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# Bone mineral density in men and children with haemophilia A and B: a systematic review and meta-analysis

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## Abstract

**Summary** Although haemophilia is not considered among the classic causes of secondary osteoporosis, the present meta-analysis provides strong evidence that men with haemophilia have a significant reduction in both lumbar spine and femoral bone mineral density, which appears to begin in childhood.

**Introduction** Haemophilia is not considered among the classic causes of secondary osteoporosis. The aim of this study was to systematically review the literature for case–control trials that have studied bone mass in males with haemophilia and to meta-analyze the best evidence available.

**Methods** Electronic databases MEDLINE, EMBASE and CENTRAL were systematically searched for case–control trials that have studied bone mass in men or boys with haemophilia. Standardized mean difference (SMD) for bone mineral density (BMD) in the lumbar spine was the main

study outcome and SMD in femoral neck and total hip BMD the secondary ones. Patient and control characteristics, such as age, body mass index (BMI), level of physical activity and blood-borne infections were recorded as possible predictors of the main outcome.

**Results** Thirteen studies were included in the systematic review and ten in the main outcome meta-analysis. Men with haemophilia demonstrated reduced lumbar spine [random effects SMD [95 % confidence interval (CI)] =  $-0.56$  ( $-0.84, -0.28$ ), between-study heterogeneity ( $I^2$ ) = 51 %] and femoral neck BMD [random effects SMD (95 % CI) =  $-0.82$  ( $-1.21, -0.44$ ),  $I^2$  = 63 %] compared with controls, which indicated a large and clinically significant association. Similar results were obtained for children [random effects SMD (95 % CI) =  $-0.92$  ( $-1.77, -0.07$ ),  $I^2$  = 92 %]. No evidence of publication bias was detected. There was no evidence that age, BMI, level of physical activity or presence of blood-borne infections predicted lumbar spine BMD.

**Conclusions** This meta-analysis shows that men with haemophilia present a significant reduction in both lumbar spine and hip BMD, which appears to begin in childhood.

**Electronic supplementary material** The online version of this article (doi:10.1007/s00198-014-2773-7) contains supplementary material, which is available to authorized users.

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**Keywords** Bone mineral density · Haemophilia A · Haemophilia B · Meta-analysis · Osteoporosis · Systematic review

## Introduction

Osteoporosis is characterized by decreased bone mass and strength, architectural deterioration and increased risk of vertebral and non-vertebral fracture [1, 2]. Although the most prevalent type is postmenopausal osteoporosis, secondary cases include alcoholism, smoking, hypogonadism, thalassaemia syndromes, haematological malignancies, endogenous or exogenous glucocorticoid excess, vitamin D deficiency,

hyperthyroidism, hyperparathyroidism and type 1 diabetes mellitus [3, 4].

Haemophilia is a rare bleeding disorder, inherited by the X-linked recessive type and characterized by deficiency of coagulation factor VIII (FVIII) (haemophilia A, 85 % of cases) or IX (FIX) (haemophilia B) [5]. In men with haemophilia, spontaneous intra-articular bleeding leads to structural transformations of the joint [6], such as synovial and vascular cell proliferation and cartilage destruction, inflammatory infiltration of synovial membrane and cartilage cells, as well as iron deposition (haemophilic arthropathy) [6, 7]. Reduced physical activity, due to haemophilic arthropathy, may compromise the acquisition of peak bone mass during childhood and affect bone mineral density (BMD) in adult life [8]. A second pathophysiologic link could be blood-borne virus infections, such as hepatitis C virus (HCV) or human immunodeficiency virus (HIV), which are highly prevalent in men with haemophilia and have been associated with low bone mass [9]. A third link could be an interaction between the coagulation cascade and factors of bone metabolism [8]. In the largest study conducted so far, physical activity and 25-hydroxyvitamin D [25(OH)D] concentrations were independent predictors of low BMD in men with haemophilia A and B [10]. Despite these considerations, the exact pathogenetic mechanisms have not been fully clarified.

In fact, a number of studies have attempted to assess the prevalence and severity of osteoporosis in men with haemophilia and to determine the factors for lower BMD, the main determining factor for bone strength [10–22]. Despite this evidence, haemophilia is not considered yet among the causes of secondary osteoporosis. The aim of the present study was to systematically review the literature for case–control studies that have studied BMD in men and boys with haemophilia and to meta-analyze the best evidence available, in an attempt to provide high-quality data on the linkage between haemophilia and osteoporosis.

## Materials and methods

### Search strategy

To identify eligible studies, the main search was conducted in the electronic databases MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL), covering the period from conception until December 2013 and using combinations of the key terms: ‘h(a)emophilia’ AND ‘bone’ OR ‘osteoporosis’ OR ‘bone mineral density’. The procedure was concluded by the following: (i) the perusal of the reference sections of all relevant studies, (ii) a manual search of key journals and abstracts from the major annual meetings in the field of haemophilia and osteoporosis, and (iii) contact with experts. The main search was completed independently by

two investigators (S.A.P. and P.A.). Any discrepancy was solved by consultation of an investigator, not involved in the initial procedure (D.G.G.).

