

# BMJ Open PHILEOS (*haemoPHILia and ostEoporOSis*) Study: protocol of a multicentre prospective case-control study

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**To cite:** Tardy-Poncet B, Play B, Montmartin A, *et al*. PHILEOS (*haemoPHILia and ostEoporOSis*) Study: protocol of a multicentre prospective case-control study. *BMJ Open* 2021;**11**:e042283. doi:10.1136/bmjopen-2020-042283

► Prepublication history for this paper is available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2020-042283>).

Received 02 July 2020  
Revised 18 December 2020  
Accepted 21 December 2020



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## ABSTRACT

**Introduction** Two meta-analyses showed lower bone mineral density (BMD) in patients with haemophilia (haemophilia type and severity were often not specified) compared with healthy controls. This finding could be related to reduced mobility and sedentary lifestyle, and/or hepatitis C or HIV infection. The aim of this study is to determine osteoporosis prevalence in patients with haemophilia classified in function of the disease type (A or B) and severity, and to evaluate the potential role of regular prophylactic factor replacement (early vs delayed initiation) in preserving or restoring BMD.

**Methods and analysis** The haemoPHILia and ostEoporOSis Study is a prospective, controlled, multicentre study that will include patients in France (13 haemophilia treatment centres), Belgium (1 centre) and Romania (1 centre). In total, 240 patients with haemophilia and 240 matched healthy controls will be recruited (1:1). The primary objective is to determine osteoporosis prevalence in patients with severe haemophilia A and B (HA and HB) without prophylaxis, compared with healthy controls. Secondary outcomes include: prevalence of osteoporosis and osteopenia in patients with mild, moderate and severe HA or HB with prophylaxis (grouped in function of their age at prophylaxis initiation), compared with healthy subjects; BMD in patients with HA and HB of comparable severity; correlation between BMD and basal factor VIII/IX levels and thrombin potential; and quantification of plasmatic markers of bone remodelling (formation and resorption) in patients with haemophilia.

**Ethics and dissemination** The protocol was approved by the French Ethics Committee and by the French National Agency for Medicines and Health Products Safety (number: 2019-A03358-49). The results of this study will be actively disseminated through scientific publications and conference presentations.

**Trial registration number** NCT04384341.

## INTRODUCTION

Haemophilia is a rare X-linked bleeding disorder, characterised by factor VIII (FVIII; haemophilia A/HA) or factor IX (FIX; haemophilia B/HB) deficiency. FVIII/FIX absence or reduction results in impaired thrombin generation and clot formation. Bleeding can

## Strengths and limitations of this study

- This is the largest prospective and controlled (1:1) study on osteoporosis in haemophilia, including patients from 15 haemophilia treatment centres in France, Belgium and Romania.
- This is the first study that evaluates osteoporosis prevalence separately in patients with haemophilia A and B, by taking into account the disease severity and the treatment modality (without or with prophylaxis, and age at prophylaxis initiation).
- Only ≥20-year-old individuals will be included because all participants must have reached their peak bone mass in order to have a homogeneous population.
- As most patients with severe haemophilia are on prophylaxis in France and Belgium, we expect that patients without prophylaxis will be mainly recruited in Romania.

occur anywhere, but particularly in joints and muscles. Haemophilia phenotype is primarily determined by the circulating level of the deficient coagulation factor: 6%–40% in mild, 1%–5% in moderate, and <1% of FVIII or FIX in severe disease that is associated with a risk of spontaneous bleeding. Prophylaxis of bleeding episodes in patients with severe haemophilia consists in the restoration of thrombin generation by FVIII or FIX substitution (current treatment) or by bypassing agents already on the market (emicizumab for HA only or in development (anti-tissue factor pathway inhibitor, anti-antithrombin III antibodies)).<sup>1</sup>

Recently, attention has been focused on osteoporosis as comorbidity of haemophilia. Osteoporosis is a systemic bone disease characterised by low bone mineral density (BMD), resulting from an imbalance of bone metabolism (ie, the cycle of bone growth and resorption). The bone weakness resulting

from BMD decrease is associated with higher risk of spontaneous fractures.

