on these factors (1/11) but that a majority stress their importance in their discussion (more than 6/11). Perhaps, this should serve as a prompt to adopt other research designs in the future (other than retrospective chart review with minimal cross-sectional survey) as chart reviews cannot address a series of key factors like individual motivation or social factors.

**Table 3** Domains of factors of adherence to rhGH studied in 11 reports (2011–2017)

Reference	Descriptive factors	Individual factors	Social factors	Practical factors	Health care factors	No domains	Factors suggested in the discussion section of the articles
Bagnasco et al (2017) <sup>18</sup> <i>Endocrine Practice</i>	x	x	x	x	x	5	
Gau and Takasawa (2017) <sup>19</sup> <i>Journal of Pediatric Endocrinology and Metabolism</i>	x			x		2	Socioeconomic factors (eg, mother's education level) Type of device Pubertal stage
Auer et al (2016) <sup>20</sup> <i>Clinical Endocrinology</i>	x			x		2	Forgetfulness Side effects of treatment Perceived treatment benefits Physician–patient relationship Patient education
de Pedro et al (2016) <sup>21</sup> <i>Growth Hormone &amp; IGF Research</i>	x					1	
Kappelgaard et al (2015) <sup>22</sup> <i>Expert Review of Medical Devices</i>				x		1	Choice of device Easy-to-use device

(Continued)

**Table 3** (Continued)

Reference	Descriptive factors	Individual factors	Social factors	Practical factors	Health care factors	No domains	Factors suggested in the discussion section of the articles
Lass and Reinehr (2015) <sup>23</sup> <i>Hormone Research in Paediatrics</i>	x			x		2	Education level Psychological and emotional problems Social issues Technical handling issues Misconceptions about consequences of missed doses Discomfort with injections Dissatisfaction with results Inadequate contact with HCPs
Spoudeas et al (2014) <sup>24</sup> <i>Patient Preference and Adherence</i>	x				x	2	Lack of choice of delivery device Person who administers the dose Injection discomfort or anxiety Patient support (injection training and contact with HCP) Too much involvement in treatment decisions
Aydin et al (2014) <sup>25</sup> <i>Endocrine Practice</i>	x			x		2	Neglecting to renew the prescription Forgetting to administer the drug Vacation/break from taking the medication Problems with the delivery device
Hartmann et al (2013) <sup>26</sup> <i>Hormone Research in Paediatrics</i>	x					1	Education Psychological, emotional, and social problems Delivery device Support for adolescents and their families
Bozzola et al (2011) <sup>27</sup> <i>BMC Endocrine Disorders</i>	x				x	2	Duration of treatment (participants become less enthusiastic and motivated) Misperceptions about the consequences of missed GH doses Discomfort with injections Dissatisfaction with treatment results Inadequate contact with HCP Patient not involved in treatment decisions Choice of the delivery device

(Continued)

**Table 3** (Continued)

Reference	Descriptive factors	Individual factors	Social factors	Practical factors	Health care factors	No domains	Factors suggested in the discussion section of the articles
							Use of complicated delivery devices Experience with the delivery device
Cutfield et al (2011) <sup>28</sup> <i>PLoS One</i>	x					1	Injection frequency Type of device Lack of perceived benefits Lack of perceived risks of noncompliance Culture and socioeconomic factors

**Abbreviations:** GH, growth hormone; HCP, Health Care Professionals; rhGH, recombinant human GH.

## Results: prophylaxis treatment in hemophilia

### Study selection

The selection process is presented in a flow diagram (Figure S2). The initial search resulted in 708 hits (PubMed: 137, Embase: 544, CINAHL: 21, PsycINFO: 6). After removing 169 duplicates, 539 items were screened on the basis of their abstract. In case of the absence of abstract, a full-text was retrieved; 489 were excluded following this pass (eg, adherence was not studied in 316, study design was not empirical in 93). Fifty were thus selected for full-text analysis and 18 of these were excluded for various reasons (eg, seven did not inquire factors and six did not define adherence clearly). Finally, 32 reports were matched to inclusion criteria and relevant to the research question. Sixteen reports were full research articles published in peer-reviewed journals and 16 were conference abstracts. Due to limited details, we could not include abstracts in the full review. The final set of 16 full research articles is summarized in Table 4.<sup>29-44</sup>

### Study description

All the studies were from a single country. Less than 44% (7/16) were performed in North America. Half of the studies were performed in Europe (8/16), and one was performed in China.

Most of the studies (13/16) included patients treated with prophylaxis regimen as respondents. The others surveyed professionals from treatment centres.<sup>41,43,44</sup> Hemophilia A was found to be the most frequent condition in the eleven patient samples that gave this detail (median 91%). The other conditions were Hemophilia B and Von Willebrand disease.

Among the studies with patients, 7 of the 13 studies included children or adolescents. As expected, samples were almost fully composed of boys/men. The median age of adults can be roughly estimated at around 29–39 years and that of children/adolescents was 12–19 years (some samples were mixed or indicated frequencies of age ranges, Table 4). Patient sample sizes varied greatly with median N=78, where 3 of the 13 studies included 100+ participants.<sup>33,34,42</sup> For studies led with professionals, this figure was N=71. Out of 16 studies, 12 reports mentioned identifying the factors or correlates of adherence as their primary or secondary objectives. More than two thirds of studies (11/16) adopted a cross-sectional data collection including those with retrospective data from chart review,<sup>29,30,32,33,35,36,39,40,42</sup> whereas two were pre-post evaluations of interventions.<sup>31,41</sup> Two had prospective follow-up designs,<sup>34,37</sup> and one was a qualitative inquiry on the experience of treatment in adults.<sup>38</sup>

