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ORIGINAL ARTICLE

Von Willebrand Disease: Gaining a global perspective

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Tweet summary:

This paper from @wfhemophilia shows #VWD registration rates vary significantly, with women underrepresented in lower income settings. In these countries, the majority of registrations are type 3 VWD, suggesting many diagnoses missed. More support is needed internationally for VWD.

Abstract

Introduction: Recent guidelines for von Willebrand Disease (VWD) highlighted the challenges in diagnosis and management. Identifying the number of persons with VWD (PwVWD) internationally will help target support to aid diagnosis of PwVWD.

Aim: To examine international registration rates of PwVWD, the influence of income status, geographical region and the age and sex profile. Cumulatively, these data will be used to inform future strategy from the World Federation of Haemophilia (WFH) to address unmet clinical and research needs.

Methods: Data from the 2018/2019 WFH Annual Global Survey (AGS) were analysed, providing a global perspective on VWD registration.

Results: Registration rates are lowest in South Asia (0.6/million population) and highest in Europe/Central Asia (50.9/million population, 0.005%), but below the expected prevalence rate (0.1%). National economic status impacted VWD registration rates,

reflecting variation in access to optimal healthcare infrastructure. Females represented the majority of PwVWD globally, however, in low-income countries (LIC) males predominated. Age profile varied, with markedly higher rates of paediatric registrations in North America, Middle East and North Africa and South Asia. Rates of type 3 VWD registrations were significantly influenced by economic status (81% of VWD diagnoses in LIC), suggesting only the most severe VWD types are diagnosed in resource limited settings.

Conclusion: Significant variation in registration rates of PwVWD exist internationally and is influenced by income status and the presence of HTC networks. Improved understanding of registration rates will enable targeting of advocacy to improve awareness, diagnosis and support for PwVWD internationally.

KEYWORDS
bleeding disorder, diagnosis, registration, von Willebrand disease, von Willebrand factor

Key points

- Registration rates of People with Von Willebrand Disease (PwVWD) vary internationally and are influenced by national income status
- Although females represent the majority of PwVWD globally, in low income countries (LIC) males predominated, possibly related to stigma surrounding gynaecological bleeding.
- Rates of type 3 VWD registration were significantly influenced by economic status (81% of VWD diagnoses in LIC), suggesting only the most severe VWD types are diagnosed in resource limited settings.

1 | INTRODUCTION

The recent publication of international consensus guidelines on the diagnosis and management of von Willebrand Disease (VWD) has highlighted many of the challenges in the diagnosis and management of this condition.[1,2] Awareness of VWD remains poor, accurate and timely diagnosis are often delayed and laboratory testing is complex.[2] VWD is characterised by mucocutaneous bleeding and is one of the most common inherited bleeding disorders. In contrast to haemophilia, pathogenic variants are autosomally transmitted affecting both men and women. However, due to the burden of excess gynaecological and obstetric bleeding, women are disproportionately impacted by VWD.[3] Prevalence studies have reported reduced plasma VWF levels in 1% of the population, associated with a bleeding phenotype in 0.1% overall.[4,5] This reported population prevalence is five to ten-fold higher than that of haemophilia (0.01%-0.02%) but despite this both public and healthcare provider (HCP) awareness of VWD continues to be poor, remaining a major barrier to referral and diagnosis.[6–10] Several studies have highlighted the significant diagnostic delay routinely experienced by persons with VWD (PwVWD), with multiple bleeding complications often experienced prior to referral for haemostatic testing.[6,11–13] Those with the most severe bleeding phenotype (type 3 VWD) may be easiest to diagnose due to the absence of VWF resulting in a secondary factor VIII deficiency. In contrast, diagnosis of other VWD types is complex, requiring specific laboratory and clinical expertise.[2]

In the past, differing diagnostic criteria internationally have hampered harmonisation of assessment. The 2021 VWD international guidelines offer an opportunity to overcome this, with diagnostic approaches shifted towards the use of bleeding assessment tools (BATs) together with improved and more automated laboratory testing of VWF activity.[2,14] Although these changes may assist VWD diagnosis, the cost and complexity of haemostatic assays involved in VWD assessment remains a significant limitation, leaving the diagnosis of VWD out of reach for many people globally.[15]