The first study on bone loss in patients with haemophilia described two clinical cases of atraumatic fracture in men with severe HA, without any known risk factor for osteoporosis.<sup>2</sup> Later, another study (small sample size, n=30) suggested that 70% of patients with haemophilia present osteopenia, 30% of them reaching the osteoporosis stage.<sup>3</sup> Two meta-analyses (n=500 patients with haemophilia) completed these observations and showed that BMD (femur neck and lumbar spine) is decreased in both paediatric and adult patients with haemophilia compared with controls (pooled standardised mean difference: -1.379, 95% CI -2.355 to -0.403 for the first meta-analysis in 2010,<sup>4</sup> and -0.82, 95% CI -1.21 to -0.44 for the second meta-analysis in 2014).<sup>5</sup>

Although both meta-analyses showed an association between haemophilia and BMD decrease, the haemophilia type, severity and presence or not of prophylactic antihemophilic treatment in patients with bone loss was often not reported.<sup>6-11</sup> Furthermore, the case-control studies included in these meta-analyses compared the mean BMD values between patients and controls, but they did not evaluate osteoporosis prevalence in function of the haemophilia type and severity.

Several hypotheses have been proposed to explain the pathophysiological mechanism of haemophilia-related osteopenia, such as reduced physical activity following joint damage, calcium/vitamin D deficiency and hepatitis C virus (HCV) infection, but none was specifically retained. Another hypothesis is that bone loss could be linked to FVIII and/or FIX deficiency through different mechanisms. Indeed, the finding of a thrombin-mediated mitogenic effect on osteoblasts (ie, the cells responsible for bone formation) suggests that the thrombin generation defect resulting from FVIII or FIX deficiency might lead to BMD reduction in patients with haemophilia.<sup>12,13</sup> Moreover, FVIII complexed to von Willebrand factor can associate with and inhibit osteoprotegerin, an anti-osteoclastogenesis receptor on the bone cell surface. Therefore, FVIII deficiency might not allow this inhibition, thus promoting bone resorption.<sup>14</sup> In function of the underlying mechanism, the osteoporosis degree could vary depending on the haemophilia type and/or severity. Additionally, as it has been suggested that anti-haemophilia treatment contributes osteopenia prevention,<sup>15,16</sup> restoration of the thrombin generation potential with bypassing agents and restoration of the FVIII/FIX level with classical prophylactic treatments could prevent osteoporosis.

Therefore, the aim of this study is to evaluate the prevalence of bone loss in patients with haemophilia, according to the disease type and severity, the presence or not of prophylaxis, and the age at prophylaxis initiation, and in a matched control population.

## Study objectives

### Primary objective

To determine, in patients with severe HA and HB without prophylaxis, the prevalence of osteoporosis (T-scores measured by DEXA bone scan of hip and spine) in comparison with age-matched and body mass index (BMI)-matched healthy controls.

### Secondary objectives

1. To determine, in patients with mild, moderate and severe HA and HB with prophylaxis (in function of the age at prophylaxis initiation), the prevalence of osteoporosis in comparison with age-matched and BMI-matched healthy controls.
2. To determine, in patients with mild, moderate and severe HA and HB without prophylaxis and with prophylaxis (in function of the age at prophylaxis initiation), the prevalence of osteopenia in comparison with age-matched and BMI-matched healthy controls using the T-scores measured by DEXA bone scans of hip and spine.
3. To compare the BMD (expressed in g/cm<sup>2</sup>) and the Z-score in patients with mild, moderate, and severe HA and HB without and with prophylaxis (in function of the age at prophylaxis initiation) and in age-matched and BMI-matched healthy controls.
4. To evaluate, in patients with mild, moderate and severe (without prophylaxis) HA and HB, the correlation between BMD (g/cm<sup>2</sup> and T-score).
  - FVIII-related or FIX-related antigen (FVIII:Ag and FIX:Ag).
  - FVIII or FIX activity.
  - The patient's potential of thrombin generation.
5. To evaluate, in patients with HA and HB, plasmatric markers of bone remodelling (formation and resorption).