In quantitative studies, adherence was measured in three different ways. Ten of the 16 studies appeared to rely on self-report to evaluate adherence. Seven studies used the VERITAS-Pro to evaluate the level of adherence in respondents.<sup>45,46</sup> This tool is a 24-item self-report questionnaire. It consists of six subscales that examine the extent to which participants take their injections at the recommended time (timing), use the recommended dose (dosing), plan ahead to ensure they have enough supplies (planning), remember to take their injections (remembering), skip injections (skipping), and communicate with the hemophilia center appropriately (communicating). Items may be summed to yield a global adherence score.<sup>29-33,35,42</sup> One study used other non-illness-specific self-reports (Morisky/Morisky Medication-taking Adherence Scale-4)<sup>39</sup>

**Table 4** Data extraction from 16 studies on factors of adherence to prophylaxis treatment in hemophilia (2011–2017)

Reference	Sample	Objectives	Data collection and analysis design	Adherence measure and level	Factors of higher adherence	Factors unrelated
Tran et al (2017) <sup>29</sup> <i>Haemophilia</i> USA (support: Bayer)	99 adults: 33±18 years Hemophilia A: 91% Severe: 78% Prophylaxis: 49% Caucasian: 69%	1. Determine the association between demographic, socioeconomic, psychosocial, and health literacy with adherence	Cross-sectional survey (self-reported) Multivariate regression analysis to predict adherence	VERITAS-Pro: 45±18, 80% adherent (score ≤57) VERITAS-Prm: 51±15, % adherent: NA	Physician trust Higher QoL No history of depression	Age Ethnicity Condition type or severity Socioeconomic factors Health literacy
van Os et al (2017) <sup>30</sup> <i>PLoS ONE</i> UK (support: Bayer)	91 young adults: 19±4 years Hemophilia A: NA Severe: 100% Prophylaxis: 100% Caucasian: NA	1. Assess self-reported adherence among young people with hemophilia 2. Provide evidence of psychosocial predictors of adherence	Cross-sectional survey and chart review Multivariate regression analysis to predict adherence	VERITAS-Pro: 82% adherent, overall mean score =42	Better log-timing planning and skipping Higher necessity beliefs Lower concern beliefs Negative emotions associated with disease (fear, anger, distress) Self-efficacy Positive expectation of treatment Social support Understanding of hemophilia (coherence)	Age
Lock et al (2016) <sup>31</sup> <i>Haemophilia</i> the Netherlands (support: Bayer)	46 children: 9.4±4.2 years Parental report: 100% Self-report: 48% Hemophilia A: 78% Severe: 91% Prophylaxis: 100% Caucasian: NA	1. To investigate the effect of home visits on adherence to treatment, health-related QoL, behavioral scores, self-efficacy, total clotting factor consumption, and number of joint bleeds	Multicenter pre-post intervention study Bivariate comparison of parametric outcome before and after the intervention	Infusion logs: percentage of weeks/year the patient respected 1) frequency (median 86 baseline vs 87 postintervention, P=0.55), 2) timing (median 91 baseline vs 85 postintervention, P=0.07), 3) total factor consumption (median 100 baseline vs 100 postintervention, P=0.24) VERITAS-Pro (parental report: score of 36 baseline, and 35 postintervention, P=0.78) Adolescent report (score of 44 baseline, and 41 postintervention, P=0.25)	New type of health care delivery (home visits) associated with better communication scores (VERITAS)	New type of health care delivery (home visits) not associated with improved adherence

Author(s)	Study Design	Study Population	Study Objective	Study Methods	Study Results	Study Limitations	Ethnic group
McLaughlin et al (2016) <sup>32</sup> <i>Racial and Ethnic Health Disparities</i> USA (support: Pfizer)	Cross-sectional survey (online)	80 adolescents and young: 13–25 years (estimated mean 18 years) Hemophilia A: 91% Severe: 91% Prophylaxis: 86% Caucasian: 76% Self-infusion: NA	I. To evaluate racial/ethnic differences in adherence, chronic pain, and QoL among AYA with moderate or severe hemophilia	Multivariable logistic regression predicting the odds of non-adherence	VERITAS-Pro (median non-white 47.5 vs white 48.0, P=0.87) VERITAS-Prm (median non-white 43.0 vs white 52.0, P=0.41)	Being younger or older associated with adherence Treatment site in subsample $\geq 20$ years	Severity Self-infusion Pain Comorbidity HIV, HCV
Miesbach and Kalmns (2016) <sup>33</sup> <i>Haemophilia</i> Germany (support: NA)	Prospective multicenter study	397 children and adults: mean =29 years including 28% children: < 15 years, and 52% adults: 20–59 years Hemophilia A: 86% Severe: 93% Prophylaxis: 100% Caucasian: NA Self-infusion: 73.8%	I. To analyze the influence of potential factors on adherence	Cross-sectional self-reported survey Multivariate regression analysis to explain adherence variance	VERITAS-Pro, mean =37 0–14 years: 100% adherent 15–19 years: 100% 20–59 years: 88.1% $\geq 60$ years: 93.9%	Parent-infusion yielded higher frequency of adherence than self-infusion (66% vs 43%, P<0.01)	
Schrijvers et al (2016) <sup>34</sup> <i>British Journal of Haematology</i> the Netherlands (support: Baxter)	Cross-sectional survey (online)	241 children and adults: mean =23 years including 30% children: 2–11 years, and 70% adolescents and adults: 12–77 years Hemophilia A: 82% Severe: 95% Prophylaxis: 100% Caucasian: NA Self-infusion in children: 0% Self-infusion in ado/adults: 70%	I. To assess patient adherence to prophylactic treatment and its association with age, bleeding events, and clotting factor consumption	Prospective multicenter study Bivariate frequency comparison and ANOVA	Infusion logs Adherent: missing < 15% infusions, < 10% dose changes, and < 30% deviation in time (66% of parents, 43% of patients) Suboptimally adherent: missing 15%–25% infusions, < 25% dose changes or > 30% deviation in time (29% of parents, 37% of patients) Non-adherent: missing > 25% infusions or > 25% dose changes (5% of parents, 20% of patients)	Adolescence associated with higher adherence in comparison with young adulthood Mothers' education	Ethnicity Bleeding disorder type
Wrikop et al (2016) <sup>35</sup> <i>Haemophilia</i> USA (support: Pfizer)	Cross-sectional survey (online)	73 adolescents and adults: mean 17 years (estimated) 56% adolescents: 13–17 years 44% adults: 18–25 years	I. To determine factors associated with better adherence	Multivariate regression analysis to explain adherence variance	VERITAS-Pro Sample median: 48, min-max (25–78) Non-adherent: 30% (score $\geq 57$ )		