### Selection of studies

Criteria for inclusion/exclusion of studies were established prior to the literature search. Eligible for the systematic review and meta-analysis were only case–control trials that have assessed osteoporosis among men or boys with haemophilia. Studies with no control group or control group including women were excluded from the systematic review and meta-analysis. Reviews, letters to the editor and studies published in language other than English were excluded as well.

### Data extraction

Information from each study was extracted independently by two reviewers using a standardized data extraction form. Main study outcome was lumbar spine BMD. Secondary outcomes were femoral neck and total hip BMD. Study general characteristics (author, journal, year of publication, design, ethnicity, number of cases, number of controls), characteristics of the cases and control groups [age, body mass index (BMI), level of physical activity, blood-borne infections, namely, hepatitis B virus (HBV), HCV and HIV, severity of haemophilia, degree of arthropathy, 25(OH)D concentrations, methodology (BMD measurement method, calcium metabolism measurements methods) and outcomes were recorded (where available) and double-checked. Where appropriate, the data set was completed through communication with the authors. Specifically, an e-mail was sent, and when no answer was received, a second one followed after a 2-week interval. Disagreement was resolved by consensus.

### Statistical analysis

Standardized mean differences (SMD) and 95 % confidence intervals (CI) were calculated for all study outcomes for all eligible studies for the meta-analyses and combined using random effects model [23]. Main study outcomes were expressed in terms of bias corrected ‘effect size’ of the difference between BMD in cases and controls, using an Effect Size Calculator worksheet (Coe’s Calculator retrieved February 5, 2014 from <http://www.cemcentre.org/evidence-based-education/effect-size-calculator>). Qualitative descriptors of the effect sizes obtained were less than 0.3 (small), 0.4 to 0.8 (moderate) and greater than 0.8 (large) [24].

Heterogeneity between the results of different studies was examined by  $I^2$  test. To assess the extent of publication bias, Egger’s test was used [25]. To ensure synthesis of the best available evidence, sensitivity analyses were performed excluding studies (1) with significant differences in the mean age and/or BMI between groups, (2) with evidence of significant

skewness in the distribution of index substance, as defined by a ratio of mean to standard deviation (SD) less than 1 [26] and (3) with discordance among reviewers upon their eligibility. Finally, sensitivity analysis was made based on the quality of each study, assessed by the Newcastle-Ottawa scale for case–control studies. The instrument uses a star system to evaluate observational studies based on three criteria: participant selection, comparability of study groups and assessment of outcome or exposure [27].

Meta-analysis was conducted using Review Manager (RevMan) for Mac (version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012). Meta-regression was conducted using STATA Special Edition (SE) 12.1 for Mac (StataCorp LP, TX, USA). The report of the study was complemented in adherence with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) group standards for reporting meta-analysis of observational studies [28].

## Results

### Systematic review

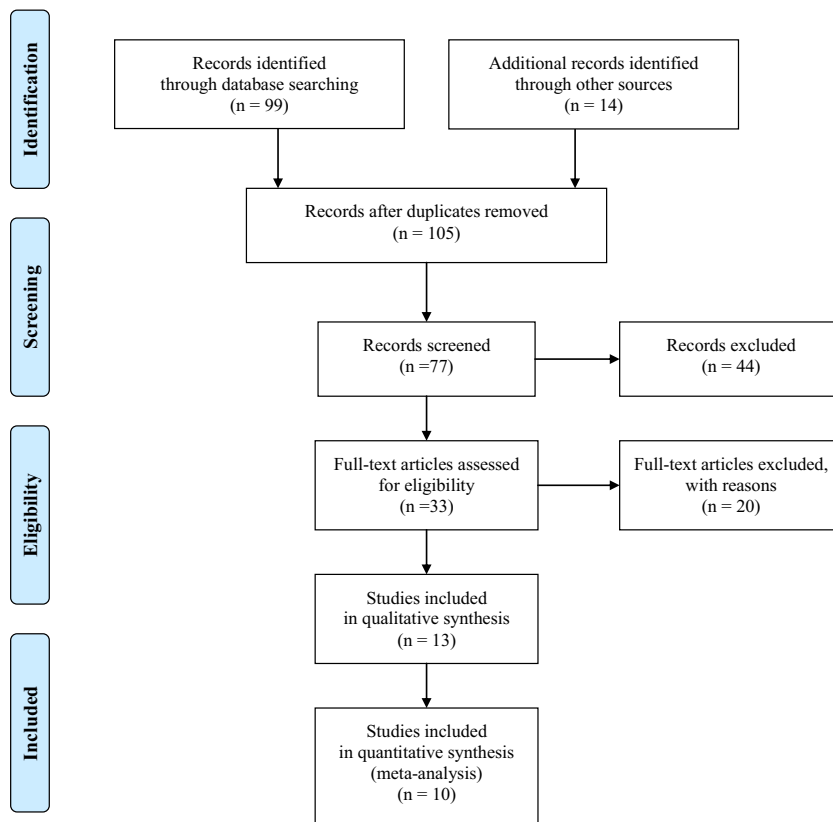
The literature search yielded 105 publications in total. After application of the inclusion/exclusion criteria, 13 studies were

included in the systematic review. A flow chart of this process is presented in Fig. 1. The main characteristics of the studies are presented in Table 1 and the main outcomes in Table 2. Detailed information on study characteristics and outcomes is presented in Online Resource 1.