Internationally, there is a scarcity of real-world data on the prevalence of VWD. While national registries provide helpful insights into local diagnostic rates, a global overview has been lacking. This contributes to the difficulties in addressing the needs of PwVWD worldwide and limits our ability to highlight areas of unmet clinical and research need. In recognition of this World Federation of Haemophilia (WFH) have included data on PwVWD in its Annual Global Survey (AGS) since 1999. In 2018 the WFH launched a Call to Action, an international campaign focusing attention on VWD to improve awareness, diagnosis and care.[16] In order to provide a baseline from which the impact of both this programme and the incoming VWD guidelines could

be assessed, we analysed VWD data from the 2018 and 2019 AGS. We sought to determine the rate and pattern of VWD registrations internationally, the influence of income status and to identify geographical areas of reduced registrations in order to focus program and advocacy development. Finally, this work forms part of series of papers from the WFH providing the first perspective on VWD registration rates globally. The aim of this series is to highlight the challenges faced in the diagnosis and registration of PwVWD worldwide.

2 | METHODS

Data was extracted from the WFH AGS, an annual, cross-sectional annual survey distributed to national member organisations (NMO) associated with the WFH.[17] NMOs are encouraged to collaborate with treating physicians and/or health officials to capture data on all affected individuals. Data is collected in a standardised manner, submitted via paper or electronically to the WFH. All data is reviewed, with clarification sought where required from the NMO as previously described.[17]

From 2018 detailed data on people living with VWD has been included in the AGS. The dataset for PwVWD has expanded to include number of registrations, sex and age distribution (where known), number of individuals with type 3 VWD, product availability and infectious complications such as hepatitis C and/or human immunodeficiency virus (HIV). Countries are divided by the World Bank geographical regions (North America, Latin America & Caribbean, Europe & Central Asia, Middle East & North Africa, Sub-Saharan Africa, South Asia, East Asia & Pacific), and income status (high income countries [HIC], upper middle income countries [UMIC], lower middle income countries [LMIC] and lower income countries [LIC]) according to the World Bank Country and Lending Groups classification which is based on 2018/2019 population data.[18] The term "registration rate" has been used throughout this paper. Registration was defined as those individuals with VWD identified, diagnosed and reported in the AGS. Registration rates were expressed as registered individuals/million population with absolute numbers for regions expressed as total registered individuals/total population of the included countries. Data regarding Haemophilia Treatment Centres (HTCs) were obtained from the WFH database of treatment centres.[19] All data were analysed and graphed using Prism 9.3.0. Non-parametric Mann-Whitney and Kruskal-Wallis analyses were used to assess data, presented as medians unless otherwise stated and a $p < .05$ considered statistically significant.

3 | RESULTS

Overall 110 countries were included in the analysis, with 103 reporting in 2019 and seven countries with data carried forward from 2018 AGS reporting. Although the inclusion of the detailed VWD dataset is relatively new in the AGS, the number of countries reporting compared favourably to haemophilia data (125 countries in 2019). The total population of included countries was 5.59 billion,[18] from which 84,142 PwVWD were identified (Figure 1A,B).

3.1 | What disparity exists in registrations of PwVWD worldwide?

Data from each country and region were analysed to determine the number of people registered with VWD. Although initial efforts were made to express the number of registered individuals as per 10,000 of the general population, due to the low frequency in many countries the data was ultimately expressed as registered persons/million population for each country. Despite relatively lower population numbers, the highest rates of registered individuals with VWD were seen in Europe & Central Asia (0.005%, 50.9/million), with markedly lower rates seen in South Asia (0.00006%, 0.6/million, Figure 2A). The variation in registration rates between individual countries was quite marked, ranging from 0.02/million (Tanzania) to 333.7/million individuals (Ireland) (Figure 1C).

3.2 | Is VWD a diagnosis limited to countries of higher income status?

We examined this question by analysing assigned national economic status and registration rates of PwVWD. Perhaps unsurprisingly, registered PwVWD significantly differed by income status, with a median rate of 45.1 registrations/million in HIC in comparison to 0.6/million and 0.5/million in LMIC and LIC countries respectively (both $p < .0001$, Figure 2B). However, significant heterogeneity in registration rates was observed even within HIC (median 45.1 registrations/million population, range 0.8-332.7/million) and UMIC (median 10 registrations/million population, range 0.1-80.2/million, Figure 2B). When HIC and UMIC data were analysed separately, markedly higher registrations were observed in North America (median 79 registrations/million) and Europe/Central Asia (median 46 registrations/million) in comparison to other regions (Figure 2C). These rates of registrations were influenced by the relative number of HTCs present in individual countries, with a highly significant correlation between increased numbers of HTCs/million population and increased registration rates of PwVWD ($r = 0.53$, $p < .0001$, Figure 2D).