(Continued)

Table 4 (Continued)

Reference	Sample	Objectives	Data collection and analysis design	Adherence measure and level	Factors of higher adherence	Factors unrelated
García-Dasi et al (2015) <sup>36</sup> <i>Haemophilia</i> Spain (support: Bayer)	Hemophilia A: 88% Severe: 90% Prophylaxis: 100% Caucasian: 78% Self-infusion: NA  78 children and adolescents: 12±4 years 50% children: <12 years 50% adolescents: ≥12 years  Hemophilia A: 100% Severe: 100% Prophylaxis: 100% Caucasian: NA Self-infusion: 44%	1. Evaluate adherence 2. Identify and compare the characteristics associated with adherence	Cross-sectional observational study Bivariate comparisons: Student's <i>t</i> -test, one-factor ANOVA, chi-squared test	Infusion logs AI: (units administered)/(units prescribed) × 100 AAI: Difference between AI and the perfect percentage of adhesion (100%) Adherence: administered exactly as prescribed (52.6%) Infra adherence: administered less than prescribed (33.3%) Over adherents: administered more than prescribed (14.1%)	QoL Primary prophylaxis Fewer negative emotions Self-image not affected by the disease Less overprotection by family No missed school days Sport practices similar to other children Satisfaction with the health care team	Age Self- or other-infusion
Mingot-Castellano et al (2015) <sup>37</sup> <i>Blood Coagulation and Fibrinolysis</i> Spain (support: NA)	18 adults: >18 years Hemophilia A: 100% Severe: 100% Prophylaxis: 100% Caucasian: NA	1. Describe patient profiles, reasons to indicate prophylaxis, type of prophylaxis, and the protocol to individualize the prophylaxis scheme 2. Adherence and adverse events were also analyzed	Prospective case series study Bivariate comparisons: Student's <i>t</i> -test, one-factor ANOVA	Infusion logs Adherence: number of weeks/year with the correct number of prophylaxis infusion Median adherence: 84% (69%–96%)	Patients qualitatively reported that poor adherence is favored by active working lives and irregular work schedules	Type of prophylaxis (primary, secondary, or tertiary)
Schrijvers et al (2015) <sup>38</sup> <i>Haemophilia</i> the Netherlands (support: Baxter)	21 adults: 39 years (19–64 years) Hemophilia A: NA Severe: 100% Prophylaxis: 100% Caucasian: 100%	1. Clarify the process underlying adherence to prophylaxis in severe hemophilia from patients' perspective	Qualitative study	Infusion logs Adherent: followed the prescribed regimen for at least 80%–100% of the time (47.6%) Non-adherent: following the prescribed regimen for <80% of the time (42.9%) Over treating: >100% of the prescribed dose, treated double during bleed (9.5%)	Acceptance of the disease Experience of bleeding Understanding hemophilia and prophylaxis Planning skills, prophylaxis ascribed into routine	



<p>Lamiani et al (2015)<sup>39</sup> <i>Haemophilia</i> Italy (support: Bayer)</p>	<p>50 adolescents and adults: 40±13 years 24%: 13–30 years 44%: 31–44 years 32%: 45+ years Hemophilia A: 100% Severe: 68% Prophylaxis: 50% Caucasian: 96%</p>	<p>1. Assess the impact of patients' health status and demographic characteristics on their illness representations and perceived adherence 2. Explore the relationship between illness representations and perceived adherence</p>	<p>Cross-sectional survey (self-report) Bivariate comparisons (t-tests, one-way ANOVA) Multivariate regression analysis to explain adherence variance by illness representation subscales</p>	<p>Perceived adherence to treatment (Morisky) Medication adherence scale (MMAS-4) Non-adherent: scores ≤2, 24%</p>	<p>Being in couple Perceived chronicity Negative emotions</p>	<p>Treatment type Severity Presence of inhibitors Education level Age</p>
<p>Ho et al (2014)<sup>40</sup> <i>Haemophilia</i> BC, Canada (support: Baxter)</p>	<p>31 adults: 29 years (18–56 years) Hemophilia A: 100% Severe: 100% Prophylaxis: 100% Caucasian: NA</p>	<p>1. Determine the accuracy of infusion logs 2. Identify the effects of age, comorbidities, duration of prophylaxis, and the presence of joints affected by hemophilic arthropathy, on adherence levels</p>	<p>Retrospective study (chart review) Multivariate regression models predicting adherence</p>	<p>Adherence based on differences in dosage and frequency per week Adherence to dosage: proportion of weeks with accurate dosage. Median: 93%, min–max (73%–97%) Adherence to frequency: Each week is coded 0, 1, 2 with 2=perfect adherence, 1=one difference detected, 0=more than one difference. Final % is total score/maximum possible. Median: 76%, 67%–85%</p>	<p>Longer exposure to prophylaxis</p>	<p>Age Comorbidities Number of bleeds Number of joints affected</p>
<p>Tang et al (2013)<sup>41</sup> <i>Haemophilia</i> China (support: Bayer)</p>	<p>125 children: 8 years Hemophilia A: NA Severe: NA Prophylaxis: 100% Caucasian: 0% (100% Chinese)</p>	<p>1. To confirm that a similar short-term low-dose secondary prophylaxis for a similar hemophilia population remains feasible and beneficial when carried out at multiple centers in different areas of China</p>	<p>Pre-post intervention study Rank-test to determine the significance of data difference between the observation and prophylaxis period</p>	<p>Factor consumption Continuous prophylaxis treatment over 6 weeks (reported by treatment centers)</p>	<p>Comprehensive care team effective Specialized team to properly administer prophylaxis Necessity beliefs (reported by treatment centers)</p>	<p>Age</p>
<p>Duncan et al (2012)<sup>42</sup> <i>Haemophilia</i> USA (support: Baxter)</p>	<p>117 children and adults: 25 years Pediatric: 45% Adult: 55% Hemophilia A: 100% Severe: 100% Prophylaxis: 60% Caucasian: 78%</p>	<p>1. Assess lifetime treatment patterns among hemophilia A patients and determine whether these treatment patterns were associated with differences in HRQoL</p>	<p>Cross-sectional survey (online) Bivariate analyses (student t-tests) to evaluate adherence differences across self-infusion status</p>	<p>VERITAS-Pro for only 70 patients (32.9% adults) Pediatric patients score 38 vs adults 45.8, P&lt;0.05</p>	<p>Younger age favored recommended dose and better communication with the health care team Children &lt;12 years old had better adherence compared to that of adolescents (12–18 years)</p>	<p>Parent-infusion (in children)</p>