The 13 eligible case–control studies included in the systematic review were published between 1994 and 2012. They involved in total 499 patients and 702 age- and sex-matched controls. Three of them originated from Iran [14, 16, 17], two from Finland [12, 13], two from Greece [10, 15] and one from Turkey [11], India [20], UK [22], Mexico [18], Egypt [19] and Australia [21]. Seven studies investigated boys/adolescents [11–13, 15, 18, 19, 21] and six adult men [10, 14, 16, 17, 20, 22]. As far as outcomes are concerned, ten studies provided data for lumbar BMD [10, 11, 14, 16–22] (either absolute values, T- or Z-scores), five for femoral neck BMD [10, 14, 16, 17, 22] (either absolute values, T- or Z-scores), two for total hip BMD [10, 20] and one for peripheral quantitative computed tomography (pQCT) in order to assess bone structure and strength in the radius [12].

Four studies [10, 13, 20, 22] provided data on fracture prevalence in men with haemophilia and controls (Table 2), with values ranging between 10 and 37 %. In the largest series [10], history of fracture was positively associated with the severity of haemophilia ( $p=0.0001$ ), the number of affected joints ( $p=0.043$ ), the level of physical activity ( $p=0.0001$ ) and HCV ( $p=0.031$ ) and HIV ( $p=0.0001$ ) infection.

**Fig. 1** PRISMA flow diagram, detailing selection of studies for inclusion



**Table 1** Main characteristics of the studies included in the systematic review

Id	First author, year, country	No. (H)	No. (C)	H type (A/B) (H)	Age (years) (H)	Age (years) (C)	BMI (kg/m <sup>2</sup> ) (H)	BMI (kg/m <sup>2</sup> ) (C)	Infected (HBV/HCV/HIV) (H)
1.	Anagnostis P, 2012, Greece	104	50	90/14	45.8±15.1	44.9±12.8	27.1±4.5	28.5±4.4	4/42/7
2.	Alioglu B, 2012, Turkey	44	40	44/0	160 (36–216) months	146 (42–240) months	N/A	N/A	N/A
3.	Ranta S, 2012, Finland	29	46	21/8	12.2±3.6	12.2±3.0	20.0±5.0	19.4±3.4	N/A
4.	Ranta S, 2011, Finland	29	58	21/8	11.0±3.6	11.6±2.8	19.3±4.5	19.2±4	0/0/0
5.	Rezaeifarid M, 2011, Iran	55	87	N/A	23.5	25.1	N/A	N/A	N/A
6.	Christoforidis A, 2011, Greece	26	13	26/0	12.1±4.4	11.5±5.3	N/A	N/A	N/A/0/0
7.	Mansouritorghabeh H, 2009, Iran	14	14	0/14	30.6±12.2	30.5±12.1	25.4±5.2	25.2±4.9	N/A/11/N/A
8.	Mansouritorghabeh H, 2008, Iran	18	18	18/0	29.1±8.6	29.1±8.6	22.4±3.3	23.6±3.7	1/11/N/A
9.	Tlacuilo-Parra A, 2008, Mexico	62	62	62/0	9.0±3.7	9.3±3.7	18.4±4.5	20.2±5.7	N/A
10.	Abdelrazik N, 2007, Egypt	30	30	21/9	5.0±3.6	5.1±3.6	16.8±2.1	17.3±2.2	0/0/0
11.	Nair AP, 2007, India	50	50	42/8	29.5±9.3	29.2±3.8	19.2±3.8	23.6±2.8	2/18/1
12.	Barnes C, 2007, Australia	19	215	19/0	12.2±3.5	12.8±2.1	N/A	N/A	N/A/8/N/A
13.	Gallacher SJ, 1994, UK	19	19	19/0	41 (18–69) months	Age-matched	N/A	N/A	0/18/0

*BMI* body mass index, *C* controls, *H* patients with haemophilia, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *HIV* human immunodeficiency virus, *N/A* non-available

### Risk of bias and study quality

According to authors' judgment (Fig. 2a, b), five of the included studies presented high risk of selection bias [11,

