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# The Cost of Von Willebrand Disease in Europe: The CVESS Study

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## Abstract

**Background:** Von Willebrand disease (VWD) is one of the most common inherited bleeding disorders, imposing a substantial health impact and financial burden. The **C**ost of **v**on Willebrand disease in **E**urope: A **S**ocioeconomic **S**tudy (CVESS) characterises the socio-economic cost of VWD across Germany, Spain, Italy, France, and the UK.

**Methods:** A retrospective, cross-sectional design captured 12 months of patient disease management, collected from August-December 2018, for 974 patients. This enabled estimation of direct medical, direct non-medical and indirect costs, utilising prevalence estimates to extrapolate to population level.

**Results:** Total annual direct medical cost (including/excluding von Willebrand factor [VWF]) across all countries was the highest cost (€2 845 510 345/€444 446 023), followed by indirect costs (€367 330 271) and direct non-medical costs (€60 223 234). Differences were seen between countries: the UK had the highest direct medical costs excluding VWF (€159 791 064), Italy the highest direct-non medical (€26 564 496), and Germany the highest indirect cost burden (€197 036 052). Total direct medical costs per adult patient increased across VWD types with Type 1 having the lowest cost (€23 287) and Type 3 having the highest cost (€133 518).

**Conclusion:** A substantial financial burden arises from the prevalence of VWD for the European healthcare systems considered.

## Keywords

Von Willebrand disease, cost, burden, Europe

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## Introduction

Inherited bleeding disorders are conditions in which the absence of a particular coagulation factor results in impaired blood clotting.[1] Patients with bleeding disorders have higher frequency, intensity, and duration of bleeds than the general population, thus many bleeding disorders have been found to entail a substantial economic burden across a number of countries.[1, 2] The most common bleeding disorder is von Willebrand disease (VWD).[1] Symptomatic VWD has an estimated prevalence of 1 in 10 000.[2–6] The World Federation of Hemophilia (WFH) show a continuous increase in the number of VWD patients reported via the WFH global survey which collects data in specific practise and reporting sites across the world.[7]

VWD is an autosomal dominant (or recessive, depending on subtype) bleeding disorder caused by quantitative or qualitative deficiency of the complex multimeric glycoprotein von Willebrand factor (VWF).[8] The reduction in available VWF reduces platelet adhesion, platelet aggregation, and factor VIII (FVIII) availability, which gives rise to an increased frequency and length of bleeds (particularly mucosal bleeding) especially in the skin, gastrointestinal tract, and uterus, as well as bleeding

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in joints, leading to deterioration in severe or poorly managed patients;[9] in the event of progressive, extensive joint damage due to bleeds, orthopaedic surgery may be carried out.[10] Female VWD patients may experience heavy menstrual bleeding so severe as to require regular hospitalisation. They may also experience particularly dangerous manifestations during pregnancy, which may be fatal.[11, 12] There remains a lack of awareness and standardised guidelines for the treatment of women with VWD[13] and this has been shown to place these women at risk of unnecessary hysterectomy[14, 15] and obstetric complications such as post-partum haemorrhage.[16]

VWD patients are usually classified as having either Type 1, in which a quantitative deficiency of VWF is observed (60%-80% of all patients), Type 2 (further categorised into Types 2A, 2B, 2M, and 2N) in which a qualitative defect is present (20%-30% of all patients), or Type 3, where VWF is virtually completely absent (2-3 people per million). Each of the aforementioned present mild, moderate, and severe symptoms, respectively.[8, 17, 18] However, symptoms may vary depending on phenotypic expression.[19]

While in 2021 the international guidelines on the management of VWD (as developed by the American Society of Hematology, International Society on Thrombosis and Haemostasis, National Hemophilia Foundation, and World Federation of Hemophilia) were released,[20] prior to this there were limited formal guidelines for standard of care of VWD across Europe. This was particularly true on a national level which saw a large variation in healthcare for VWD. In general terms, VWD treatment can be divided into treatments that increase the plasma levels of VWF and FVIII, and adjunctive therapies that aim to provide an indirect haemostatic benefit.[21] Specific agents include Desmopressin (1-deamino-8-d-arginine vasopressin, DDAVP) or VWF-FVIII concentrates, and antifibrinolytic agents (tranexamic acid (TXA), epsilon aminocaproic acid (EACA)) or hormone therapy respectively.[21] Type 1 patients are often effectively treated with desmopressin which facilitates release of endogenously stored VWF.[22, 23] Type 2 patients are characterised by various qualitative defects resulting in low levels of VWF activity and/or FVIII, and treatment can include desmopressin, plasma-derived or recombinant VWF± FVIII dependent on the subtype and the response to the desmopressin test. Type 3 patients cannot produce VWF so replacement treatment with plasma-derived or recombinant VWF± FVIII is required; Type 3 patients require replacement therapy for all but minor bleeds. If high purity or recombinant VWF is used, then initial co-administration of FVIII may also be required until sufficient endogenously produced FVIII has accumulated.[21–25]