(Continued)

Table 4 (Continued)

Reference	Sample	Objectives	Data collection and analysis design	Adherence measure and level	Factors of higher adherence	Factors unrelated
Thornburg et al (2012) <sup>43</sup> <i>Haemophilia USA</i> (support: Bayer)	Self-infusion in children: 0% Self-infusion in adolescents: 76% 56 professionals in HTC Age: NA Physician: 64% Nurse: 25% Nurse pract: 11% No other description	2. Assess the level of treatment adherence among hemophilia patients in the USA and explore the potential factors 1. Determine whether the prescription of prophylaxis for children with hemophilia and perceptions of adherence to prophylaxis have changed since the publication of the JOS	Cross-sectional survey of HTCs Bivariate comparison of adherence levels and factors with original levels found by Thornburg	Reported average prescription as reported by professionals Excellent adherence: administering $\geq 80\%$ of prescribed infusions. 42% of respondents reported that $> 75\%$ of their patients have excellent adherence ( $\geq 80\%$ of prescribed doses) with prophylaxis	Patient age: professionals report more frequently excellent adherence in the very young 1–5 years (70% of respondents) as compared to adolescents (22%)	Professional role Years of experience Size of treatment program Pediatric–adult facility
Zappa et al (2012) <sup>44</sup> <i>Haemophilia USA</i> (support: Baxter)	71 HTCs Nurses responded on sample: 10,375 patients Children: 40% Hemophilia A: 74.1% Severe: 45.3% On-demand: 63.1%	1. To compare the treatment practices for hemophilia A with those for hemophilia B in relation to on-demand and prophylactic factor replacement therapy, adherence to treatment, optimal care, and approaches to inhibitor management	Cross-sectional survey of HTCs Documentation of adherence included nurses' definitions of adherence, rates of adherence, and adherence barriers Nurses reported that influencing and tracking patient adherence is difficult because existing tools to track or influence adherence are unreliable (prescription refills, patient-reported adherence, treatment logs)	Patients deemed to follow recommended treatment Definition in high volume centers: having no breakthrough bleeding episodes, except for severe trauma in patients with hemophilia A; no breakthrough bleeding episodes except for severe trauma and no deterioration in joint health in hemophilia B. Definition in low volume centers: for hemophilia A and B, the patient followed the physician's prescription Adherence rate: reported number of prophylactic doses per month/by the prescribed number of prophylactic doses per month. Mean rate reported by nurses for severe hemophilia B (78%) vs hemophilia A (80%)	Reported barriers to adherence 1. Inconvenience/interference of treatment with the activities of living (94% of respondents) 2. Low perceived benefits: 79% of respondents 3. Low perceived negative consequences or vulnerability if non-adherent: 67% of respondents Age: adherence is greatest in patients $\leq 2$ years (90%) and lowest in young adults 18–24 years (64%)	Type of hemophilia A or B except in senior patients. B: 87% vs A: 79%

**Abbreviations:** AI, adherence index; AAI, absolute adherence index; AYA, adolescents and young adults; HRQoL, health-related quality of life; HTC, hemophilia treatment center; JOS, Joint Outcome Study; QoL, quality of life; MMAS, Morisky Medical-treatment Adherence Scale; NA, Not available.

and two reports collected perceived frequencies of adherence in adult patients<sup>38</sup> and professionals.<sup>43</sup> Five studies also used infusion logs or diaries.<sup>31,34,36–38</sup> Finally, five studies used an objective adherence index, computed from a ratio of units administered divided by units prescribed.<sup>34,36,40,41,44</sup> However, a wide variety of definitions of adherence was observed among these studies: a high adherence could refer to a perfect administration (no errors)<sup>36</sup> or to limited errors in infusing, dosing, or timing<sup>34</sup> or to the absence of consequent bleeding episodes.<sup>44</sup> Suboptimal and non-adherence on infusing frequency was generally defined as >15%–25% missed infusions.<sup>47</sup> Although several measures bore a documented validity, including self-report tools, they probably described different aspects of treatment behavior.

