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Macroscopic hematuria as a risk factor for hypertension in ageing people with hemophilia and a family history of hypertension

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Abstract

Ageing people with hemophilia (PWH) have a higher prevalence of hypertension than the general population. This study aimed to determine whether macroscopic hematuria was associated with hypertension in PWH in a post hoc analysis using data from a cross-sectional study conducted by the ADVANCE Working Group (the H3 study), which included PWH ≥ 40 years of age. Data from 16 contributing centers, located in 13 European countries and Israel, were analyzed using logistic regression models. Of 532 recruited PWH in the H3 study, 117 had hypertension and a positive family history of hypertension (hypertension FH+), 75 had hypertension and a negative family history of hypertension (hypertension FH−), 290 had no diagnosis of hypertension, and the remaining 50 had missing hypertension data. Logistic regressions showed that macroscopic hematuria was associated with hypertension FH+, both in the univariate (OR = 1.84 [1.17–2.90], $P = .01$) and in the multivariate model (OR = 1.80 [1.03–3.16], $P = .04$). Macroscopic hematuria was not associated with hypertension FH−. Moreover, in a multivariate logistic regression the odds of hypertension FH+ were increased with the number of macroscopic hematuria episodes. The association between macroscopic hematuria and hypertension was significant for PWH with a family history of hypertension.

Abbreviations: BMI = body mass index, CAD = coronary artery disease, CI = confidence interval, EGFR = estimated glomerular filtration rate, FH− = negative family history of hypertension, FH+ = positive family history of hypertension, HTN = hypertension, IQR = interquartile range, NSAIDs = non-steroidal anti-inflammatory drugs, PWH = people with hemophilia.

Keywords: ageing, hematuria, hemophilia, hypertension, logistic regression models

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1. Introduction

Hemophilia is an inherited deficiency of clotting factors VIII or IX that is associated with recurrent and spontaneous bleeding, most commonly internal bleedings into joints or muscles.[1] Hematuria, the presence of blood in the urine that is either visible (macroscopic) or non-visible (microscopic), is a common condition in people with hemophilia (PWH).[2,3]

We have known that adult PWH have a higher incidence of hypertension than the general population since Rosendaal et al[4] published their results in 1990. Later studies of cohorts from Europe and North America[5–8] have confirmed this finding, but causes for the increased prevalence remain uncertain.[8]

Studying renal disease in more than 3000 PWH, Kulkarni et al[5] found higher prevalence of hypertension in PWH admitted for kidney bleeds than in those admitted for other reasons. Drygalski et al[7] found a positive association between hypertension and risk factors known from the general population, such as age, body mass index (BMI), diabetes, and renal function. Overall, 49.1% of the PWH had hypertension compared with 31.7% in the control group. However, the study lacked data on macroscopic hematuria. Recent research has attempted to establish whether an association between macroscopic hematuria and hypertension exists. Two papers, Holme et al and Sun et al[9,10] have concluded that no such associations are discernible in the cohorts analyzed. In sum, the evidence on this topic is mixed.

It is well known that at least two factors increase the likelihood of developing hypertension. First, there exists a genetic component – family history of hypertension significantly

increases the risk of developing hypertension.[11] Second, environmental or lifestyle factors, such as obesity, insulin resistance, high alcohol intake, and high salt intake may cause hypertension.[12] In addition, prevalence increases with age.

In this paper, we acknowledged that familial and lifestyle risk factors of hypertension need not be identical. In particular, we disentangled familial from non-familial associations by examining whether the association between hematuria and hypertension in PWH was contingent on a family history of hypertension.

2. Materials and methods

2.1. Data collection

The dataset, consisting of 532 patients aged 40 years and older, was collected between June 2011 and September 2013 by researchers in 16 participating centers, located in 13 European countries and Israel, where Germany had 3 centers and Italy had 2. All data were gathered from consecutive PWH attending their routine clinical visit using a case report form and from laboratory data collected no earlier than 1 year before the clinical visit. The case report form included items about patient characteristics, demographics, past and current treatment, and medical history including a lifetime history of comorbidities. Both a known history of hypertension and a family history of hypertension were recorded as either existent or not. Two consecutive blood pressure measurements were performed as recommended by the European Society of Hypertension,[13] and hypertension was defined as either systolic blood pressure above 140 mmHg or diastolic blood pressure above 90 mmHg, or both. Patient-reported hypertension in first-degree relatives was recorded as a positive family history of hypertension (FH+). A history of macroscopic hematuria was recorded as present or absent. Given a positive history of macroscopic hematuria, the number of such episodes was also recorded. Diabetes was considered present if a patient had a known diagnosis or if currently on medication for diabetes. Estimated glomerular filtration rate (EGFR) values were calculated from the measured serum creatinine concentration using the Chronic Kidney Disease Epidemiology Collaboration equation.[14] Consenting patients, with any severity of hemophilia A or B, were included in the study. Respective national ethical committees or the institutional review boards approved the study.[9,15]