There is limited research available on patient-reported outcomes relating to disease burden in VWD. For example, a small number of studies have explored Health-Related Quality of Life (HRQoL) among VWD patients, which is lower overall than the average reported for the general population in Canada, and in Finnish and Dutch patients, especially for Types 2 and 3.[26–29] Female-specific elements of disease burden have also been explored; HRQoL is often reduced as a result of menorrhagia, pain, and pregnancy complications.[30–32] One study in the United States reported the occurrence of target joints, missing days from work/school, and surgery-related bleeds (e.g., following dental procedures) as notable aspects of disease burden for VWD.[33] Although some facets of disease burden have been investigated previously, such as post-surgical complications, hospitalisation costs, and costs of VWD testing procedures,[34, 35] research regarding economic aspects of the disease is still lacking (for example costs to the healthcare system) and therefore requires more attention in order to obtain a more complete perspective of the burden of VWD.

The aim of the **C**ost of **v**on Willebrand disease in **E**urope: A **S**ocioeconomic **S**tudy (CVESS) was to explore the socioeconomic burden of VWD in adult and paediatric patients across Germany (DEU), France (FRA), Spain (ESP), Italy (ITA), and the United Kingdom (UK), in a real-world setting. This paper examines the cost of VWD across the aforementioned countries in CVESS. Specifically, it assesses the per-patient and population burden costs of VWD for each country and each VWD type with a view to estimating the overall cost burden for VWD for a healthcare system.

## Methods

### Ethical Approval, Patient Consent and Confidentiality

Ethical approval was granted by the Research Ethics Sub Committee of the Faculty of Health and Social Care within the University of Chester, and the study was overseen throughout by an Expert Reference Group (ERG) consisting of academics, patient advocates, patients, and clinicians with substantial expertise in VWD. Patients who participated in the study provided informed consent.[36] All patient identities were anonymised and patient confidentiality was maintained by assigning each patient a unique patient ID.[36]

### Study Design

This study used a retrospective, prospective, bottom-up, cross-sectional methodology. Physicians specialising in haematology from hospitals across the 5 countries were invited to participate and subsequently recruited patients into the study, and were remunerated for their time. Patients were eligible for inclusion in the CVESS study if they were aged one year or older and were diagnosed with hereditary VWD that had been classified as Type 1, 2 (any subtype), or 3. Patients were excluded for reasons such as language barriers, diagnosis of acquired VWD, or the presence of a physical or mental condition resulting in diminished decision making.[36] Recruitment of patients was specified as the next ten consecutive VWD patients who were consulting with the physician and who met the inclusion criteria.

### Data Collection

The study was conducted between August 2018 and December 2018. Physicians were asked to complete electronic Case Report Forms (CRFs) detailing direct medical resource

utilisation and clinical data from medical records. After their consultation, patients were invited to complete a Patient and Public Involvement and Engagement questionnaire (PPIE), which yielded information about direct non-medical and indirect costs via patient-reported resource use and outcomes. Data were checked by the ERG with clinician input. Retrospective data covering 12 months of patient disease management were collected, with the point of consultation (and data abstraction) as the index date, for the previous year. These data were used to calculate total healthcare resource use and costs for the 12-month time period collected. The electronic format of the CRFs ensured that the numeric responses were limited to realistic boundaries and that non-feasible responses were kept to a minimum. However, a small amount of post hoc data processing was conducted based on expert clinical guidance by the ERG.

### Cost Evaluation

Costs were categorised into 3 groups; direct medical, direct non-medical and indirect costs.[37] Direct medical costs were derived from clinical data which included, but were not limited to, information such as hospitalisations, consultations, surgical procedures, professional caregivers and treatments. Direct non-medical costs were obtained via the PPIE, and encompassed elements of resource use such as use of alternative therapies (including over-the-counter medication) and need for home alterations/medical devices. Finally, indirect costs were valued according to the Human Capital Approach (HCA) as the cost of employment which includes the loss of earnings, for the patient or unpaid caregiver, and the loss of productivity due to absenteeism.[37, 38] Further details about the cost categories can be found in Table A1 in the appendix.

### Statistical Analysis

Descriptive analyses were performed on patients' demographic and cost data with continuous information being presented as means with standard deviations, and categoric information reported as counts and percentages. Patient data were assessed separately in two patient groups: Paediatrics (Aged 1-17) and Adults (18+). The analysis was further stratified to assess the paediatric and adult patient cohorts by VWD type and by country.