3.3 | In countries with limited resources, are registrations heavily skewed towards type 3 VWD?

Given the lower rate of VWD registrations in LMIC and LIC, we hypothesised that in limited healthcare resources settings the diagnosis of VWD may be skewed towards the most severe forms, that is, type 3 VWD. We analysed data from the countries which reported the number of patients with type 3 VWD (65 countries in total). Rates of type 3 VWD registrations differed markedly by income status, with lower relative percentages seen in HIC (median 2.8% of all registrations) and

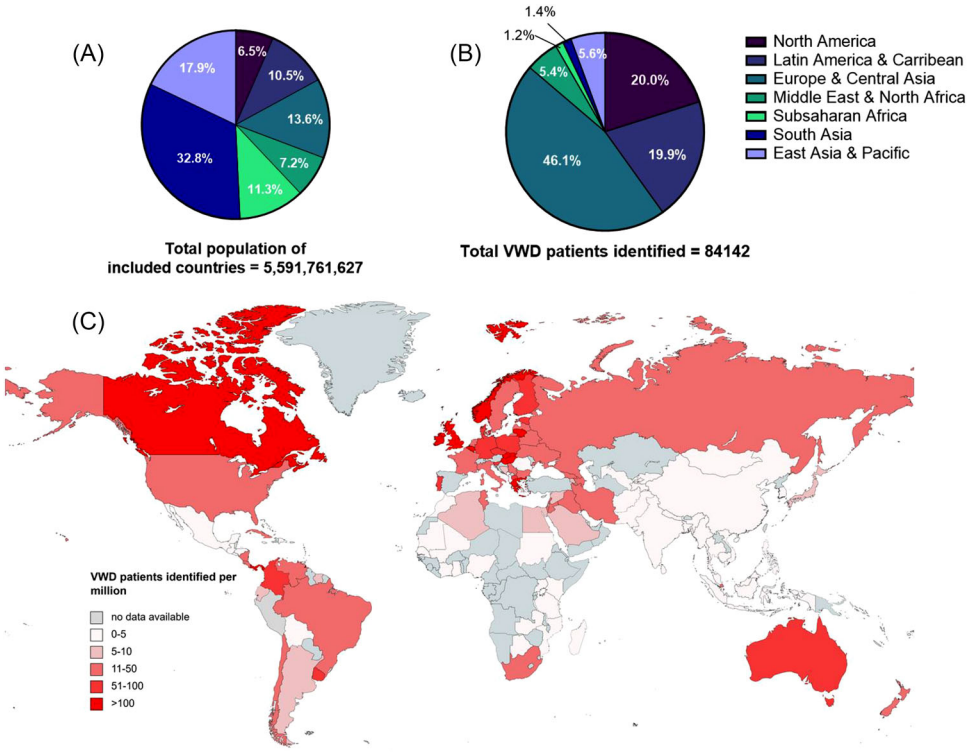

FIGURE 1 (A) The relative population of countries that submitted data to the 2018/2019 AGS per geographical region. (B) Total number of individuals identified with VWD per million population per region. (C) Global distribution of people registered with VWD per million population.

UMIC (median 8.6%) in comparison to LMIC (median 41.3%) and LIC (median 81%) (Figure 3A). In seven countries, people with type 3 VWD accounted for >90% of all registrations; undoubtedly there are many more undiagnosed people living with milder forms of VWD in these countries (Figure 3A,B). When examined by geographical region, the highest registrations of type 3 VWD were seen in the Middle East & North Africa (median 40.5%, 10 countries reporting) and South Asia regions (median 60.4%, two countries reporting) (Figure 3B). Rates of type 3 VWD may be higher in regions with increased levels of consanguinity, however it is likely that the locally available diagnostic facilities contribute to these geographical variations. To understand this relationship we analysed overall registration rates of VWD and the percentages of people with type 3 VWD registered for each country. A clear inverse relationship was seen between registration rates of PwVWD and the percentage of people diagnosed with type 3 VWD ($r = -0.44$, $p = .0003$, Figure 3C). As evidenced in Figure 3D, there was a highly significant correlation between the percentage of type 3 VWD and moderate/severe haemophilia registrations ($r = 0.4395$, $p = .0004$), suggesting that in these settings, registration is skewed towards the most severe forms of bleeding disorders. Overall these data indicate that national income status influences both the overall registrations of PwVWD and the percentage found with type 3 VWD. If national health structures are poorly equipped to recognise and diagnose VWD, then diagnosis of VWD is weighted towards the most extreme phenotypes (type 3 VWD), even in HIC and UMICs. This further underscores the need for increased and focused supports to improve awareness, testing and identification of PwVWD.