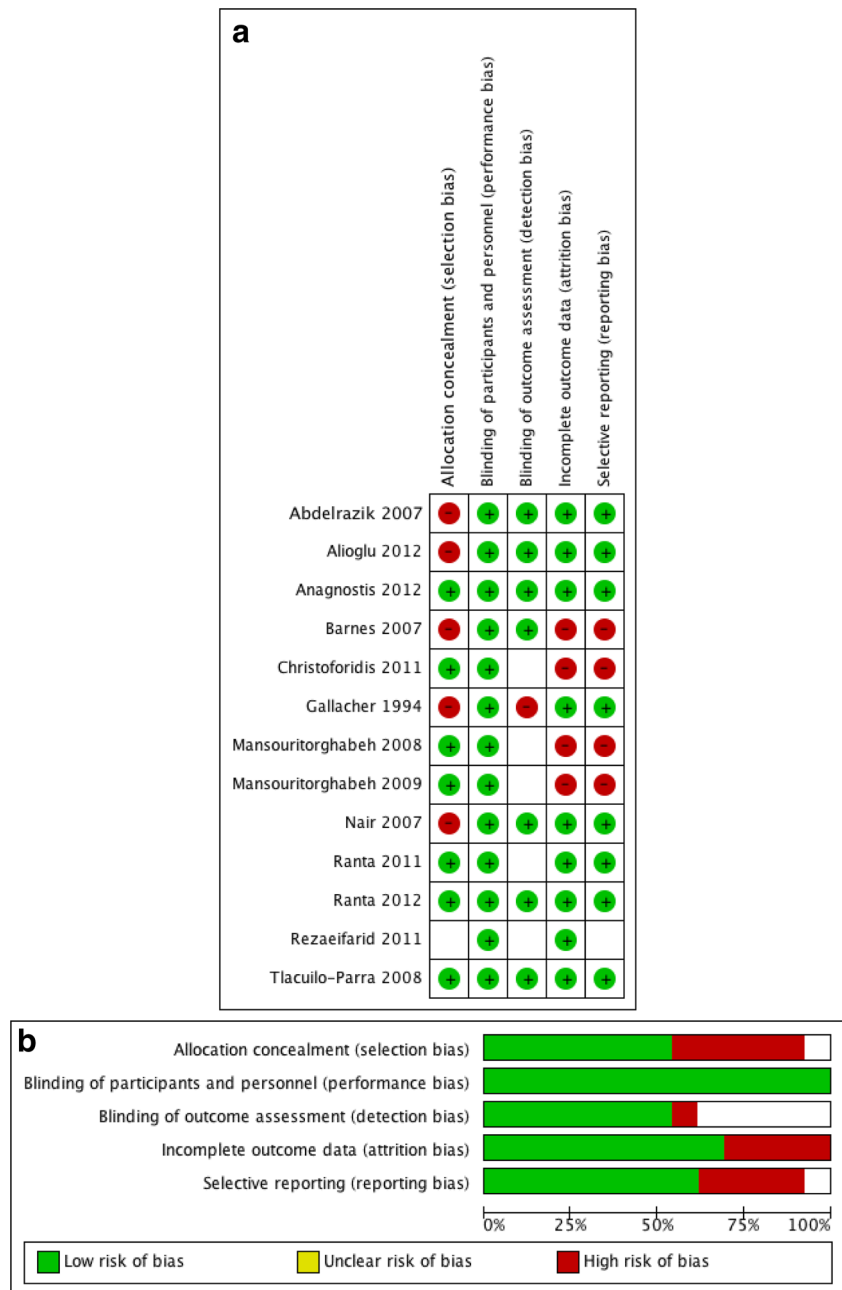
19–22], and one of them had unclear risk [14]. All studies had low performance risk. One of them demonstrated detection bias [22], yet five had unclear risk [13–17]. Four studies were characterized as high risk [15–17, 21] for attrition bias.

**Table 2** Main outcomes of the studies included in the systematic review

Id	First author, year, country	Lumbar spine BMD (g/cm <sup>2</sup> ) (H)	Lumbar spine BMD (g/cm <sup>2</sup> ) (C)	Femoral neck BMD (g/cm <sup>2</sup> ) (H)	Femoral neck BMD (g/cm <sup>2</sup> ) (C)	Total hip BMD (g/cm <sup>2</sup> ) (H)	Total hip BMD (g/cm <sup>2</sup> ) (C)	Fracture Prevalence
1.	Anagnostis P, 2012, Greece	1.047±0.169	1.065±0.156	0.938±0.163	1.015±0.176	0.929±0.161	1.018±0.189	H 17/104 (16 %) C N/A
2.	Alioglu B, 2012, Turkey	0.520±0.140	0.980±0.230	N/A	N/A	N/A	N/A	N/A
3.	Ranta S, 2012, Finland	N/A	N/A	N/A	N/A	N/A	N/A	N/A
4.	Ranta S, 2011, Finland	N/A	N/A	N/A	N/A	N/A	N/A	H 3/29 (10 %) C 3/58 (5 %) <i>p</i> =0.369
5.	Rezaeifarid M, 2011, Iran	0.908±0.13	0.987±0.19	0.889±0.18	0.969±0.11	N/A	N/A	N/A
6.	Christoforidis A, 2011, Greece	N/A	N/A	N/A	N/A	N/A	N/A	N/A
7.	Mansouritorghabeh H, 2009, Iran	1.09±0.24	1.21±0.15	0.99±0.21	1.17±0.30	N/A	N/A	N/A
8.	Mansouritorghabeh H, 2008, Iran	1.13±0.11	1.29±0.23	0.802±0.23	1.45±0.50	N/A	N/A	N/A
9.	Tlacuilo-Parra A, 2008, Mexico	0.568±0.13	0.632±0.16	N/A	N/A	N/A	N/A	N/A
10.	Abdelrazik N, 2007, Egypt	0.48±0.13	0.55±0.14	N/A	N/A	N/A	N/A	N/A
11.	Nair AP, 2007, India	0.82±0.14	0.93±0.11	N/A	N/A	0.725±0.145	0.939±0.110	H 6/50 (12 %) C 0/50 (0 %) <i>p</i> =0.011
12.	Barnes C, 2007, Australia	0.72±0.19	0.79±0.19	N/A	N/A	N/A	N/A	N/A
13.	Gallacher SJ, 1994, UK	1.109±0.18	1.234±0.12	0.877±0.15	1.067±0.14	N/A	N/A	H 7/19 (37 %) C 0/19 (0 %) <i>p</i> =0.003