## Adherence

The levels were difficult to synthesize given the variety of measures used. If we rely on definitions given by authors of suboptimal levels in adherence, frequencies varied from 12%<sup>33</sup> to 43%.<sup>38</sup> In those reports indicating frequencies according to existing thresholds, most indicated a low adherence rate of around a median of 20% for the infusion frequency. However, this rate of non-adherence was far lower in younger children who were infused by their parents (eg, 5% in Schrijvers).<sup>34</sup> When examining self-report data only with high measure homogeneity, VERITAS-Pro levels were at a median of 45.5/100 (higher scores = lower adherence) in six self-report studies performed in 857 individuals who self-infused. Overall, reports from years 2011–2017 indicated that approximately one fifth of participants, children, adolescents, and adults, had issues with adherence to factor replacement treatment.

## Factors of adherence

A wide range of factors have been studied since 2011, from new types of health care delivery<sup>31</sup> to overprotection in the family.<sup>36</sup>

When classifying these factors in the categories from the diabetes literature (Table 1), we found a significant subset of five studies investigating exclusively non-modifiable sociodemographics and contextual factors such as current age, diagnosis, parent-infusion vs self-infusion (Table 5). Reports agreed on the observation that self-infusion at the adolescence and among young adulthood represented a risk for adherence.<sup>34,42</sup> However, in contrast with the rhGH literature, individual factors have been more frequently studied in relation to hemophilia prophylaxis during the recent period 2011–2017 (seven reports). These reports found that neces-

sity beliefs or perceived vulnerability (eg, experience of bleeding) as well as perceived benefits of treatment were fundamental aspects of motivation underlying adherence.<sup>30,41,44</sup> We also found arguments suggesting that negative emotions or the absence of history of depression would be associated with lower adherence rates.<sup>29,30,36,39</sup> Finally, understanding hemophilia and feeling capable of planning were also associated with higher adherence.<sup>30,38</sup>

Health care factors were studied through communication issues with the treatment centers and professional caregivers (5/16 studies). Although an intense follow-up did not yield stronger results on adherence, communication quality and trust in health care providers were found to be core factors of adherence.<sup>29,31,36</sup> Interestingly, a mere two reports found an impact of social factors such as relations with parents (in children) or working schedules (in adults).<sup>36,37,44</sup>

Importantly, most studies explored one or two domains of factors of adherence (median number of domains = 1.5), but modifiable domains were only investigated two thirds of the time. This means that one third of studies still only considers non-modifiable correlates. This is probably related to the high frequency of chart-based studies among the reports.

When examining factors whose relation was found significant with the measures of adherence, we found arguments suggesting that individual and health care factors would explain adherence. Yet reports found negative results on the impact of age when considered in isolation. This is probably because age is confounded with self-other infusion. When age was controlled for, parent-infusion was systematically related with higher levels of adherence.<sup>34,42,43</sup> A higher level of education in parents was also associated with better adherence. Finally, studies tended to show no relation with diagnosis type, but hemophilia B concerned a very small number of individuals. Overall, this broad picture of the results from Table 4 suggests that transition periods, including the passage to self-care, deserve a particular attention and that social factors including relationships with parents are still under investigated.

We also collected comments or interpretations of study authors in the discussion sections on which key factors may explain treatment adherence and thus should be studied in the future (Table 5). This analysis reveals that a large number of authors recommended to address social factors such as social support, social stigma, communication with parents and the health care team, social norms or the sense that the treatment is normal, as well as transition points in autonomy.<sup>29,31,35,36,42</sup> This recommendation strongly contrasts with the available literature and points to a gap in knowledge. Cost and financial

**Table 5** Domains of factors of adherence to prophylaxis treatment in hemophilia in 16 reports (2011–2017)

Reference	Descriptive factors	Individual factors	Social factors	Practical factors	Health care factors	No domains	Factors suggested in the discussion
Tran et al (2017) <sup>29</sup> <i>Haemophilia</i>		x			x	2	Family support Social support Social stigma Necessity beliefs Concern beliefs Health-system factors: individual formularies, prior-authorization requirements, cost sharing
van Os et al (2017) <sup>30</sup> <i>PLoS ONE</i>		x	x			2	Treatment cost
Lock et al (2016) <sup>31</sup> <i>Haemophilia</i>					x	1	Communication between parents and the treatment center
Mclaughlin et al (2016) <sup>32</sup> <i>Racial and Ethnic Health Disparities</i>						0	NA
Miesbach and Kalnins (2016) <sup>33</sup> <i>Haemophilia</i>	x				x	2	Infusion timing Frequency of infusions Perceived benefits of treatment
Schrijvers et al (2016) <sup>34</sup> <i>British Journal of Haematology</i>	x					1	Accepting the disease Self-management skills Infusion timing
Witkop et al (2016) <sup>35</sup> <i>Haemophilia</i>	x					1	Attitudes toward prophylaxis treatment Parental support Motivation and encouragement Sense of normality (treatment is normal) Perceived benefits, experience of results
García-Dasí et al (2015) <sup>36</sup> <i>Haemophilia</i>	x	x	x	x	x	5	Puberty Emotional aspects Accepting the disease Family attitude: watchfulness vs overprotection
Mingot-Castellano et al (2015) <sup>37</sup> <i>Blood Coagulation and Fibrinolysis</i>				x		1	NA
Schrijvers et al (2015) <sup>38</sup> <i>Haemophilia</i>	x	x		x		3	Perception of self- monitoring Self-management skills Age (position of hemophilia in adolescent patients)
Lamiani et al (2015) <sup>39</sup> <i>Haemophilia</i>	x	x				2	NA

(Continued)