3.4 | Are registrations of females with VWD equally distributed internationally?

As previously discussed, women are disproportionately impacted by VWD due to gynaecological bleeding. Internationally females account for the majority of registered individuals with VWD (total = 84142; females = 46271, 55%; males = 28217, 33.5%; sex not stated = 9654, 11.5%, Figure 4A). However, this female predominance was not consistent worldwide, with registrations in males reaching or exceeding parity with females in the Middle East and North Africa, Sub-Saharan Africa and South Asia regions (Figure 4B). Income status influenced sex distribution, with females accounting for the majority of registrations in HIC (62.2%) and UMIC (65.2%) but not in LMIC (49.9%) and LIC (43.4%, Figure 4C). The increased registration rates in males in LMIC and LIC may be related to more limited diagnostics or a referral bias for males to exclude haemophilia. It may also be related to cultural or societal factors such as taboos or stigmatization of gynaecological bleeding. When trends of registered females were examined over time, the numbers of females in the AGS increased from 2007 to 2019 in HIC (20,900 to 30,411) and UMIC (806 to 12,285, data not shown). While the relative increase (56 fold, 26–1458) in female registrations in LMIC over this time was striking, the absolute numbers of registered females in LMIC remain low, underscoring the need for increased awareness and education about women and girls with bleeding disorders (WGBD) and female specific bleeding symptoms. As sex was not reported in LIC data from 2007 no comparisons could be made.