*BMD* bone mineral density, *C* controls, *H* patients with haemophilia, *N/A* non-available

**Fig. 2** Risk of bias. Authors' judgments about each risk of bias item **a** for each included study and **b** presented as percentages across all included studies



Finally, four studies [15–17, 21] were characterized as high risk and one as unclear risk for reporting bias [14]. The quality of each study, assessed by the Newcastle-Ottawa scale for case–control studies is presented in Online Resource 2.

**Meta-analysis of main and secondary outcomes**

Ten of the 13 studies were included in the meta-analysis; as for the remaining three, there were no data for the primary or the secondary outcomes. They involved in total 415 patients and 585 age- and sex-matched controls. The results of the meta-

analysis in the adult, paediatric and total population are shown in Fig. 3.

A total of ten studies were eligible for the meta-analysis of lumbar spine BMD, six regarding adult population [10, 14, 16, 17, 20, 22] and four regarding paediatric population [11, 18, 19, 21]. Men with haemophilia demonstrated reduced lumbar spine BMD when compared with controls, yet with significant between-study heterogeneity [random effects SMD (95 % CI)=−0.56 (−0.84, −0.28),  $I^2=51\%$ ] (Fig. 3a). In a similar way, boys with haemophilia demonstrated reduced lumbar spine BMD when compared with controls, with significant between-study heterogeneity [random effects SMD

(95 % CI) =  $-0.92$  ( $-1.77$ ,  $-0.07$ ),  $I^2=92$  %] (Fig. 3a). Consequently, the meta-analysis of the total population demonstrated reduced lumbar spine BMD for patients compared with controls [random effects SMD (95 % CI) =  $-0.72$  ( $-1.08$ ,  $-0.36$ ),  $I^2=83$  %] (Fig. 3a). Finally, a summary random effect size (95 % CI) of  $0.72$  ( $0.34$ ,  $-1.09$ ) was found. This represents a large association of haemophilia with lower lumbar spine BMD [29], which is clinically significant [30]. Using the ‘Common Language Effect Size’ approach, the probability is about 72 % that an individual without haemophilia would have higher lumbar spine BMD than an individual with haemophilia, if both individuals were chosen at random from a population [31].

A total of five studies were eligible for the meta-analysis of femoral neck BMD, all regarding adult population [10, 14, 16, 17, 22]. Men with haemophilia demonstrated reduced femoral neck BMD when compared with controls, yet with significant between-study heterogeneity [random effects SMD (95 % CI) =  $-0.82$  ( $-1.21$ ,  $-0.44$ ),  $I^2=63$  %] (Fig. 3b). The summary random effect size (95 % CI) of  $0.83$  ( $0.44$ ,  $1.22$ ) indicated a ‘large’ and ‘clinically significant’ association of haemophilia with lower femoral neck BMD [29, 30].

Two studies were eligible for the meta-analysis of total hip BMD, all regarding adult population [10, 20]. Men with haemophilia demonstrated marginally reduced total hip BMD when compared with controls, with significant between-study heterogeneity [random effects SMD (95 % CI) =  $-1.07$  ( $-2.18$ ,  $0.03$ ),  $I^2=93$  %] (Fig. 3c).

Finally, men with haemophilia demonstrated reduced lumbar spine T-score when compared with controls [three studies, random effects SMD (95 % CI) =  $-1.05$  ( $-1.90$ ,  $-0.20$ ),  $I^2=81$  %] (Online Resource 3). In a similar way, boys with haemophilia demonstrated reduced lumbar spine Z-score when compared with controls [four studies, random effects SMD (95 % CI) =  $-0.84$  ( $-1.37$ ,  $-0.31$ ),  $I^2=82$  %] (Online Resource 3).

#### Explanation of heterogeneity

#### Sensitivity analysis

The study by Alioglou et al. [11] demonstrated a much higher difference in lumbar spine BMD between children with haemophilia and controls (SMD  $-2.42$  vs  $< -1$  g/cm<sup>2</sup> in all other studies). In addition, it achieved the lowest score in the Newcastle-Ottawa scale (Online Resource 2). When this study was excluded, the  $I^2$  statistic for the paediatric population reduced from 92 to 0 %, losing its statistical significance ( $p=0.920$ ) and the new SMD was  $-0.43$  g/m<sup>2</sup>. A similar result was found for the total (i.e. adult and paediatric population) population ( $I^2$  from 83 to 24 %,  $p=0.230$ ).