## METHODS AND ANALYSIS

### Study design

This is an international multicentre prospective controlled (1:1) study, with a 2-year enrolment period, performed at 15 haemophilia treatment centres in France, Belgium and Romania. The study started in September 2020; the end date is planned in October 2022.

### Study population

In men, peak bone mass (maximal BMD) is achieved at around 20 years of age. Then, in the absence of risk factors, BMD remains relatively stable until 60 years of age, when a physiological and inevitable BMD decrease is observed.<sup>17</sup> As bone metabolism is rather stable between 20 and 60 years of age, patients with haemophilia in this age range will be included.

In patients with severe haemophilia and inhibitors (ie, inactivating antibodies against therapeutic FVIII or FIX), haemarthrosis rate and joint damage are increased compared with patients without inhibitors. In these patients, reduced physical activity due to early

**Table 1** Inclusion and exclusion criteria for patients with haemophilia

Inclusion	Exclusion
<ul style="list-style-type: none"> <li>▶ Patients with haemophilia A and B, irrespective of the disease form (mild, moderate, severe, with or without prophylaxis)</li> <li>▶ Age between 20 and 60 years</li> <li>▶ Patients with severe haemophilia A: last FVIII injection 48–120 hours (depending on the prophylactic treatment) before blood sampling for this study</li> <li>▶ Patients with severe haemophilia B: last FIX injection 5–21 days (depending on the prophylactic treatment) before blood sampling for this study</li> </ul>	<ul style="list-style-type: none"> <li>▶ Age &lt;20 years</li> <li>▶ Age &gt;60 years</li> <li>▶ Participants with current or history of anti-FVIII or anti-FIX inhibitors (&gt;5 Bethesda units)</li> <li>▶ Participants treated with emicizumab</li> <li>▶ Past or present anti-osteoporosis treatment other than vitamin D and calcium</li> <li>▶ Presence of two total hip prostheses</li> <li>▶ History of disease known to influence bone metabolism and not related to haemophilia (hyperthyroidism, hyperparathyroidism, hypercorticism, hypogonadism, diseases that require long-term corticoid use)</li> <li>▶ Documented HIV infection</li> <li>▶ Documented HCV infection at the cirrhotic stage</li> </ul>

FIX, factor IX; FVIII, factor VIII; HCV, hepatitis C virus.

haemophilic arthropathy may affect the acquisition of peak bone mass during childhood, and BMD level in adult life.<sup>18</sup> Consequently, patients with haemophilia and inhibitors will not be included in this study.

As HIV infection and initiation of antiretroviral therapy are associated with significant bone loss resulting in osteopenia and osteoporosis,<sup>19</sup> patients with haemophilia and documented HIV infection will not be included in this study.

Although an increased risk of osteoporosis in patients with HCV has been suspected, it was shown that bone mass is comparable in patients without cirrhosis with HCV and controls.<sup>20</sup> Therefore, only patients with haemophilia and documented HCV infection at the cirrhotic stage will not be included in this study. To avoid other confounding factors that may influence BMD loss, other exclusion criteria have been defined (table 1). Plasmatic markers of bone metabolism will be measured to take into account other potential causes of osteopenia.

As age and BMI are factors that can lead to lower BMD, each patient with haemophilia will be matched

with a healthy male participant of similar age ( $\pm 2$  years) and BMI ( $\pm 2$  kg/m<sup>2</sup>). BMI is calculated as weight (kg)/height (m<sup>2</sup>). The inclusion and exclusion criteria for age-matched and BMI-matched controls are listed in table 2.