Cost sources were obtained from publicly available data (further information on cost sources can be found in the Appendix: Table A2) and the selection of resources to be included in the present study was defined by the healthcare, societal, and participant / family perspectives. Average country-specific salary was employed as a means of calculating salary losses. All local currency total costs were converted to EUROs (€) using the conversion rate on the date of 10th of September 2018. The per-patient costs were calculated by multiplying the quantities of each resource used with the respective national unit price. To extrapolate the sample costs to country population level, the mean per-patient costs of each country were multiplied by national prevalence weights.[7, 39] Sensitivity analysis was also run altering the prevalence rates to a standard of 1/5000 and 1/10 000 for each country.

### Equation: Burden Cost Calculation

$$P_i \times Q_i = Cost_i$$

$$Cost_i \times Prevalence\ Weights = Population\ Cost$$

$$Where\ P = price,\ Q = resource\ use,\ and\ i = 1 \rightarrow n\ (where\ n = number\ of\ cost\ items)$$

## Results

### Patient Characterstics and Costs

A total of 94 physicians (18 DEU, 22 ESP, 17 FRA, 17 UK, 20 ITA) participated and provided a total of 974 unique patient CRFs, with adults comprising 73% (n = 708) of the total CRF sample, and paediatrics comprising 27% (n = 266). The split of patients by VWD type was 48%, 44% and 7% for adults, and 66%, 23% and 10% for paediatrics, for Types 1, 2 and 3,

**Table 1.** Characteristics (Adults).

| | Type 1 (N = 340) | Type 2 (N = 311) | Type 3 (N = 52) | DEU (N = 116) | ESP (N = 145) | FRA (N = 132) | UK (N = 129) | ITA (N = 186) | Overall (N = 708) |
|---|---|---|---|---|---|---|---|---|---|
| **Gender:** | | | | | | | | | |
| *Male: n (%)* | 207 (61%) | 170 (55%) | 28 (54%) | 67 (58%) | 75 (52%) | 71 (54%) | 69 (53%) | 127 (68%) | 409 (58%) |
| *Female: n (%)* | 133 (39%) | 141 (45%) | 24 (46%) | 49 (42%) | 70 (48%) | 61 (46%) | 60 (47%) | 59 (32%) | 299 (42%) |
| **Age:** | | | | | | | | | |
| *Mean (SD)* | 36.4 (12.6) | 41.5 (15.1) | 38.5 (15.8) | 39.2 (12.6) | 40.3 (15.8) | 32.1 (11.7) | 39.6 (14.6) | 41.7 (13.8) | 38.8 (14.2) |
| **VWD Type** | | | | | | | | | |
| *Type 1: n (%)* | 340 (100%) | - | - | 71 (61%) | 63 (43%) | 80 (61%) | 66 (51%) | 60 (32%) | 340 (48%) |
| *Type 2: n (%)* | - | 311 (100%) | - | 36 (31%) | 76 (52%) | 49 (37%) | 43 (33%) | 107 (58%) | 311 (44%) |
| *Type 3: n (%)* | - | - | 52 (100%) | 7 (6%) | 6 (4%) | 3 (2%) | 17 (13%) | 19 (10%) | 52 (7%) |
| *Uncertain: n (%)* | - | - | - | 2 (2%) | 0 (0%) | 0 (0%) | 3 (2%) | 0 (0%) | 5 (1%) |

**Table 2.** Direct Medical Costs (Adults).

| | Type 1 | Type 2 | Type 3 | DEU | ESP | FRA | UK | ITA | Male | Female | Overall |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Direct Medical Cost (annual)** | | | | | | | | | | | |
| **Number of patients (n)** | 340 | 311 | 52 | 114 | 145 | 132 | 126 | 186 | 405 | 298 | 703 |
| ***Consultations: Mean (SD)*** | €1 060 (3 560) | €1 207 (1 474) | €5 309 (14 234) | €166 (119) | €2 023 (1 498) | €166 (96) | €4 693 (10 517) | €465 (443) | €1 211 (3 359) | €1 750 (6 233) | €1 439 (4 796) |
| ***Tests: Mean (SD)*** | €311 (428) | €582 (545) | €748 (1 452) | €249 (165) | €736 (521) | €314 (339) | €447 (1 077) | €498 (553) | €459 (574) | €469 (699) | €463 (629) |
| ***Hospitalisations: Mean (SD)*** | €2 014 (9 047) | €5 685 (24 326) | €11 948 (33 257) | €1 027 (4 390) | €6 199 (33 405) | €1 020 (2 677) | €9 135 (27 361) | €4 154 (7 171) | €3 770 (12 711) | €5 192 (26 425) | €4 373 (19 720) |
| ***Treatment VWF: Mean (SD)*** | €18 818 (57 578) | €72 506 (171 655) | €113 228 (132 261) | €52 968 (237 205) | €53 841 (118 483) | €26 021 (76 843) | €25 281 (55 596) | €77 258 (104 301) | €50 246 (145 722) | €48 610 (104 876) | €49 552 (129 903) |
| ***Treatment Other:[a] Mean (SD)*** | €1 047 (2 746) | €3 478 (8 227) | €2 285 (7 431) | €6 135 (12 442) | €996 (5 013) | €2 148 (3 597) | €851 (2 282) | €1 731 (2 953) | €1 822 (4 648) | €2 746 (7 880) | €2 214 (6 238) |
| ***Prof. Carer: Mean (SD)*** | €37 (677) | €205 (2 342) | €0 (0) | €0 (0) | €86 (1 036) | €0 (0) | €0 (0) | €342 (3 024) | €8 (153) | €245 (2 491) | €108 (1 628) |
| ***Direct Medical Costs (exc. VWF): Mean (SD)*** | €4 468 (11 847) | €11 158 (25 803) | €20 290 (40 761) | €7 577 (13 489) | €10 040 (34 147) | €3 648 (4 528) | €15 126 (33 034) | €7 190 (9 502) | €7 270 (15 222) | €10 402 (29 494) | €8 598 (22 445) |
| ***Direct Medical Costs: Mean (SD)*** | €23 287 (59 337) | €83 663 (174 228) | €133 518 (133 979) | €60 545 (242 385) | €63 881 (123 206) | €29 669 (78 071) | €40 407 (65 767) | €84 448 (103 601) | €57 516 (147 654) | €59 012 (110 431) | €58 150 (133 067) |