#### Publication bias

No evidence of publication bias was detected for studies having as outcome lumbar spine (Egger’s test,  $p=0.154$ ) or femoral neck ( $p=0.292$ ). Funnel plots of summary mean difference versus standard error to investigate possible publication bias were broadly in the pseudo 95 % confidence limits, confirming the absence of publication bias (Online Resource 4). Publication bias cannot be estimated for total hip BMD, due to small number of studies ( $n=2$ ).

#### Meta-regression

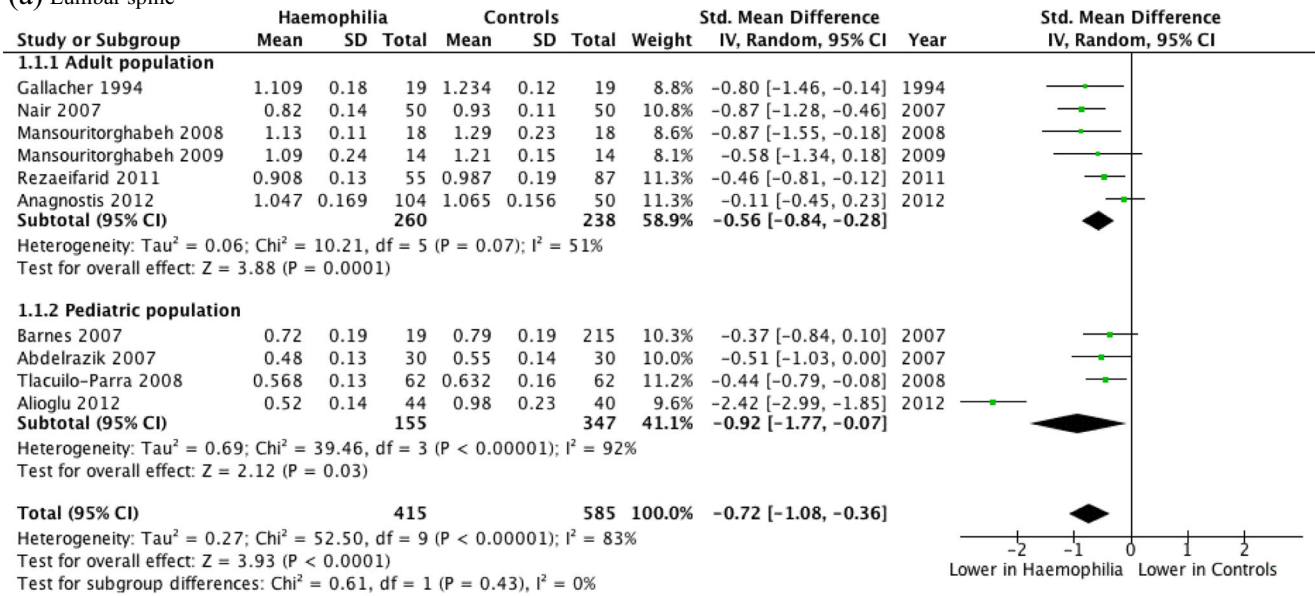
Age, BMI, level of physical activity and percentage of blood-borne infections were used as predictors of the SMD in lumbar spine BMD between men/children with haemophilia and controls. Meta-regression for physical activity and percentage of blood-borne infections was not possible due to small number of studies, different ways of quantification (physical activity) and different inclusion criteria (blood-borne infections, especially HBV and HIV). There was no evidence that age (Fig. 4a), BMI (Fig. 4b) or HCV (Fig. 4c) predicted SMD between men/children with haemophilia and controls (Monte Carlo permutation test,  $p=0.488$ ,  $0.353$  and  $0.515$ , respectively). Data were inadequate to permit meta-regression analysis of the other potential predictors for lower BMD in men with haemophilia, such as disease severity of haemophilia, degree of arthropathy or 25(OH)D concentrations.

## Discussion

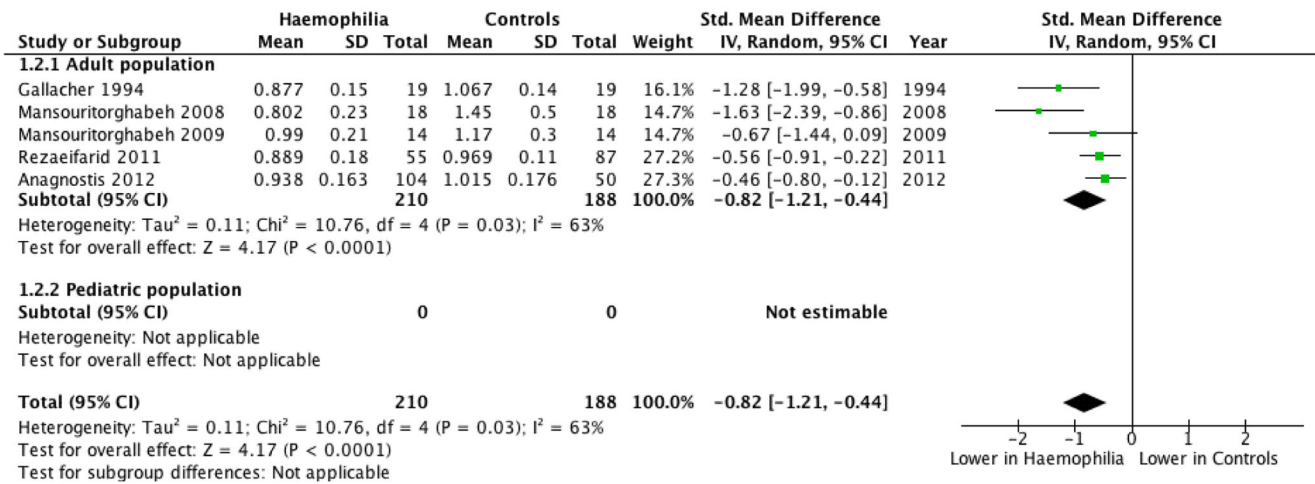
The aim of the present study was to systematically review the literature for case–control studies that have studied men and boys with haemophilia for osteoporosis and to meta-analyze the best evidence available. Lumbar spine BMD was significantly lower in both paediatric and adult haemophilic populations compared with controls. In adult populations, femoral neck BMD was significantly lower in patients with haemophilia compared with controls.