**Table 5** (Continued)

Reference	Descriptive factors	Individual factors	Social factors	Practical factors	Health care factors	No domains	Factors suggested in the discussion
Ho et al (2014) <sup>40</sup> <i>Haemophilia</i>	x					1	Intensity of treatment regimen Cost of treatment
Tang et al (2013) <sup>41</sup> <i>Haemophilia</i>		x			x	2	Economic constraint Limitation in factor concentrate availability Education (potential benefits on the child's well-being and quality of life)
Duncan et al (2012) <sup>42</sup> <i>Haemophilia</i>	x					1	Transition points: shift from infused by family or nurse to self-infusion and switch from a prophylaxis regimen to on-demand treatment
Thornburg et al (2012) <sup>43</sup> <i>Haemophilia</i>	x					1	Financial concerns Accessibility of treatment Self-infusion vs other-infusion Education Frequency of infusion
Zappa et al (2012) <sup>44</sup> <i>Haemophilia</i>	x	x		x		3	NA

**Abbreviation:** NA, not available.

issues were also recommended as an important target in countries where full coverage is not warranted.<sup>29,30,40,43</sup> Finally, as transition points were recognized as vulnerability periods, self-management skills and self-infusion were recommended to be studied thoroughly. It is noticeable that no intervention during the study period sought to influence adherence through improving self-management during the transition period. This is reflected by the very limited number of pre-post intervention studies or prospective studies performed over recent years.<sup>31,37,41</sup>

## Discussion

The present research is an original attempt to review and compare factors of adherence of two resembling treatment regimen, rhGH and blood factor replacement therapy. From the examination of 27 reports dated 2011–2017, we estimated that approximately one in four to one in five participants (20%–25%) had issues with adherence. When exploring factors, we found a consistent pattern suggesting that adolescent or older children caring for themselves had lower adherence levels than children whose treatment was managed by parents. Importantly, about one third to half of the body of research did not investigate modifiable factors. Individual and relational predictors were clearly understudied, an

observation that pointed to a great potential of development for future research in this field, especially in rhGH-treated conditions. This contrasted with study authors' statements in discussion sections of their articles to study individual and relational factors in future research, in both of the studied clinical domains.

The systematic review of adherence factors yielded the observation that some factor domains have scarcely been studied and would deserve sustained attention by future researchers. It is particularly the case of individual factors in rhGH therapy and social factors in hemophilia prophylaxis treatment. This contrasts with the body of research on the effect of device and choice of device, which is not surprising as most of this research is supported by the industry. Unsurprisingly in rhGH therapy, the research showed that choice of device or device reducing pain and discomfort yielded improved adherence and that electronic devices giving feedbacks and prompts may help improve adherence. It is important to note that the lack of information on certain domains is probably not attributable to the fact that such factors do not influence treatment behaviors in GH-treated conditions and hemophilia, but most probably because of a lack of research. As evidenced in the high frequencies of studies focusing on non-modifiable factors, the research in

this field has mainly been descriptive and focused on simple easy-to-measure factors, such as age, sex, or type of device. However, the picture emerging from the recent literature reviewed here suggests that modifiable factors of adherence have somewhat been more investigated in hemophilia prophylaxis than in rhGH treatment. Although the research on non-modifiable factors may be informative, it cannot lead to appropriate intervention. Consequently, future research endeavors should complement the evidence, particularly in the domains of modifiable factors, such as coping styles, health beliefs and perceptions (individual and family), parental involvement, peer support, or social stigma. Although the choice among these target factors can be guided by theory,<sup>48</sup> it would be appropriate to confirm them with patients or families, probably in a set of qualitative inquiries identifying the views of participants themselves on barriers and facilitators of adherence. Notably, such inquiries have been performed in hemophilia<sup>49</sup> but, to our knowledge, they are not available in GH-treated conditions.

Based on the evidence reviewed, one could bridge the identified domains with theoretical models that are commonly employed to predict and change health behaviors in risk prevention research to favor a better articulation with intervention development. Although no systematic analysis has been done to date, a first look at the factors identified here and in previous reviews<sup>6,11</sup> suggest that a few core factors from the two right columns of Tables 2 and 4 are strongly anchored in social-cognitive theories of change:<sup>50</sup> 1) individual's self-efficacy or confidence in one's ability to complete treatment behaviors; 2) outcome expectancies or the positive or negative consequences of each behavior one anticipates (eg, necessity/concern balance); 3) illness-related family conflict and the position of illness in child-parent relationships, 4) communication in the family, 5) parental involvement and monitoring, 6) parental support; 7) the interplay of factors at multiple levels, including the children, their family, community, and the health care system.<sup>50</sup> A large body of treatment behavior research actually uses the framework of the Theory of Planned Behavior<sup>48</sup> to design surveys and interventions to predict health behaviors. This includes social norms and practical barriers, which are relevant domains of factors in adherence research. Finally, although psychological issues have seldom been studied in rhGH and hemophilia treatments (with the exception in rhGH<sup>18</sup> and in hemophilia<sup>29,30,36,38,39,41,44</sup>), it is probable that distress, depression, anxiety, and other internalized or externalized issues hamper adherence,<sup>51</sup> as it is the case with diabetes self-management.<sup>52</sup>

The methodological rigor of the literature on factors of adherence should also be discussed. In both treatment types, we found important limitations to causal hypotheses linking factors and adherence measures as a large majority of studies were cross-sectional.<sup>53</sup> As we are interested in modifiable factors, it is necessary that the measurement of factors precedes the measurement of adherence.<sup>53</sup> This points to the necessity of more frequent longitudinal follow-ups to collect real-world data or intervention designs where factors are manipulated. We found no reports in the study period attempting at systematically modifying knowledge, understanding, perceived necessity or concern, and their effect on adherence. Consequently, there is huge potential for interventional pre-post research in this field, including those increasing patients' perceived benefits of adherence and perceived vulnerability to adverse consequences of non-adherence. Coherent with a recent systematic review, such intervention should be age-specific, include the family, and enhance access to care.<sup>54</sup>