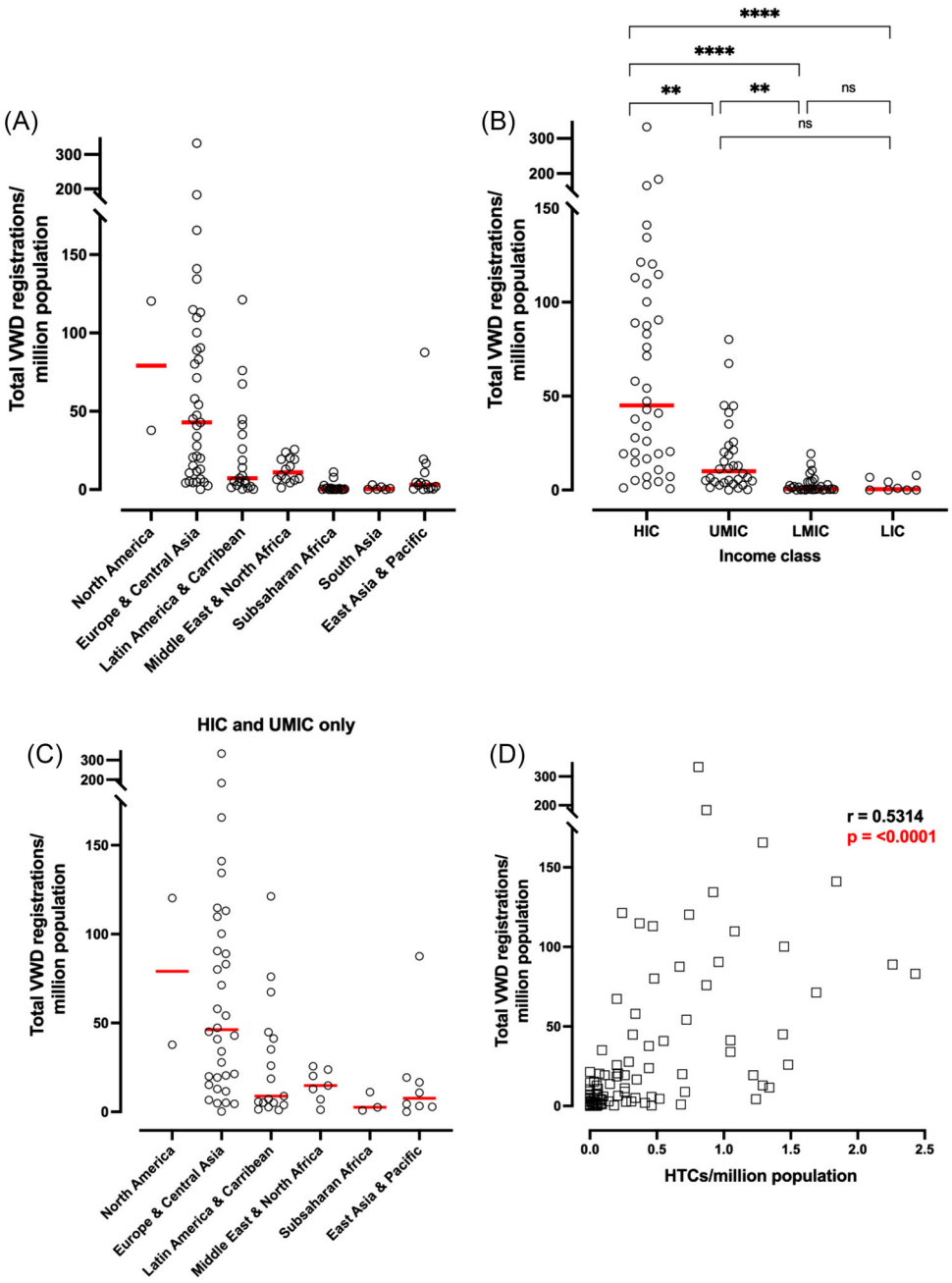

FIGURE 2 VWD registrations per million population per geographical region location (A) and per country income status (B). (C) Analysis of VWD registrations per million population of HIC and UMIC only by geographical regions. (D) The relationship between the number of HTCs and number of VWD registrations per million population. HIC, high income countries; UMIC, upper middle income countries; LMIC, lower middle income countries; LIC, lower income countries, HTC haemophilia treatment centres.

3.5 | Does the age profile of registered PwVWD vary internationally?

Data was collected on the current age of PwVWD as part of the AGS, with data available for 78.8% ($n = 66313$) of the individuals reported. Overall 30.5% of individuals were ≤18 years old (yo), 41.3% 19–44yo and 28.2% ≥45yo. The age profile varied by region with fewer paediatric patients (<18yo) in Europe (20.7%), East Asia & Pacific (20.8%) and Latin America & Caribbean (24.36%) but markedly higher rates in North America (47.5%), Middle East and North Africa (49.8%) and South Asia (43%) (Figure 5A). Income status influenced the age profile of individuals with VWD with higher proportions of paediatric patients in LMIC (50.1%) and LIC (63.8%) in comparison to HIC (30.9%) and UMIC (26%) (Figure 5B).