2.2. Study design and statistical analyses

In this post hoc analysis, we constructed a categorical hypertension variable that divided the sample into 3 groups:

(1) No hypertension,
(2) Hypertension with a positive family history of hypertension (hypertension FH+), and
(3) Hypertension with a negative family history of hypertension (hypertension FH–).[11,16]

Figure 1 details the categorization. To determine associations between hypertension and potential risk factors in PWH, we performed both univariate and multivariate logistic regression analyses for 2 specifications of the dependent variable, that is, 4 regression models in total. First, we created a categorical dependent variable with 3 levels according to the specification above. Second, we collapsed the 2 types of hypertension into one and constructed a binary dependent variable with the levels diagnosis of hypertension vs no hypertension. No hypertension was set as the baseline for both dependent variables. For the models with a nominal categorical dependent variable, we estimated a multinomial logistic regression (see Level 3 in Fig. 1). For the models comparing no hypertension to a known diagnosis of hypertension, we performed a binomial logistic regression (see Level 4 in Fig. 1).

Differences in baseline characteristics between individuals with and without hypertension and between hypertensive groups FH+ and FH– were assessed using analysis of variance (ANOVA) for continuous variables and the chi-squared test of independence for categorical variables. When these tests implied rejection of the null hypothesis, we performed pairwise comparisons in which we corrected the P values for multiple comparisons using Tukey's honestly significant difference test on continuous and the Bonferroni correction on categorical variables.

As shown in Figure 1, 16 observations were lost in the transition from the multinomial (Level 3) to the binomial (Level 4) model due to missing data. The binomial model included family history of hypertension as an independent variable and hence this value was needed for all observations. In contrast, the multinomial model used family history of hypertension only to distinguish between different types of hypertension in the construction of the dependent variable. Consequently, a valid value was not needed for patients without a hypertension diagnosis.

We used R version 3.6.1[17] for all analyses, and we considered a two-tailed P value less than .05 to be statistically significant.

3. Results

3.1. Study population

The patients in the study population were 98% Caucasian with median age 52 years (range 40–98). Of the 532 study participants, 87% had hemophilia A and 13% had hemophilia B; 58% had severe, 11% had moderate, and 31% mild hemophilia. A known diagnosis of hypertension was present in 239 individuals, 290 had no hypertension diagnosis, and 3 had missing values for hypertension. Among the 239 hypertensive, a family history of hypertension was present for 117 individuals, no family history for 75, and missing data for the remaining 50 (Levels 1 and 2 in Figure 1).

Table 1 shows descriptive statistics by category of hypertension. Prophylactic therapy was more common among hypertensive FH+ (41%) than among hypertensive FH– (25%). At 67%, the prevalence of macroscopic hematuria was much higher in the hypertensive FH+ group than among other patients, where it was 51%. There was a higher incidence of regular (>3 months per year) non-steroidal anti-inflammatory drugs (NSAIDs) use and diabetes among those classified as hypertensive FH+.

After correcting for multiple comparisons, we found that prevalence of diabetes and history of renal disease was significantly higher for hypertensive than non-hypertensive individuals, while there was no significant difference between hypertensive groups FH+ and FH–. Macroscopic hematuria was significantly more prevalent for hypertensive FH+ than for those with no hypertension. Multiple comparison results for continuous variables showed differences between hypertensive and non-hypertensive and no difference between hypertensive groups FH+ and FH–.