Importantly, the adherence research reviewed here consistently points to a vulnerable period during early teenage until young adulthood. Previous reports in rhGH and blood factor replacement therapy have demonstrated that adolescence is a vulnerable period especially as young people will transition to self-care.<sup>55,56</sup> This is postulated to result from the extra burden that managing injections imposes on the already challenging nature of adolescence.<sup>7,57</sup> For many adolescents, injecting may be viewed as a nonessential or meaningless task. The need to manage injections may significantly affect their ability to completely partake in day-to-day activities, which are commonplace for their peer group. Another difficulty for them is also the tendency to focus on the here and now, sometimes because they lack the proper planning competencies, and which makes it hard for them to comprehend the long-term benefits of adhering to the injection regimen.<sup>54</sup> It is thus necessary to address this specific period when exploring the factors of adherence.<sup>7,58</sup> In fact, self-management promotion may be most effective if strategically delivered at times of maximal impact. For example, patients' and families' readiness for self-management intervention is probably optimal during the developmental transition of early adolescence when the routine parent-injected treatment is due to change to self-injection. Consequently, measurement of factors of adherence and intervention initiatives should target this time period.

Two ranges of factors have traditionally appeared as strong predictors of adherence and self-management behaviors in the youth. In younger children, as injections are made by a third party, most often a parent, effectiveness of treatment behaviors lies into how treatment is integrated in



the daily routine and the position of treatment and illness in the child–parent relationship. For instance, treatment as any other elements may be used by the child to relate with, control or resist to the parent who performs the injection. As the illness is silent in the short-term, with few symptoms, being ill remains abstract for many children, whereas the treatment is very concrete. This is all the more significant as many parents feel guilty to inject because the treatment imposes constraints on the child or makes them feel uncomfortable or painful. Therefore, a large part of adherence issues in younger children may be subsumed to the parent–child relations.<sup>50,51,59</sup> In older school-age children and teenagers, peer influence may have a major impact on adherence. Recent work has found that young patients often mistakenly believed that friends would have negative reactions to their condition, even though empirical work suggested that friends tend to provide encouragement. Consistently, a link between anxiety in social situations and poor adherence was found, particularly in boys. “Fitting in” appears to drive a part of the issues with adherence in teens.<sup>60</sup> Similarly, public embarrassment and stress issues were cited by both adult patients and providers to explain missed injection in diabetes.<sup>61</sup> As the sense of normalcy becomes more acute during adolescence, social norms become a core explanatory factor of adherence in this age range. Consequently, there are both empirical and theoretical arguments to develop a strong endeavor to study individual and relational factors of adherence in GH-treated conditions and hemophilia treated with prophylaxis.

We should acknowledge the limitations of the present work. First, the review is limited to a recent period of 8 years (2011–2017). Although a longer time lapse would have been appropriate, the results would probably have overlapped with pre-existing reviews.<sup>6,11</sup> As a result, conclusions should only be considered as reflective of the recent period. Second, although the taxonomy emerging from diabetes research in Table 1 is based on reviews and guidelines of the diabetes literature, we cannot rule out that another classification would be equally pertinent. Yet, this taxonomy has good face validity and helped identify gaps in the literature from the point of view of a more frequent illness where adherence research is far more advanced. Third, although we initially wished to include the gray literature and conference abstracts, this revealed inappropriate given the insufficient information to document the retrieved information categories. This led us to discard conference abstracts post hoc. Finally, in order to include as many studies as possible in this very rarely studied field, we did not use any formal instrument to assess the methodology

of individual studies. It must also be noted that the two treatments address different situations across conditions with long-term issues ranging from poor joint function (hemophilia) to low stature (GHD). These may trigger a variety of perceptions, concerns, and anticipatory beliefs. Consequently, comparisons across conditions based on the present review should be limited to the broad categories of factors studied in this review.

## Conclusion

In a systematic review of empirical reports documenting factors of adherence in GH-treated conditions (N=11) and prophylaxis-treated hemophilia (N=16) from 2011 to 2017, we found a level of suboptimal adherence in 20%–25%, comparable to previous reports. We found consistent arguments across conditions suggesting the transition to self-care may be a vulnerability period during the late childhood/early adolescents. When classifying studied factors according to categories emerging from diabetes research, we found the domains of individual factors (eg, perceptions, knowledge, motivation), relational factors (eg, parenting, social norms, stigma), and health care (eg, trust with professional, relationship quality with care team) to be understudied, in comparison with that of demographic context (eg, age, sex, pubertal status) and practical issues (eg, delivery device). Future research should focus on how modifiable factors may explain adherence variability and study how these factors may be targeted by psychosocial and behavioral interventions.<sup>51</sup>