This is the second meta-analysis that reports a link between reduced BMD and haemophilia. The first one [32], published 4 years ago, included seven case–control studies that compared BMD in patients with haemophilia ( $n=211$ ) and age-matched controls ( $n=307$ ). Lumbar spine BMD was found to be significantly lower in both paediatric and adult populations with haemophilia compared with controls. The present meta-analysis included all these seven studies, plus six new ones [12–15], resulting in a larger number of cases and controls, as well as more quantitative and qualitative data from each study, such as femoral neck BMD.

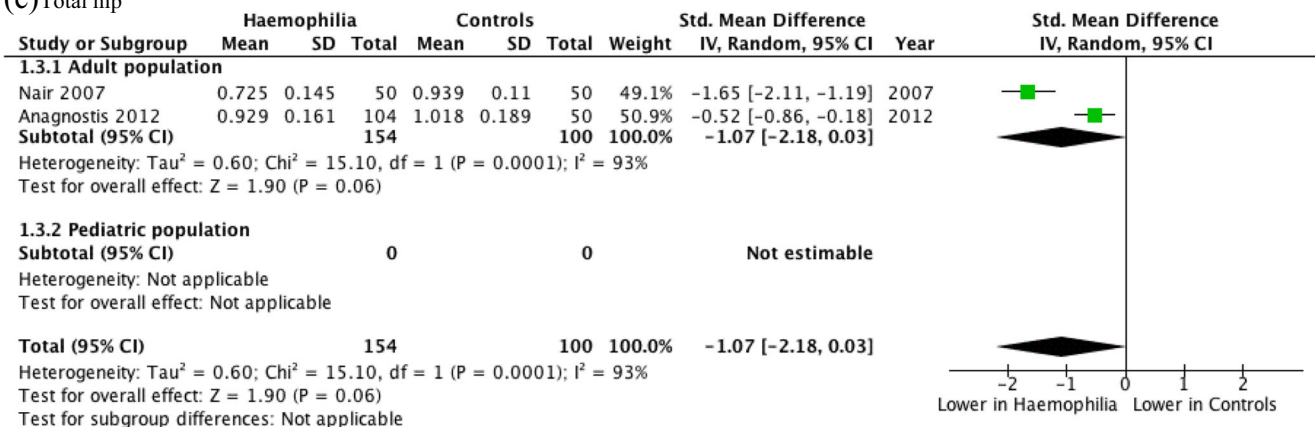
(a) Lumbar spine



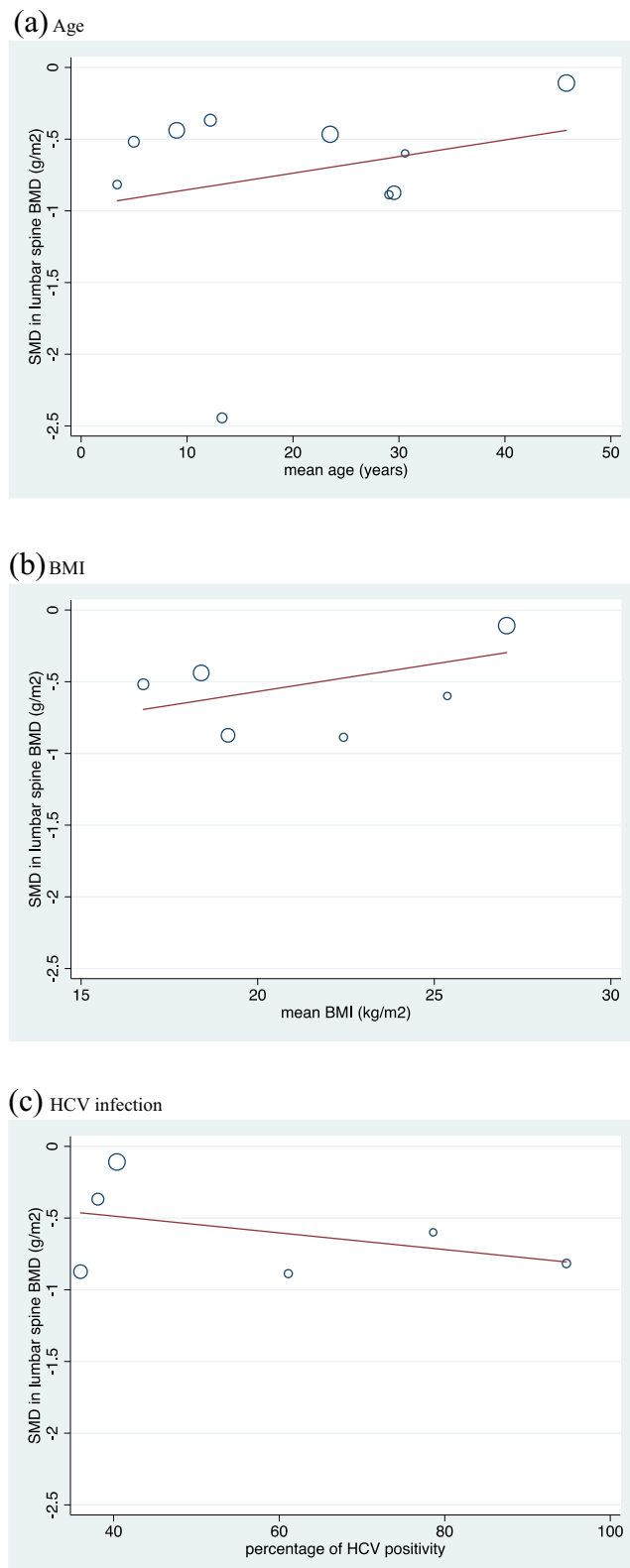
(b) Femoral neck



(c) Total hip



**Fig. 3** Forest plot of comparison between men with haemophilia and controls in study outcomes: **a** lumbar spine, **b** femoral neck and **c** total hip bone mineral density



**Fig. 4** Meta-regression plot of lumbar spine bone mineral density (BMD) in men with haemophilia and controls according to **a** age, **b** body mass index (BMI) and **c** percentage of hepatitis C virus (HCV) infection

In the present meta-analysis, adult men with haemophilia demonstrated reduced lumbar spine BMD when compared

with controls, with lower heterogeneity compared with the previous meta-analysis ( $I^2=51$  vs 87.9 %) [32]. Regarding the paediatric population, the present meta-analysis demonstrated higher between-study heterogeneity compared with the previous one ( $I^2=92$  vs 0 %). When the study by Alioglou et al. [11], which was selected in the present meta-analysis only, was excluded in a further step, the  $I^2$  statistic reduced from 92 to 0 %, losing its statistical significance. The study by Alioglou et al. [11] demonstrated a much higher difference in lumbar spine BMD between children with haemophilia and controls (SMD  $-2.42$  vs  $< -1$  g/cm<sup>2</sup> in all other studies). According to our judgment, this study presents a high risk of selection bias. It included boys that attended a tertiary care haemophilia centre, who had severe disease, defined as FVIII activity lower than 1 %. Boys with haemophilia B, HBV, HCV or HIV infections, as well as those taking calcium and vitamin D supplements were excluded. On the other hand, we did not find any evidence of performance, detection, attrition or reporting bias for this study.