Panels a and b in Figure 2 show occurrence of hypertension and macroscopic hematuria and reveal considerable variation

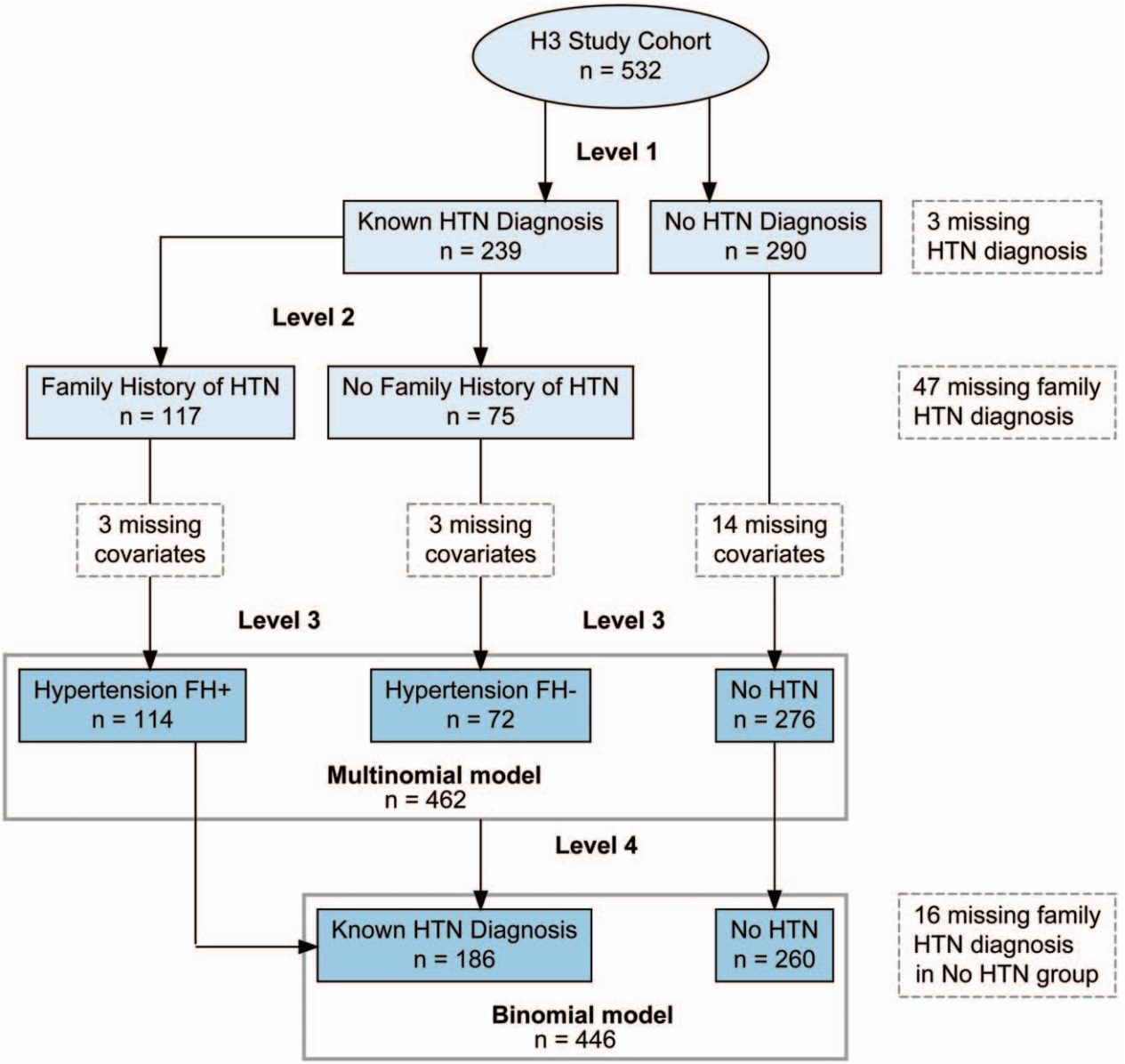

Figure 1. The figure shows the filtering process that leads to the leaf nodes that constitute the levels of the response variables in the two models. FH− = negative family history of hypertension, FH+ = positive family history of hypertension, HTN = hypertension.

between countries. Panel b shows a scatter plot of the fraction of PWH with macroscopic hematuria and hypertension FH+, where each point represents a country. The regression line indicates that prevalence of hypertension FH+ increases with prevalence of hematuria, when considered at the country level.

3.2. Regression models

Table 2 shows results from univariate logistic regressions of hypertension on macroscopic hematuria and several other covariates. The reference level is no hypertension for all models. Panel A in the table reveals that macroscopic hematuria was only significantly associated with hypertension FH+. There was no effect from hematuria on hypertension FH–, nor when not distinguishing by type of hypertension. Panel B shows univariate results for control variables included in the multivariate models. For all categories of hypertension, each control was significantly associated with hypertension except severe hemophilia. Significant covariates not included in the multivariate models are shown in Panel C. The first column in the table shows that the odds of contracting hypertension when FH+ was present were 1.84 (1.17–2.90) times higher for patients with macroscopic hematuria, with a $P = .01$. To examine the robustness of this finding, we included clinically relevant controls in multivariate analyses.