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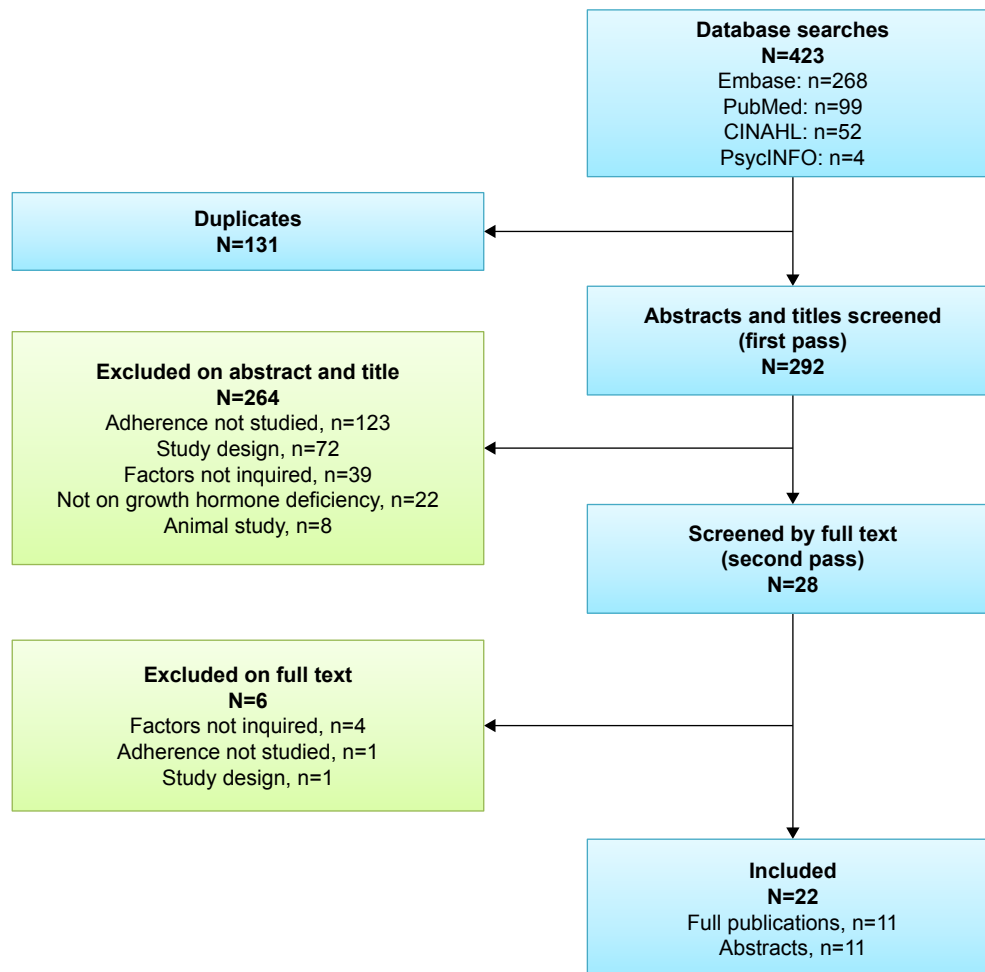
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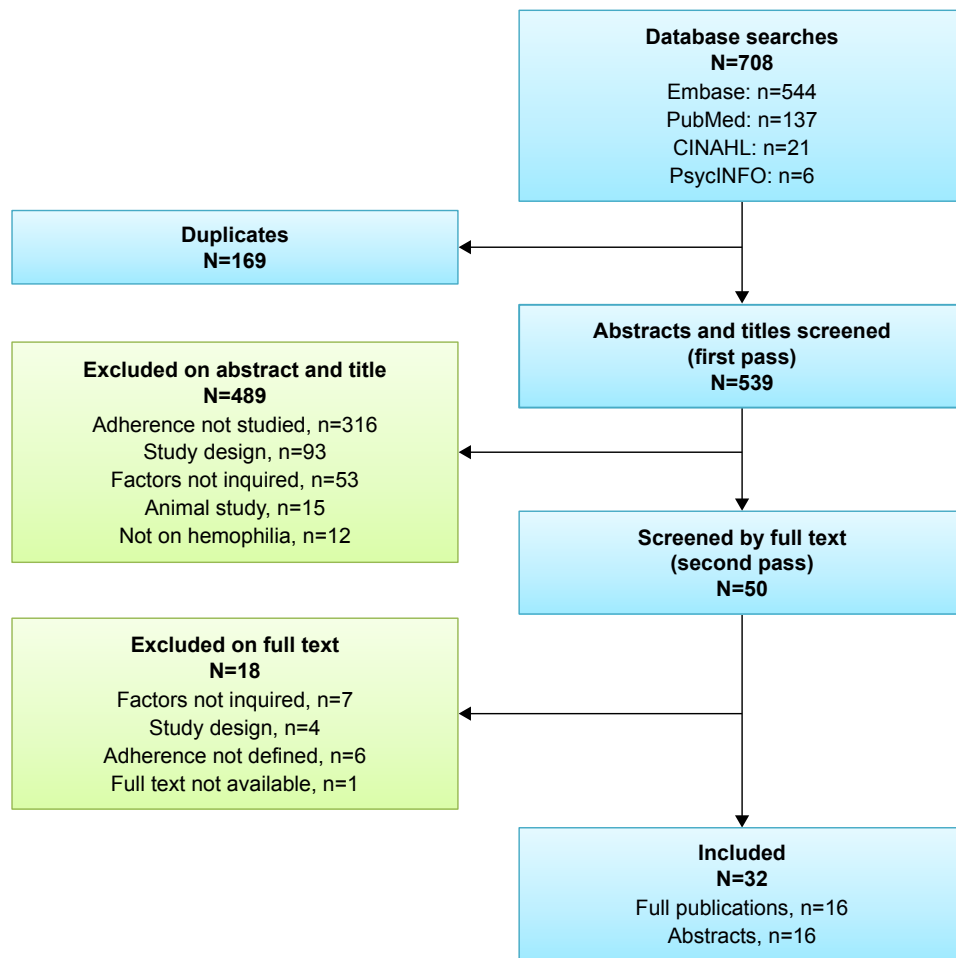
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## Supplementary materials



**Figure S1** Flow diagram of retrieved studies in the review of factors of adherence in patients treated with recombinant human Growth Hormone (rhGH), 2011–2017.



**Figure S2** Flow diagram of retrieved studies in the review of factors of adherence in hemophilia patients treated with prophylaxis, 2011–2017.

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