On top of above-mentioned study, four others presented high risk of selection bias. In the studies by Nair et al. [20], Barnes et al. [21] and Gallacher et al. [22], patients with severe haemophilia only were recruited. In the study by Abdelrazik et al. [19], patients with HBV, HCV or HIV infections were excluded. Finally, the study by Rezaeifarid et al. [14] presented unclear risk for selection bias, as very few patient information were available.

A clinical implication of this meta-analysis is that lower BMD constitutes a major concern for men/children with haemophilia. This reduction in bone mass affects both lumbar spine and hip and appears to begin in childhood. Physicians treating such populations may request BMD assessment in both adult and paediatric patients. Although neither the quantity nor the quality of fracture data allowed for a meta-analysis to be performed, men with haemophilia seem to have higher fracture prevalence, as compared to controls. Prospective, case-control studies with fracture prevalence and incidence as primary outcomes are needed to further clarify whether haemophilia actually increases fracture risk.

An essential difficulty of this meta-analysis was the evaluation of the physical activity among different studies. Some of them used scores, other numeric estimations and some other descriptive phrases; thus, there was no way to further analyze these data. The same was true for the assessment of haemophilic arthropathy. Different studies used different ways to describe the number of the affected joints as well as joint function. It would be very useful if future studies adopt a common report of physical activity and haemophilic arthropathy.

In conclusion, this meta-analysis reports that patients with haemophilia exhibit severe reduction in bone mass. This reduction affects both lumbar spine and hip and appears to begin in childhood. The clinical relevance of these findings, in term of fracture risk, should be assessed in prospective clinical

trials, which will further elucidate the pathogenetic mechanisms linking haemophilia to osteoporosis. Physicians caring such patients should be aware of the association between these two entities, in order to screen, prevent and treat them properly.

**Conflicts of interest** None.

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