The multivariate analyses (Table 3) confirmed that macroscopic hematuria was a significant covariate, but only for hypertension FH+ ($P = .04$). Age and BMI, well-known risk factors for hypertension in the general population, were both highly significant for all categories of hypertension. Additionally, low EGFR and severe hemophilia were associated with hypertension of all classifications. Severe hemophilia only became a significant covariate after adjusting for age and BMI. On

Table 1

Descriptive statistics by type of hypertension.

	Total		Hypertension FH+		Hypertension FH–		No hypertension		
	n	(%)	n	(%)	n	(%)	n	(%)	*P* value
Type									
Hemophilia A	419	(87)	100	(85)	63	(84)	256	(88)	.54
Hemophilia B	63	(13)	17	(15)	12	(16)	34	(12)	
Severity									
Mild	150	(31)	39	(33)	27	(36)	84	(29)	.55
Moderate	52	(11)	10	(9)	6	(8)	36	(12)	
Severe	279	(58)	68	(58)	42	(56)	169	(58)	
Measures									
Age, mean (IQR)	55	(45–62)	59	(51–68)	62	(52–71)	51	(43–56)	<.001*,†
BMI, mean (IQR)	25.7	(23.2–27.5)	27.4	(24.1–29.4)	26.3	(23.9–27.7)	24.8	(23.0–26.6)	<.001,* .01†
EGFR, mean (IQR)	94	(85–107)	88	(74–103)	84	(69–98)	100	(91–109)	<.001*,†
Treatment									
On demand	294	(61)	67	(57)	53	(71)	174	(60)	.37
No treatment	1	(0)	0	(0)	0	(0)	1	(0)	
Bypass	16	(3)	2	(2)	3	(4)	11	(4)	
Prophylaxis	171	(35)	48	(41)	19	(25)	104	(36)	
Smoker									
No	239	(50)	56	(48)	40	(54)	143	(50)	.32
Yes	112	(23)	24	(21)	13	(18)	75	(26)	
Previously	127	(27)	37	(32)	21	(28)	69	(24)	
Alcohol consumption									
Abstinent	185	(39)	42	(37)	31	(42)	112	(40)	.47
Low	214	(46)	53	(46)	28	(38)	133	(47)	
High	71	(15)	19	(17)	14	(19)	38	(13)	
Comorbidities									
NSAIDs	93	(19)	29	(25)	12	(16)	52	(18)	.20
Diabetes	45	(9)	24	(21)	12	(16)	9	(3)	<.001*,†
History of renal disease	27	(6)	11	(9)	11	(15)	5	(2)	.01,* <.001†
Macroscopic hematuria	264	(55)	78	(67)	38	(51)	148	(51)	.03,* >.99†
<3 bleeds	123	(26)	34	(29)	14	(19)	75	(27)	
3–10 bleeds	75	(16)	22	(19)	14	(19)	39	(14)	
>10 bleeds	67	(14)	22	(19)	10	(14)	35	(12)	

This table shows descriptive statistics by category of hypertension. The numbers in parentheses report percentages per corresponding group, except for the comorbidities group where they are reported per hypertension category. Deviations from the corresponding total are due to rounding. *P* values are estimated using analysis of variance (ANOVA) for continuous and the chi-squared test of independence for categorical variables. If the *P* value implies that the null hypothesis is rejected, we report instead pairwise *P* values using Tukey's honestly significant difference test for continuous and Bonferroni's post hoc test for categorical variables.

BMI = body mass index, EGFR = estimated glomerular filtration rate, FH− = negative family history of hypertension, FH+ = positive family history of hypertension, IQR = interquartile range, NSAIDs = non-steroidal anti-inflammatory drugs.

* *P* value obtained by comparing the hypertensive FH+ group with the no hypertension group.