### Sample size

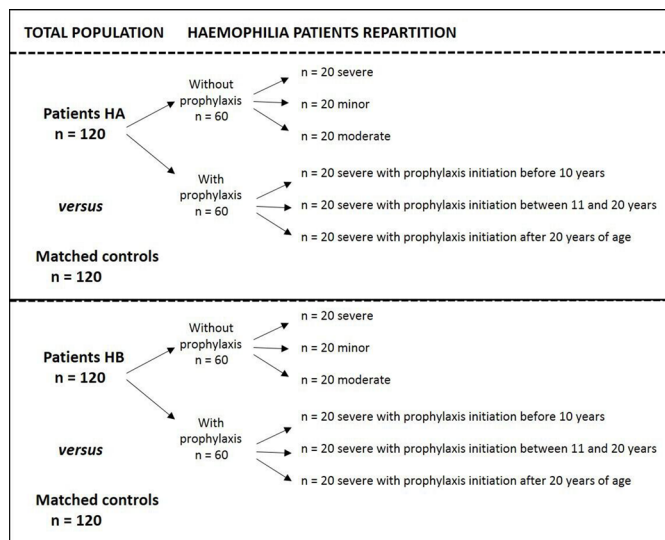
Based on previous observational studies, the prevalence of osteoporosis in young healthy men and in patients with severe haemophilia can be estimated at 5% and 30%, respectively.<sup>21 22</sup> In view of these results, it is necessary to include 40 healthy controls and 40 patients with severe HA and HB without prophylaxis to detect a difference in osteoporosis prevalence between patients and controls (primary objective), with a 5% alpha risk and a 15% beta risk.

To reach the primary and secondary objectives, 240 patients with haemophilia (n=120 HA and n=120 HB, of different severity and with/without prophylaxis) and 240 age-matched and BMI-matched healthy controls will be included (figure 1).

**Table 2** Inclusion and exclusion criteria for healthy controls

Inclusion	Exclusion
<ul style="list-style-type: none"> <li>▶ Healthy men aged between 20 and 60 years</li> </ul>	<ul style="list-style-type: none"> <li>▶ Healthy men &lt;20 years of age</li> <li>▶ Healthy men &gt;60 years of age</li> <li>▶ History of disease known to influence bone metabolism (hyperthyroidism, hyperparathyroidism, hypercorticism, hypogonadism, diseases that require long-term corticoid use)</li> <li>▶ Past or present treatment with anti-osteoporosis medication (other than calcium and vitamin D)</li> <li>▶ Past or present treatment with antiaggregant or anticoagulant drugs</li> <li>▶ Presence of two total hip prostheses</li> <li>▶ Documented HIV infection</li> <li>▶ Documented HCV infection at the cirrhotic stage</li> </ul>

HCV, hepatitis C virus.



**Figure 1** Distribution of subjects in this study protocol. HA, haemophilia A; HB, haemophilia B.

### Patient and public involvement

No patient was involved in the protocol design.

### Measurement of outcomes

#### Assessment of BMD and osteoporosis diagnosis in patients with haemophilia and matched controls

BMD ( $\text{g}/\text{cm}^2$ ) of hips and lumbar vertebrae (L1–L4) will be measured using a DEXA instrument HOLOGIC or GE.LUNAR. To cover intermachine variation of measure linked to the multicentric design of this study, each machine will be calibrated using an anthropomorphic phantom in order to standardise the results.

BMD values will be expressed as T-scores and Z-scores (only for subject younger than age 50 years). According to the WHO, the degree of bone loss in adults is defined by the T-score value that is the SD above or below the mean BMD of the sex-matched young adult reference population. A T-score higher than  $-1.0$  indicates normal BMD; when lower than  $-1.0$  but higher than  $-2.5$ , it indicates osteopenia; and when lower than  $-2.5$ , it indicates osteoporosis.<sup>21</sup> T-scores have been clinically validated in  $\geq 20$ -year-old men, and they are appropriate for our outcome (osteoporosis/osteopenia) assessment.

Z-score of  $-2.0$  or lower is defined as ‘below the expected range for age’, and a Z-score above  $-2.0$  is ‘within the expected range for age’. Z-score will be used to compare BMD between the different groups of patients and the controls (in men aged 20–50 years only).