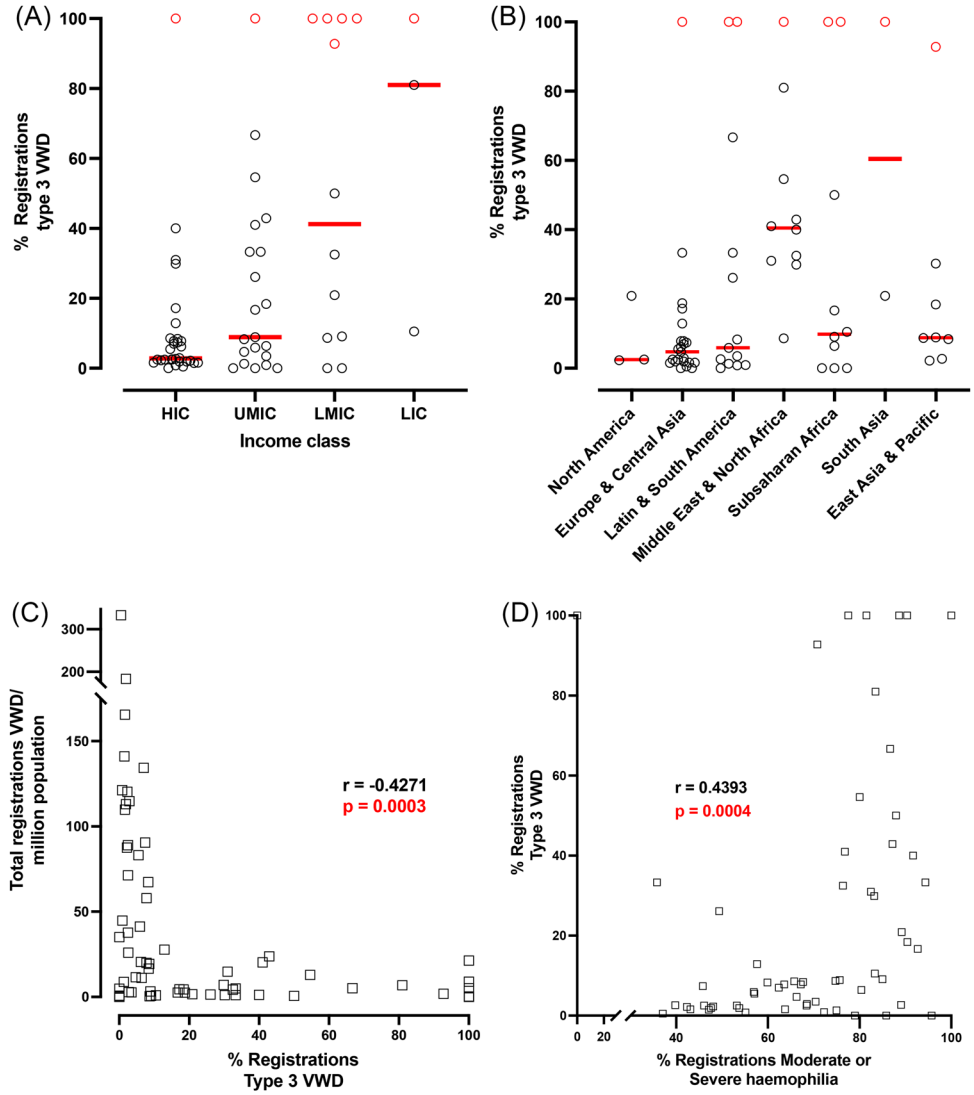

FIGURE 3 (A) Type 3 VWD registrations as a percentage of total VWD registrations by country income status (B) and geographical region. Countries with type 3 VWD registrations comprising > 90% of all VWD registrations highlighted in red. (C) Inverse correlation between percentage of individuals with type 3 VWD versus proportion of diagnosed individuals per million population. (D) There was a highly significant correlation between the percentage of individuals with type 3 VWD and percentage of individuals with moderate/severe haemophilia in an individual country ($r = 0.4395$, $p = .0004$).

4 | DISCUSSION

Despite the expected prevalence of VWD of 0.1%,[4,5] registration rates for PwVWD are markedly below this figure, with the highest reported registrations rates of only 0.005% in Europe & Central Asia. In South Asia, awareness, diagnosis and registration of PwVWD appears particularly problematic, with registration rates of only 0.00006% or 0.6/million population reported. We recognise that not all PwVWD may be registered or reported into the AGS but analysis of these data still provide insights into the current global status of VWD. Our data indicate that higher income status and the presence of a HTC network both positively influences VWD registration rates, likely related to healthcare spending and resource allocation to the recognition and treatment of people with bleeding disorders. The variability in registration rates of PwVWD in HIC and UMIC also merits further consideration to understand the barriers that may influence recognition in these settings. National income status is but one metric and does not always correlate with healthcare budgetary allocation; this was not analysed in this work. While healthcare costs will undoubtedly remain a long-term issue impeding VWD diagnosis for many countries, support through the WFH twinning, training and advocacy programmes may help build towards future HTCs networks in emerging economies.[20]

It is clear from the data that in lower income settings the majority of VWD registrations are of people with type 3 VWD. Males with type 3 VWD may be identified earlier in countries where circumcision is more prevalent; this may also contribute to a younger age profile in these regions. Bleeding over time is significantly higher in type 3 VWD patients in comparison to other types, resulting in earlier or more frequent presentations to medical services.[21] Give the rarity of type 3 VWD, high registrations of type 3 VWD in comparison to other