† *P* value obtained by comparing the hypertensive FH– group with the no hypertension group.

average, individuals with severe hemophilia were younger and had lower BMI than those with non-severe hemophilia among the patients included under the heading "Hypertension FH+" in Tables 1 and 2. Therefore, in order to assess the association between severity of hemophilia and hypertension, we needed to control for these 2 risk factors. Macroscopic hematuria and severity of hemophilia were highly correlated, as evidenced by a chi-squared test strongly rejecting independence ($P < .001$). As is often the case with correlated covariates, removing one will increase the significance of the remaining. Unreported results showed that removing severity of hemophilia from the multivariate regression reduced the *P* value for macroscopic hematuria to .001. We chose to include severity in the regression, however, to demonstrate that macroscopic hematuria remained a significant association even after controlling for severity. Only for hypertension FH- was diabetes not significant at the 5% level ($P = .12$). As expected, a family history of hypertension was highly significant for undifferentiated hypertension ($P < .001$). We cannot include a family history of hypertension as a covariate in the multinomial regression, however, since we used this variable in the construction of the dependent variable. We found no evidence of interaction effects among the explanatory variables.

We performed the Cochran–Mantel–Haenszel test to assess the association between hypertension FH+ and macroscopic hematuria, stratified by country. Consistent with the logistic regression results, the test rejected independence with a *P* value equal to .03.

We further examined whether the effect from macroscopic hematuria on hypertension was binary, or whether more occurrences of macroscopic hematuria increased the likelihood of hypertension FH+. In Table 4, we substituted the dichotomous variable macroscopic hematuria with the number of bleeding episodes and dropped severity of hemophilia due to its strong correlation with the number of bleeding episodes. The odds of hypertension FH+ increased with the number of macroscopic hematuria episodes, from 1.98 (1.05–3.72) for less than 3 bleeding episodes to 3.14 (1.51–6.55) for more than 10 episodes. All 3 levels were significant compared to the baseline, which was