Physical activity impairment will be assessed using a very simple scale (6).

The number of target joints in the lower limbs and the number of lower limb prostheses will be recorded. BMD will be measured on the dominant leg (meaning the less affected leg) to reduce the impact of arthropathy on BMD measured at the femoral neck.

### Laboratory tests in patients with haemophilia

The following coagulation parameters will be evaluated: FVIII/FIX clotting activity, FVIII:Ag/FIX:Ag levels and thrombin generation potential using a thrombin generation assay.

The following bone parameters will be measured in a central lab (Saint-Etienne): plasmatic calcium, phosphate, creatinine, vitamin D25, C reactive protein, testosterone, carboxy-terminal collagen crosslinks, alanine aminotransferase, aspartate aminotransferase, parathyroid hormone, bone phosphatase alkaline and procollagen type 1 intact N-terminal propeptide concentration.

### Statistical analyses

#### Descriptive analyses

The study population will be described, by group of patients, using number of available data, mean, SD, median, first and third quartiles, minimum and maximum for quantitative variables, and absolute and relative frequencies (expressed in %) for qualitative variables.

#### Primary outcome analyses

The primary outcome is the prevalence of osteoporosis, defined by a T-score lower than  $-2.5$ . The frequency of individuals with osteoporosis and the 95% CI will be estimated in the group with severe haemophilia without prophylaxis and in matched controls. To compare the percentage of individuals with osteoporosis in these two groups, the McNemar’s test (paired data) will be used. ORs with the 95% CI will also be estimated.

In the event of significant differences for one or more confounding factors, a multivariate logistic model will be considered. No imputation of missing data will be applied and no subgroup analysis is planned.

#### Secondary outcome analyses

To compare the osteoporosis and osteopenia prevalence in the different groups of patients with haemophilia and matched controls, the same statistical methods described for the primary outcome analyses will be used.

To compare BMD and Z-score (quantitative variables) in the different groups of patients with haemophilia and matched controls (paired data), the Student’s t-test will be used in case of normal distribution, or the Wilcoxon’s rank test if the normal distribution of data is not confirmed by the Shapiro-Wilk test.

As the plasmatic markers of bone metabolism are quantitative variables, results will be analysed as described for BMD.

Finally, correlations between BMD levels and FVIII:Ag/FIX:Ag level, and activity and thrombin generation potential will be evaluated using the Pearson correlation coefficient in case of normal distribution, or the Spearman’s correlation coefficient  $r_s$ , if the normal distribution is not confirmed. A graphical representation, such as scatter plots, will be used.

### Limitations

The majority of patients with severe haemophilia without prophylaxis will be enrolled in Romania, because in France

and Belgium most of these patients are on prophylactic treatment. However, a bias related to the country of inclusion should be avoided if the matched controls are enrolled in the same country.

## CONCLUSIONS

To our knowledge, this will be the first study to investigate osteoporosis prevalence in patients with haemophilia by taking into account the type (HA or HB) and severity of disease and prophylaxis status (absent, early or delayed). Our results could give some information on the level of FVIII and FIX required to ensure normal BMD. We hypothesise that FVIII and/or FIX could be involved in osteoporosis, either directly via an impact on bone remodelling, or indirectly via the thrombin generation defect. Our results could predict the efficacy for osteoporosis prevention of antihemophilic prophylaxis depending on the nature (FVIII/FIX or bypassing agents) of the treatment.

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**Contributors** BT-P, PD and BP—conception and design. BT-P, EP and E0—development of methodology. EP—statistical analysis. BT-P, PD, AM, AG and BP—draft of the protocol. BT-P, BP and BT—review of the protocol.

**Funding** This study was supported by a grant from the French Ministry of Health (PHRCI 2019-PHILEOS). This work is also supported by Grants from Pfizer (52930211), Novo Nordisk, SOBI (2019-144), CSL Behring (4539), Octapharma, Shire and Roche.

**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not required.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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