[a]Other treatment consists of desmopressin (DDAVP) and antifibrinolytic (TXA/EACA) use.

respectively. Of the entire patient cohort, 7 patients' VWD type was deemed uncertain due to multiple types being reported in the CRF, hence these patients were excluded from the cost analyses. The gender split of the adult cohort (Table 1) was 58% male and 42% female across all countries. France and Germany had the highest proportion of adult Type 1 patients with 61%, and Italy had the lowest proportion with 32%. For Type 3 adults the UK had the highest proportion with 13%, and France the lowest with 2%. Average age among adult patients was 38.8 years, with the lowest mean age in France (32.1 years) and the highest in Italy (41.7 years). For the paediatric patients (Table A3), mean age was approximately 13.5 years old with a gender split of 57% male patients and 43% female patients. Of the CRF sample, 22% (215 patients) completed and returned the PPIE forms, of which 176 were adults (82%), and the remainder paediatric (18%).

Annual direct medical costs for adults were generally higher for more severe VWD types across all CRF variables (see Table 2). The highest physician-reported direct medical costs for adult patients were for VWF treatments (€49 552 overall), expenditures for which ranged from €25 281 in the UK to €77 258 in Italy, when comparing across countries. The majority of treatment cost was cost associated with VWF use, comprising costs of any VWF use including prophylaxis and on-demand treatment. Type 3 patients reported the greatest VWF treatment costs (€113 228), with Type 2 reporting €72 506 and Type 1 reporting the lowest at €18 818. Male patients had a similar mean VWF treatment cost (€50 246) to female patients (€48 610). Hospitalisation costs were the second highest direct medical item (€4 373), and the highest cost across subtypes was similarly observed for Type 3 VWD patients (€11 948), progressively decreasing for Type 2 (€5 685) and Type 1 (€2 014). Additionally, higher hospitalisation costs were observed for female (€5 192) compared to male patients (€3 770). Overall, of the VWD types, the largest direct medical costs were observed in Type 3 VWD, including and excluding treatment costs (€133 518/€20 290) with Type 2 patients second highest (€83 663/€11 158) and Type 1 patients reporting the lowest (€23 287/€4 468). Additionally, overall direct medical costs including and excluding treatment costs by gender showed that women (€59 012/€10 402) had a higher direct medical cost burden compared to men (€57 516/€7 270). Comparison between countries indicates that the direct medical cost (including treatment) is highest in Italy (€84 448) and lowest in France (€29 669). Direct medical costs (with treatment excluded) are also lowest in France (€3 648) but highest for the UK (€15 126).

Among paediatrics (Table A4), CRF variables with the exception of VWF treatment had higher costs for Type 2 patients. As observed in adults, VWF treatment expenditures were the highest physician-reported cost (€24 785). Expenditure on VWF treatment was lowest for Type 1 (€14 267) and highest for Type 3 (€45 950) patients in the paediatric population, similar to the adult population. When comparing across countries, the overall per-patient direct medical cost including treatment for paediatrics was highest in Italy