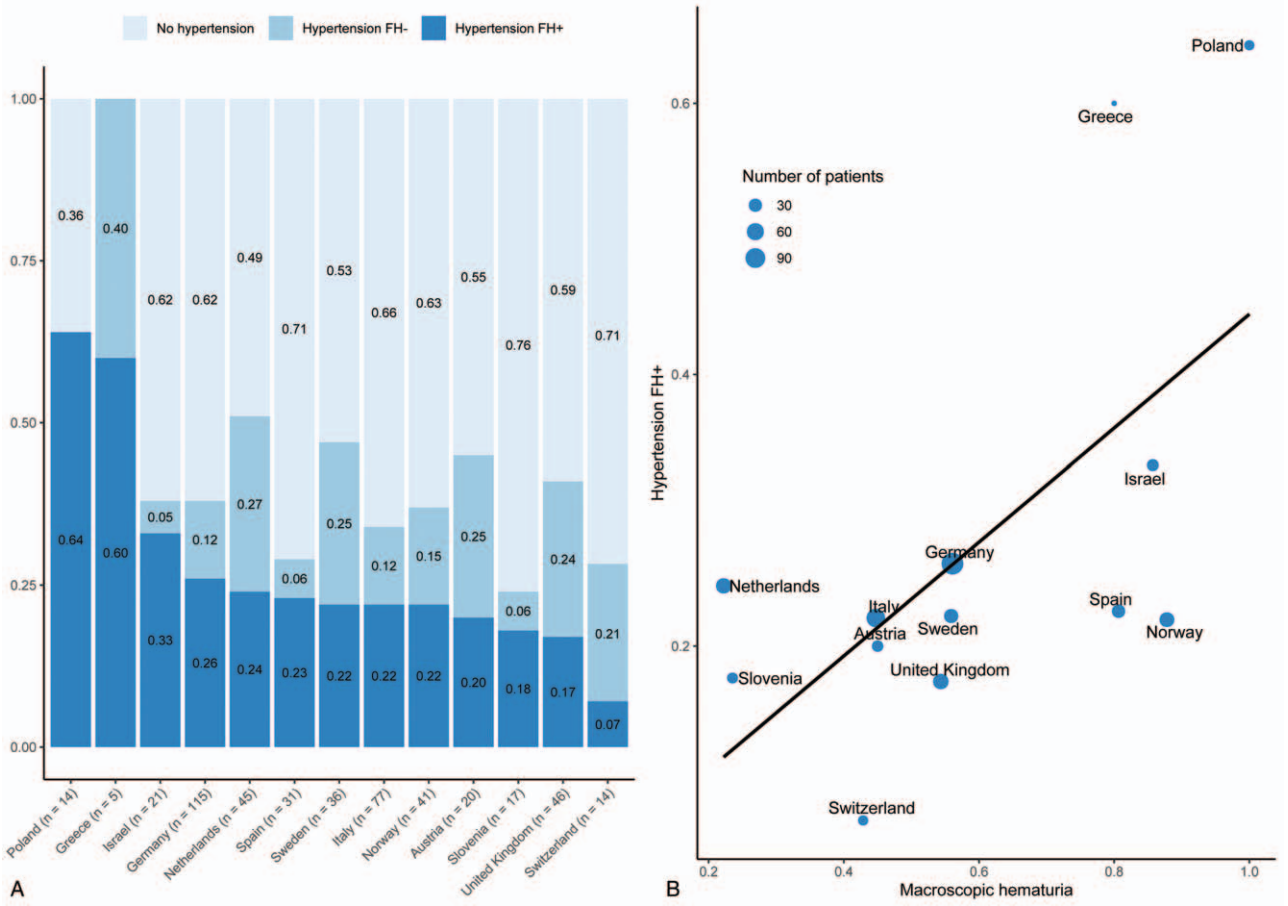

Figure 2. The figure shows plots of occurrence of hypertension and macroscopic hematuria by country. Panel a shows the fraction of patients with hypertension FH+, hypertension FH–, and no hypertension per country, sorted by prevalence of hypertension FH+. Panel b shows a scatter plot with macroscopic hematuria on the horizontal axis and hypertension FH+ on the vertical axis. The size of each point reflects the number of recruited patients per country. The slope is a least squares regression line where each country is equally weighted. FH− = negative family history of hypertension, FH+ = positive family history of hypertension.

Table 2

Univariate logistic regressions of hypertension on macroscopic hematuria and covariates.

	Hypertension FH+			Hypertension FH–			Hypertension (all)		
Variable	**Odds Ratio**	**95% CI**	***P* value**	**Odds Ratio**	**95% CI**	***P* value**	**Odds Ratio**	**95% CI**	***P* value**
Panel A:									
Macroscopic hematuria	1.84	(1.17, 2.90)	.01	0.95	(0.57, 1.58)	.84	1.23	(0.86, 1.75)	.25
Panel B: Controls included in the multivariate models									
Age	1.08	(1.06, 1.11)	<.001	1.10	(1.07, 1.13)	<.001	1.09	(1.07, 1.11)	<.001
BMI	1.18	(1.11, 1.25)	<.001	1.11	(1.04, 1.19)	<.001	1.16	(1.11, 1.23)	<.001
EGFR	0.96	(0.95, 0.97)	<.001	0.95	(0.94, 0.97)	<.001	0.96	(0.95, 0.97)	<.001
Diabetes	8.00	(3.59, 17.83)	<.001	6.00	(2.42, 14.86)	<.001	7.07	(3.53, 15.77)	<.001
Severe hemophilia	0.99	(0.64, 1.52)	.95	0.90	(0.54, 1.51)	.70	1.02	(0.72, 1.45)	.90
Family history of HTN	–	–	–	–	–	–	3.28	(2.24, 4.85)	<.001
Panel C: Significant covariates not included in multivariate models									
History of renal disease	5.85	(1.99, 17.24)	<.001	9.69	(3.25, 28.87)	<.001	6.45	(2.62, 19.39)	<.001
NSAIDs	1.52	(0.91, 2.55)	.11	0.88	(0.44, 1.75)	.71	1.62	(1.06, 2.49)	.02
History of CAD	8.97	(3.20, 25.10)	<.001	6.86	(2.17, 21.65)	<.001	7.49	(3.08, 22.39)	<.001

This table shows univariate logistic regressions for several covariates for hypertensive individuals with FH+ and FH-, and for all hypertensive individuals (ie, not differentiated by a family history of hypertension). The baseline category is no hypertension for all categories of hypertension. Dashes represent a covariate not analyzed in that regression model.

BMI = body mass index, CAD = coronary artery disease, CI = confidence interval, EGFR = estimated glomerular filtration rate, FH− = negative family history of hypertension, FH+ = positive family history of hypertension, HTN = hypertension, NSAIDs = non-steroidal anti-inflammatory drugs.

Table 3

Multinomial and binomial logistic regressions of hypertension on macroscopic hematuria and controls.