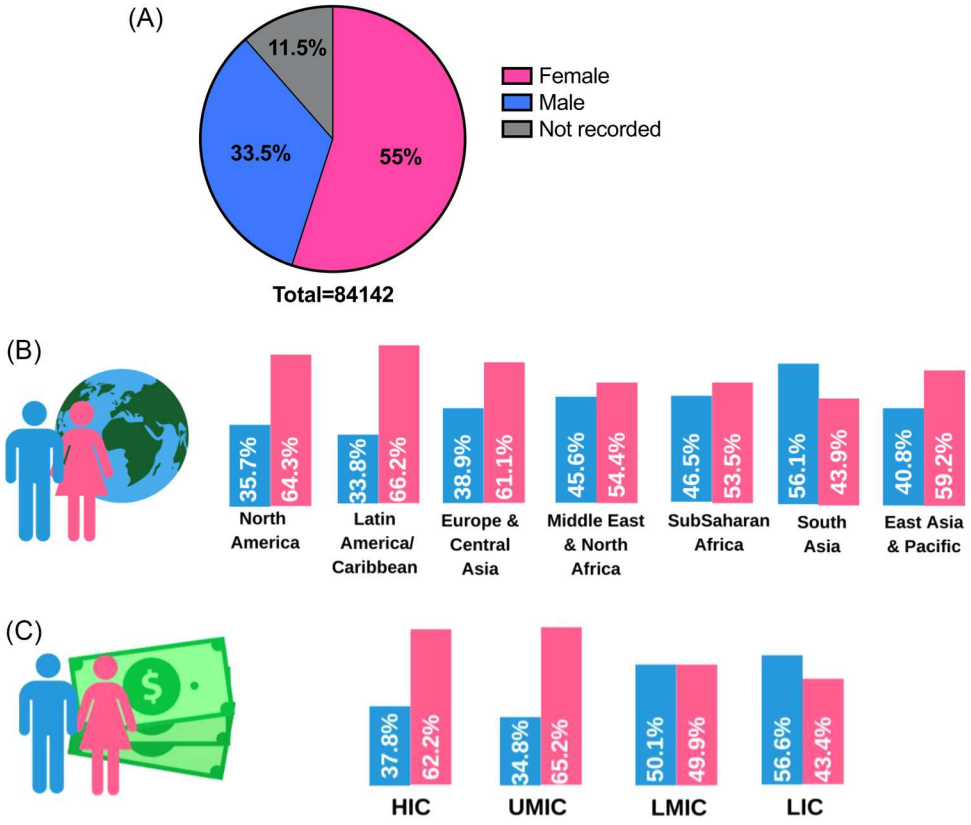

FIGURE 4 (A) Sex distribution of people registered with VWD. (B) Sex distribution of VWD by geographical regions and (C) by income status. Male indicated by blue columns, female by pink columns. HIC, high income countries; UMIC, upper middle income countries; LMIC, lower middle income countries; LIC, lower income countries.

VWD types may serve as a quality indicator identifying health care systems that are failing to diagnose other forms of VWD. While type 3 VWD is considered the most severe form, significant variability exists among those with type 1 and 2 VWD; with severe bleeding experienced by some people. Recognising the importance of diagnosis of all PwVWD will require significant and focused resource allocation, education and both laboratory and clinical investment to improve testing and awareness.

While the awareness of haemophilia has grown in the past decades this may have inadvertently reinforced beliefs that bleeding disorders only affect men.[22] It was promising to see that the majority of registered PwVWD internationally were female. However geographical variations were evident, with the percentage of males approaching or exceeding parity in the Middle East, Africa and South Asia. Income status influenced the sex of registrations, with female registrations predominating in HIC and UMIC but not lower income settings. Lower rates of females registered with VWD may relate to poor awareness of bleeding disorders in females, cultural and/or religious taboos relating to gynaecological bleeding or differences in access to healthcare for women in these settings. Lack of openness in society and healthcare surrounding discussions about heavy menstrual bleeding and postpartum haemorrhage result in missed or delayed diagnosis of bleeding disorders in women and girls.[22] These data provide an evidence base to support the development of targeted supports to improve awareness, recognition and diagnosis of bleeding disorders in women, particularly in LMIC/LIC settings.

The data regarding age of people registered with VWD is limited, reflecting their current age rather than age at diagnosis. The higher rates of paediatric registrations in LIC and LMIC may relate to younger populations in these countries or the increased numbers of individuals with type 3 VWD, who are more likely to be diagnosed at a younger age due to the severity of bleeding.[6] Unfortunately, in resource limited settings, the younger age profile may also reflect lack of access to care and shorter life expectancy. Interestingly, paediatric registrations in North America (47.5%) are second only to the Middle East and North Africa (49.8%). This may relate to higher referral rates in children in North America in comparison to adults or perioperative screening programmes, for example, prior to tonsillectomy. It may also suggest that diagnosis and/or registration of VWD in adults in North America may lag behind that of children. These data can also assist in the direction of outreach programmes, indicating that VWD awareness campaigns may be needed among HCP managing adults.