**Table 3.** Total Economic Cost Burden.

| | DEU | ESP | FRA | UK | ITA |
|---|---|---|---|---|---|
| **Country Population** | 82 695 000 | 47 042 984 | 67 118 648 | 66 022 273 | 60 551 416 |
| Prevalence (from Literature) | 0.016% | 0.016% | 0.016% | 0.016% | 0.016% |
| Total Cases - Base Case | 13 231 | 7 527 | 10 739 | 10 564 | 9 688 |
| *Total Cases - Sensitivity Analysis (1/5 000)* | 16 539 | 9409 | 13 424 | 13 204 | 12 110 |
| *Total Cases - Sensitivity Analysis (1/10 000)* | 8 270 | 4 704 | 6 712 | 6 602 | 6 055 |
| CRF Sample, n | 114 | 145 | 132 | 126 | 186 |
| Direct Medical Per Patient Cost | €60 545 (242 385) | €63 881 (123 206) | €29 669 (78 071) | €40 407 (65 767) | €84 448 (103 601) |
| **Direct Medical Cost Burden** | € 801 070 895 | €480 832 287 | €318 615 391 | €426 859 548 | €818 132 224 |
| *Sensitivity Analysis (1/5 000)* | €1 001 353 755 | €601 056 329 | €398 276 656 | €533 534 028 | €1 022 665 280 |
| *Sensitivity Analysis (1/10 000)* | €500 707 150 | €300 496 224 | €199 138 328 | €266 767 014 | €511 332 640 |
| Direct Medical Per Patient Cost (Excl. VWF) | €7 577 (13 489) | €10 040 (34 147) | €3 648 (4 528) | €15 126 (33 034) | €7 190 (9 502) |
| **Direct Medical Cost Burden (Excl. VWF)** | €100 251 287 | €75 571 080 | €39 175 872 | €159 791 064 | €69 656 720 |
| *Sensitivity Analysis (1/5 000)* | €125 316 003 | €94 466 360 | €48 970 752 | €199 723 704 | €87 070 900 |
| *Sensitivity Analysis (1/10 000)* | €62 661 790 | €47 228 160 | €24 485 376 | €99 861 852 | €43 535 450 |
| PPIE Sample, n | 6 | 53 | 24 | 24 | 69 |
| Direct Non-Medical Per Patient Cost | €1 677 (1 350) | €1 167 (2 416) | €78 (59) | €175 (134) | €2 742 (3 319) |
| **Direct Non-Medical Cost Burden** | €22 188 387 | €8 784 009 | €837 642 | €1 848 700 | €26 564 496 |
| *Sensitivity Analysis (1/5 000)* | €27 735 903 | €10 980 303 | €1 047 072 | €2 310 700 | €33 205 620 |
| *Sensitivity Analysis (1/10 000)* | €13 868 790 | €5 489 568 | €523 536 | €1 155 350 | €16 602 810 |
| Indirect Per Patient Cost | €14 892 (23 031) | €5 040 (12 058) | €6 141 (14 010) | €275 (362) | €6 555 (11 560) |
| **Indirect Cost Burden** | €197 036 052 | €37 936 080 | €65 948 199 | €2 905 100 | €63 504 840 |
| *Sensitivity Analysis (1/5 000)* | €246 298 788 | €47 421 360 | €82 436 784 | €3 631 100 | €79 381 050 |
| *Sensitivity Analysis (1/10 000)* | €123 156 840 | €23 708 160 | €41 218 392 | €1 815 550 | €39 690 525 |

(€55 298), as seen in the adult population, and the lowest in Spain (€7507). Excluding VWF treatment, the direct medical costs for paediatrics were lowest in the UK (€3146) and highest in France (€7037). This is the reverse of what is seen in the adult population.

### *Total Economic Burden of Illness*

In order to extrapolate annual population-level VWD-related costs, disease prevalence estimates were obtained from existing literature (see Table 3). The prevalence rate of 0.016%[7, 40] used was based upon data from the UK in 2017/2018 and applied to the adult population of all countries. The total direct medical cost (including VWF) burden in adults was highest in Italy (€818 132 224) followed by Germany (€801 070 895), Spain (€480 832 287), the UK (€426 859 548) and France (€318 615 391). When we exclude VWF costs, we see that the total direct medical was the highest in the UK (€159 791 064) and lowest in France (€39 175 872). The per patient direct non-medical costs were highest for Italy (€2742) and consequently they had the highest total direct non-medical cost burden of €26 564 496. The indirect cost burden ranged from €197 036 052 in Germany to €2 905 100 in the UK, with the UK presenting with the lowest per patient cost (€275) and Germany the highest (€14 892). The results from the sensitivity analysis show that when the prevalence rate of 1/5 000 is applied, the burden cost is higher for all countries and when using a prevalence rate of 1/10 000, the cost is lower than base case cost.

## Discussion

This study reveals a high socio-economic cost burden of VWD. The CVESS study aimed to quantify the economic burden of VWD in the European countries surveyed, the first study of its kind to do so. We achieved this via estimation of direct medical, direct non-medical and indirect costs generated from data on clinical, economic, and societal costs related to the condition.

Direct medical costs per-patient for each country were the largest of the three cost categories, with VWD treatments (principally VWF treatment costs) and hospitalisations being the specific drivers of costs, especially for patients with more severe VWD. This was followed by indirect costs. The lowest annual costs were direct non-medical costs. The overall direct medical cost burden across all the countries totalled €2 845 510 345, with direct non-medical costs and indirect costs totalling €60 223 234 and €367 330 271 respectively.