	Multinomial (n = 462)						Binomial (n = 446)		
	Hypertension FH+			Hypertension FH-			Hypertension (all)		
Variable	Odds Ratio	95% CI	*P* value	Odds Ratio	95% CI	*P* value	Odds Ratio	95% CI	*P* value
Age	1.07	(1.03, 1.10)	<.001	1.09	(1.05, 1.12)	<.001	1.08	(1.05, 1.11)	<.001
BMI	1.21	(1.14, 1.30)	<.001	1.14	(1.05, 1.23)	<.01	1.17	(1.10, 1.26)	<.001
EGFR	0.98	(0.96, 0.99)	.01	0.97	(0.95, 0.99)	.01	0.98	(0.96, 0.99)	.01
Diabetes	3.21	(1.32, 7.78)	.01	2.21	(0.80, 6.09)	.12	2.75	(1.16, 7.01)	.03
Severe hemophilia	2.17	(1.19, 3.94)	.01	2.65	(1.33, 5.28)	.01	2.46	(1.41, 4.38)	<.01
Macroscopic hematuria	1.80	(1.03, 3.16)	.04	0.82	(0.44, 1.53)	.53	1.16	(0.69, 1.94)	.58
Family history of HTN	–	–	–	–	–	–	3.63	(2.27, 5.87)	<.001

This table shows a multinomial logistic regression for hypertensive individuals with FH+ and FH-, and a binomial logistic regression for all hypertensive individuals (ie, not differentiated by a family history of hypertension). The baseline category is no hypertension for all categories of hypertension. Dashes represent a covariate not analyzed in that regression model. The number of patients included in each model estimation is included in the header.

BMI = body mass index, CI = confidence interval, EGFR = estimated glomerular filtration rate, FH− = negative family history of hypertension, FH+ = positive family history of hypertension, HTN = hypertension.

no bleeding episodes, that is, absence of macroscopic hematuria (Table 4). The results for hypertension FH- were similar to those reported in Table 3. Replacing macroscopic hematuria with number of bleeding episodes altered none of our previous inferences for hypertension FH-.

4. Discussion

Age, BMI, EGFR, and severe hemophilia were associated with hypertension regardless of type. However, macroscopic hematuria was significant only when a family history of hypertension was present.

Using the same dataset as Holme et al,[9] we confirmed their finding that age, BMI, EGFR, and diabetes were significant risk factors in the multivariate model. These risk factors are well-established for the general population as well.[18,19] Hypertension in diabetics may have several causes, among them increased peripheral vascular resistance and insulin resistance. Prevalence of hypertension in patients with diabetes is nearly twice that of those without.[20] In our regressions, odds ratios for diabetes ranged from 2.21 (0.80–6.09) to 3.21 (1.32–7.78) and was a significant covariate at the 5% level for hypertension FH+ and undifferentiated hypertension. After adjusting for age and BMI, and only for hypertension FH–, was diabetes not significant at the 5% level (12.4%). Sun et al[10] found that only age was a significant explanatory variable, perhaps due to a small sample size and many covariates included in the multivariate regression.

Severity of hemophilia has been linked to the increased prevalence of hypertension in PWH, but the results on this topic are inconclusive. Van de Putte et al[6] found a significant association between hypertension and severity of hemophilia in an age-adjusted multivariate logistic regression, whereas Holme et al and Sun et al[9,10] reported a non-significant association. We found that severity of hemophilia was a significant covariate for all categories of hypertension. When the sample size is limited, and in the presence of highly correlated covariates, removing the redundant variables can improve the precision of the estimates. By not including non-significant covariates, the confidence intervals narrowed markedly compared to Holme et al and Sun et al, rendering severity of hemophilia significant.

Unlike the North American studies by Kulkarni et al and Drygalski et al,[5,7] 33% of patients in a European study by van de Putte et al[6] had a history of macroscopic hematuria. Although not reaching statistical significance, their study indicated a higher risk of hypertension in patients with macroscopic hematuria. As demonstrated in the binomial logistic regression in Table 3, without distinguishing between hypertension FH+ and FH–, the significance of macroscopic hematuria disappeared, consistent with prior research. Thus, a distinction between hypertension FH+ and FH– is necessary to identify the positive association between macroscopic hematuria and hypertension.

An Italian prospective study[21] documented that hypertension was transmitted to recipients from normotensive families when

Table 4

Multinomial logistic regression of hypertension on number of macroscopic hematuria episodes and controls.

	Multinomial (n = 462)					
	Hypertension FH+			Hypertension FH-		
Variable	Odds Ratio	95% CI	*P* value	Odds Ratio	95% CI	*P* value
Age	1.06	(1.03, 1.09)	<.001	1.07	(1.04, 1.11)	<.001
BMI	1.19	(1.12, 1.27)	<.001	1.11	(1.03, 1.20)	.01
EGFR	0.98	(0.96, 1.00)	.02	0.98	(0.96, 0.99)	.01
Diabetes	3.11	(1.29, 7.50)	.01	2.14	(0.78, 5.85)	.14
Bleeding episodes <3	1.98	(1.05, 3.72)	.03	0.71	(0.33, 1.55)	.39
Bleeding episodes 3–10	2.36	(1.14, 4.86)	.02	1.69	(0.77, 3.70)	.19
Bleeding episodes >10	3.14	(1.51, 6.55)	<.01	1.33	(0.55, 3.17)	.53

This table shows results from a multinomial logistic regression of the categorical variable hypertension on the number of macroscopic hematuria episodes and controls. The levels of the dependent variable are hypertensive FH+ and FH–, and reference level no hypertension. The baseline level for the covariate macroscopic hematuria episodes is no bleeding episodes.

BMI = body mass index, CI = confidence interval, EGFR = estimated glomerular filtration rate, FH− = negative family history of hypertension, FH+ = positive family history of hypertension.

transplanted with kidneys from donors with hypertension FH+. Moreover, van Hooft et al[22] found lower renal blood flow and higher renal vascular resistance in individuals with hypertensive parents than in those with normotensive parents, and that these hemodynamic changes take place at an early stage in the development of hypertension when FH+ was present. When combined with a new stressor such as macroscopic hematuria, this predisposition can be accelerated and result in hypertension. In our view, the impact of hematuria on renal function is a possible cause of hypertension when FH+ is present.

Several variables were significant in univariate regressions (Table 2), but became non-significant after the inclusion of additional controls. For example, the regular use of NSAIDs, known to induce various sorts of kidney damage,[23] was associated with hypertension in univariate analysis for undifferentiated hypertension only. Regular NSAIDs use and severe hemophilia were highly correlated, as the use of NSAIDs was more common among people with severe than mild hemophilia. After controlling for age, BMI, and severity of hemophilia, use of NSAIDs became non-significant in multivariate analysis. A history of renal disease was also a significant covariate in univariate analysis, but very few patients had this diagnosis (Table 1) whereas EGFR was available for nearly the entire cohort. Renal disease became non-significant after controlling for EGFR. We found a positive association between hypertension and a history of coronary artery disease (CAD) both in univariate and multivariate regressions. However, this was most likely a consequence of reverse causation, as hypertension is a well-known risk factor for the structural and vascular changes that develop in CAD.[24,25] Hence, this variable was not included in the final model.

It has generally been thought that macroscopic hematuria is a benign condition in PWH. However, this paper demonstrated its association with hypertension FH+. This result is clinically important as hypertension in turn can lead to further renal damage, cardiac disease, peripheral vascular disease, and stroke. An increased attention given to macroscopic hematuria may restrict these adverse outcomes. In a recent study,[26] we documented that frequent prophylaxis is negatively associated with macroscopic hematuria. The results in this paper indicate that frequent prophylaxis and treatment of hematuria may reduce the likelihood of developing hypertension FH+. Although a family history of hypertension by itself is an immutable risk factor, awareness of the possible development of hypertension FH+ is important for appropriate prevention and intervention. Monitoring blood pressure at regular visits will identify the patients with hematuria at risk for hypertension and progression to renal damage.

5. Limitations

This study has some limitations. As the study is from cross-sectional data, it is statistically difficult to differentiate between causes and consequences of hypertension, although theory and previous studies guide our hypotheses regarding causality. Additional limitations were that most data were collected retrospectively, possibly susceptible to misclassification due to recall bias, and that missing data caused the removal of some patients in the regression analyses. Also, inherited causes of hematuria such as certain familial kidney diseases could potentially explain the correlation between hematuria and hypertension. Unfortunately, this information was not available in our study. These limitations notwithstanding, the paper adds new insight to hypertension in PWH. The H3 study[9] represents a comprehensive multi-country hemophilia sample that adds to the generalizability of the strong association between macroscopic hematuria and hypertension FH+.

6. Conclusion

In this paper, we demonstrated the need to differentiate hypertension FH+ from FH– in order to recognize that macroscopic hematuria is in fact associated with hypertension. To our knowledge, this distinction has not been applied in the previous literature. We acknowledge that the results pertain to this study sample only, and encourage more research to establish out of sample evidence to ascertain whether the association between hypertension FH+ and hematuria holds more generally.

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Author contributions

CQ designed the research study, performed the research, analyzed the data, and wrote the paper. LQS designed the research study and participated in the research, data analysis, and in writing the manuscript. RCT, PdM, and PAH designed the research study and participated in writing the manuscript.

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