With regard to total costs per country, considerable differences were observed with the highest direct medical cost burden (including VWF) being in Italy (€818 132 224) but the lowest in France (€318 615 391). While population size is a factor in these differences, the pattern of highest to lowest cost is similar when these costs are considered on a per-patient level with the highest and lowest direct medical cost burden

remaining in Italy (€84 448) and France (€29 669) respectively. This suggests that additional factors play a significant role in these variations. One such factor may be differences in treatment practice; in several of these countries (such as Italy and Germany), there are no national VWD guidelines to follow.[41] However, the European guidelines state that prophylaxis dosing should be tailored to each patient based on their VWD severity, and risk of and tendency towards bleeding, which may account for some of the variation in bleeds, hospitalisations and treatment costs observed in CVESS.[42] When comparing the direct costs excluding VWF, we still see large differences in burden across countries, for example in the UK compared to France (€159 791 064 vs €39 175 872). These differences are driven by the unit costs for healthcare services sourced within each country, with the UK having generally higher healthcare costs than the other countries included. The findings of this study have provided an insight into the cost of VWD across countries and how these costs differ between the participating countries and by VWD type, for both adult and paediatric populations.

This research also sheds light on the burden of VWD compared to other bleeding disorders examined in the literature. For example, the CHESS study found the total costs of haemophilia per country ranged from €94 010 111 in Spain to €700 257 680 in Germany, with the total costs incorporating the direct (including factor treatment), non-direct cost and indirect cost burdens.[43] When we compare the CVESS total cost burden we see France (€385 401 232) with the lowest burden and Germany (€1 020 295 334) with the highest, which is likely influenced by population size. In addition, when comparing the total per patient cost (direct cost including VWF, non-direct cost, indirect cost) we see that the cost in Germany (€77 414 vs €319 024), Spain (€70 088 vs €173 771), France (€35 888 vs €196 117), UK (€40 857 vs €129 365) and Italy (€93 745 vs €220 344) is lower for VWD patients in CVESS than it is for haemophilia patients in CHESS. However, there are some important differences between the two studies; the CHESS study examined only severe haemophilia patients, where long-term prophylaxis with factor is the standard of care treatment,[44] which will inflate the per patient costs. In contrast, CVESS included mild, moderate, and severe forms of VWD. Additionally, only male patients were included in CHESS, whereas CVESS included male and female patients as VWD is prevalent among both male and female patients.[45] Nevertheless, the research provides interesting findings that are comparable to other bleeding disorder burden of illness studies.

The evidence the CVESS study has provided will be utilised by the stakeholder community to further understand the health economic landscape of VWD in Europe. Due to the extensive nature of this retrospective, cross-sectional study, it offers scope to further investigate the drivers behind the findings in resource use and associated costs for the patient cohort. In particular, these findings highlight the high treatment and hospitalisation costs for VWD in all European countries, especially for Type 3 patients. Additionally, there has previously been a lack of data on the burden of VWD for paediatric patients, however CVESS demonstrated the high treatment costs in this population, which are highest for paediatric patients with more severe disease. In light of this, the findings may be used to improve treatment pathways and policies regarding access to appropriate support for both adults and children with severe VWD. Furthermore, these findings may facilitate better access to resources and consultations for patients with Type 1 and 2 VWD, particularly those experiencing high levels of bleeding, as their VWD-related costs were shown to be substantial.

This information could also be used to further tailor appropriate treatment guidelines for VWD, building on the 2021 recommendations for the management of VWD[20] or to highlight the need for national guidelines in countries that do not yet have any (e.g., Germany).[42] Future work with the CVESS dataset could explore the impact age has on VWD burden. Patient advocacy organisations may also make use of the CVESS data, particularly in relation to patient education, strategy and service development, marketing strategies, and supporting grant applications and funding for further research. Nonetheless, it ought to be acknowledged that cost considerations can sometimes overshadow the human implications in "burden of illness" research, and the patient-reported costs (despite not being as high as the healthcare system costs) should not be overlooked.

### Limitations

Patients were recruited to the study via haematologists who enrolled their next ten consecutive patients, which increased the likelihood that this study included patients who consulted their physician more frequently (and thus, increased likelihood of per patient cost over-estimation). Due to this recruitment methodology the sample may not be fully representative of expected disease demographics such as gender. A further limitation in this regard is recall bias, particularly for outpatient visits and consultations with other specialists or professional caregivers which the physician may not be fully aware of.

Furthermore, the cost estimates are sourced using publicly available reimbursement data, rather than the specific costs to hospital providers and patients, which aren't easily captured. This limitation means any difference between the sourced and real-life costs may lead to an under or over-estimation of the actual realised costs. In patient reported outcomes regarding costs, minor expenditure by patients may be unobserved when reporting use of devices, aids, and over-the-counter (OTC) medications. In addition, the findings of the patient reported outcomes may be subject to selection bias as certain types of people have time or want to fill out these questionnaires. This appears to be the case in Germany, and also for Type 3 patients for which there were limited numbers of completed PPIEs. With regard to the aforementioned response rates of Type 3 VWD patients, it should also be acknowledged that the low sample size yielded may result in underestimation of the costs associated with greater disease severity.

Prevalence rates of VWD were also difficult to source from the literature, with the reported amounts of patients being less than suggested prevalence rates per country. Application of the UK prevalence rate to all countries is a limitation as our cost estimates may not truly represent the landscape of each country. However, using the same prevalence rate allows our results to be more comparable across countries, as some of the countries have limited data on prevalence rates in the existing literature whereas the UKHCDO (United Kingdom Haemophilia Doctors' Organisation) provides extensive information about the VWD population in the UK.[40] To account for this limitation, two sensitivity analyses were performed to help add to understanding the cost of VWD in Europe. Other limitations included the fact that caregivers had to fill in some parts of the PPIE on behalf of paediatric patients (thus the data was not truly patient reported in all cases but via proxy) and the inability to validate patient-reported data by making direct contact with the patient to confirm or question their responses (which can't be avoided due to patient anonymity and confidentiality). It should be noted the CVESS study was only conducted with a number of European countries and therefore the findings are only applicable within these markets. Further investigation into other markets, specifically the United States, may be of interest to set these results in a worldwide context.

## Conclusions

The results from CVESS highlight the considerable economic burden to not only the healthcare systems, but also to the patients and caregivers across Germany, Spain, Italy, France and the UK, and is the first study of its kind to do so. Nonetheless, there remains scope to shed further light on drivers of cost and outcomes in VWD disease by delving deeper into the dataset, thus enabling a better understanding of the costs to patients and healthcare systems across countries.

### Data Availability Statement

All data relevant to the study are included in the article or uploaded as supplementary information.

### Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: GM, SB and BF are employees of HCD Economics, and received research support from Baxalta US Inc., a Takeda company, to perform this study. ML has been in receipt of research support (grant) from Biomarin trial funding, and honoraria or consultation fees from Takeda, LFB, Roche, SOBI, Bayer, Pfizer, CSL, Biomarin. ML has also participated in company sponsored speaker's bureaus for Pfizer, Bayer, Octopharma, Takeda, Leopharma, and SOBI.

### Ethics Approval

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### Informed Consent

Written informed consent was obtained from the patient(s) or authorised representative for their anonymized information to be published in this article.

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# Appendices

**Table A1.** CVESS Resource Use and Cost Components.

| Cost type | Category | Element |
|---|---|---|
| **Direct medical** | Hospitalisations | Day case |
| | | Outpatient |
| | | Inpatient – and lengths of stay |
| | Surgical procedures | Number and type of surgeries |
| | | Length of stay |
| | | Time spent in intensive care |
| | Consultant visits | Physicians and nurses (includes routine & emergency visits) |
| | | Primary care and specialties (includes routine & emergency visits) for reasons relating to VWD |
| | Tests and examinations | Blood and serum tests (including tests required for diagnosis/ subtyping) |
| | | Diagnostic imaging |
| | Requirement for aids / equipment | Medical devices |
| | Professional caregiver | Hourly wage / hours per week |
| | Current treatment (and past 12 months) including haemostatic & non haemostatic treatments | Brand (current / previous) |
| | | Dosage |
| | | Frequency |
| **Direct non-medical** | Travel costs | Car / Public transport |
| | Informal care | Hours per week / loss of earnings |
| | Alternative therapies | Over-the-counter (OTC) medications |
| | | Exercise and physiotherapy etc. |
| | | Holistic therapies |
| | | Dietary supplements |
| **Indirect costs** | Work productivity impact (for patients) | Absenteeism |
| | | Early retirement |
| | | Hours per week |

**Table A2.** CVESS Cost Sources.

| Country | Cost sources |
|---|---|
| France | OECD.stat, Ameli, sante.gouv, ViDAL.fr |
| Germany | OECD.stat, Kbv.de, meinpharmaversand.de, Einheitlicher Bewertungsmaßstab, rote-liste service |
| Italy | OECD.stat, trovanorme.salute.gov.it, Ordinary supplement n. 8 to the OFFICIAL JOURNAL, Tariffa minima degli onorari per le prestazioni medico-chirurgiche, starbene.it drug search |
| Spain | OECD.stat, Oblikue e-salud, Agencia espanola de medicamentos y productos sanitarios, Various regional goverment documents |
| United Kingdom | ONS.gov.uk, National Schedule of Reference Costs, the electronic Medicines Compendium, NICE BNF |

**Table A3.** Characteristics (Paediatrics).

| | Type 1 (N = 175) | Type 2 (N = 62) | Type 3 (N = 27) | DEU (N = 62) | ESP (N = 65) | FRA (N = 50) | UK (N = 33) | ITA (N = 56) | Overall (N = 266) |
|---|---|---|---|---|---|---|---|---|---|
| **Gender:** | | | | | | | | | |
| *Male: n (%)* | 103 (59%) | 36 (58%) | 12 (44%) | 35 (56%) | 36 (55%) | 30 (60%) | 21 (64%) | 29 (52%) | 151 (57%) |
| *Female: n (%)* | 72 (41%) | 26 (42%) | 15 (56%) | 27 (44%) | 29 (45%) | 20 (40%) | 12 (36%) | 27 (48%) | 115 (43%) |
| **Age:** | | | | | | | | | |
| *Mean (SD)* | 13.7 (3.7) | 12.9 (3.6) | 13.7 (4.2) | 14.5 (2.3) | 14.7 (2.9) | 11.9 (4.9) | 14.4 (2.4) | 12.1 (4.4) | 13.5 (3.7) |
| **VWD Type** | | | | | | | | | |
| *Type 1: n (%)* | 175 (100%) | 0 (0%) | 0 (0%) | 44 (71%) | 46 (71%) | 31 (62%) | 27 (82%) | 27 (48%) | 175 (66%) |
| *Type 2: n (%)* | 0 (0%) | 62 (100%) | 0 (0%) | 17 (27%) | 4 (6%) | 11 (22%) | 6 (18%) | 24 (43%) | 62 (23%) |
| *Type 3: n (%)* | 0 (0%) | 0 (0%) | 27 (100%) | 1 (2%) | 15 (23%) | 8 (16%) | 0 (0%) | 3 (5%) | 27 (10%) |
| *Uncertain: n (%)* | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 2 (4%) | 2 (1%) |

**Table A4.** Direct Medical Costs (Paediatrics).

| | Type 1 | Type 2 | Type 3 | DEU | ESP | FRA | UK | ITA | Male | Female | Overall |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Direct Medical Cost (annual)** | | | | | | | | | | | |
| **Number of patients (n)** | 175 | 62 | 27 | 62 | 65 | 50 | 33 | 54 | 151 | 113 | 264 |
| ***Consultations: Mean (SD)*** | €636 (691) | €901 (977) | €838 (662) | €351 (246) | €1 137 (774) | €342 (310) | €1 672 (1 121) | €404 (367) | €709 (800) | €732 (734) | €719 (771) |
| ***Tests: Mean (SD)*** | €242 (205) | €423 (323) | €362 (274) | €233 (211) | €454 (218) | €246 (270) | €167 (145) | €305 (297) | €291 (256) | €304 (257) | €297 (256) |
| ***Hospitalisations: Mean (SD)*** | €1 132 (3 592) | €6 534 (15 085) | €1 629 (3 339) | €692 (2 084) | €1 449 (3 417) | €5 897 (16 084) | €759 (2 747) | €3 522 (7 314) | €2 207 (5 884) | €2 778 (10 589) | €2 452 (8 220) |
| ***Treatment VWF: Mean (SD)*** | €14 267 (53 993) | €45 255 (81 583) | €45 950 (72 019) | €21 497 (68 406) | €3 862 (17 421) | €35 180 (81 394) | €15 141 (26 461) | €50 012 (84 862) | €25 292 (70 391) | €24 107 (56 870) | €24 785 (64 835) |
| ***Treatment Other:[a] Mean (SD)*** | €689 (2 354) | €2 281 (4 086) | €733 (2 281) | €2 255 (4 521) | €605 (2 838) | €552 (1 297) | €548 (1 258) | €1 054 (2 027) | €828 (2 120) | €1 388 (3 711) | €1 067 (2 916) |
| ***Prof. Carer:[b] Mean (SD)*** | €0 (0) | €0 (0) | €0 (0) | €0 (0) | €0 (0) | €0 (0) | €0 (0) | €0 (0) | €0 (0) | €0 (0) | €0 (0) |
| ***Direct Medical Costs (excl.VWF): Mean (SD)*** | €2 699 (4 632) | €10 139 (16 056) | €3 561 (4 834) | €3 532 (5 891) | €3 645 (5 099) | €7 037 (17 451) | €3 146 (3 516) | €5 286 (7 534) | €4 035 (6 490) | €5 201 (12 035) | €4 534 (9 276) |
| ***Direct Medical Costs: Mean (SD)*** | €16 966 (55 208) | €55 394 (82 046) | €49 511 (71 981) | €25 028 (69 444) | €7 507 (18 822) | €42 217 (83 103) | €18 287 (28 163) | €55 298 (86 229) | €29 327 (71 522) | €29 309 (58 877) | €29 319 (66 285) |

[a]Other treatment consists of desmopressin (DDAVP) and antifibrinolytic (TXA/EACA) use.
[b]Professional care costs were not collected in paediatric patients, hence this is 0 for all.