Cumulatively, these data highlight that the expected prevalence of VWD does not translate to real-life diagnoses. Although VWD affects more individuals than haemophilia, in 2019 there were 195,263 people registered with haemophilia in contrast to only 80,302 PwVWD globally recorded in the countries analyzed. Diagnosis of VWD is technical and challenging, requiring multiple laboratory assays and expert

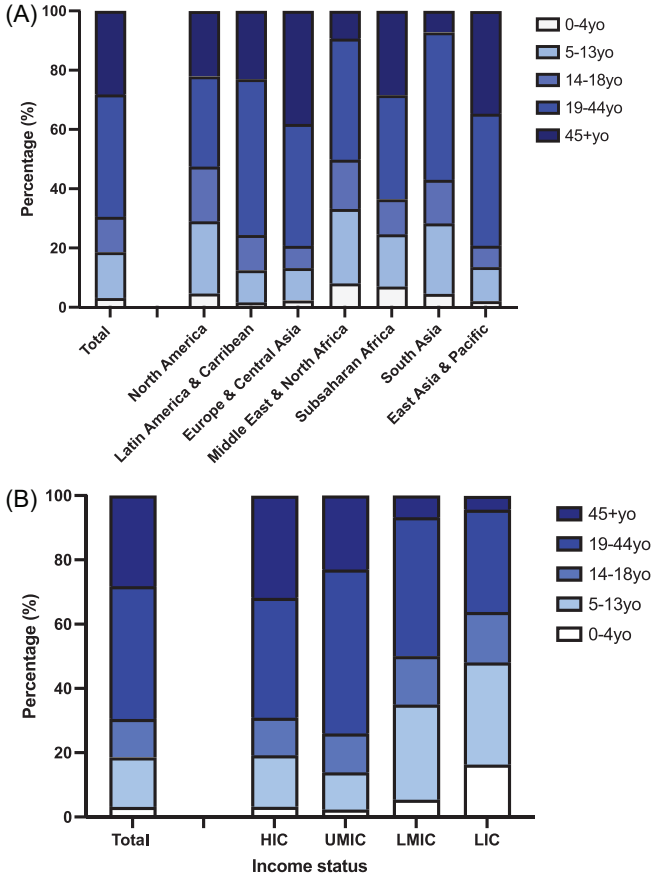

FIGURE 5 Age distribution of individuals registered with VWD by geographical region (A) and income status (B).

interpretation. This may in fact limit diagnosis and registrations and altered recommendations for VWD subtyping in resource limited settings should be considered. A simplified diagnostic pathway (e.g., diagnosis of reduced VWF levels and either DDAVP responsive/non-responsive) could encourage testing and diagnosis of VWD. Ultimately, registration is key to allow visibility and resource allocation for people with VWD. The WFH has committed to supporting this effort through (1) greater inclusion of detailed VWD data in the AGS, (2) creation of the WFH VWD Call to Action programme and (3) collection of VWD data in the World Bleeding Disorders Registry (WBDR). The WFH VWD Call to Action launched in 2018 and invites national member organizations (NMO) to commit to integrating and recognizing VWD and other rare bleeding disorders in their work, with 48 NMOs participating to date. The WBDR provides a free data collection tool to HTCs to collect patient level information on PwVWD. These tools are complimented by WFH outreach grants, twinning and mentorship programmes to encourage further education, outreach and clinical diagnostics for VWD in recipient countries.

There are limitations to acknowledge in this work. The data returned to the AGS is optional and reliant on the NMOs cooperation and participation. Data may be incomplete, especially in countries that lack national bleeding disorder registries or when detailed VWD data is not collected. With data from 110 countries internationally, this work provides important insights into the global diagnosis of VWD. Gaps still remain, particularly in Africa, but recognition of the countries not yet involved highlights those that may benefit from future enhanced VWD related supports. Furthermore, data about numbers of HTCs relies on reporting which may be incomplete. Nonetheless, these analyses provide a baseline to assess the impact of current WFH outreach programmes. In addition, these data will be used to guide and direct future advocacy and training programmes in order to improve awareness and diagnosis of VWD. This is key to ensure earlier recognition and enhanced care for PwVWD globally.

5 | CONCLUSIONS

Registration rates of PwVWD exhibit significant international variation, underscoring the need for improved programmes to tackle awareness, recognition and diagnosis of this complex but common disorder. When healthcare resources are limited, registrations of the most severe, but rare, phenotypes (type 3 VWD) predominate. These data highlight that many PwVWD remain undiagnosed and/or unregistered internationally, depriving them of access to medical care and peer support networks. Through the VWD Call to Action programme the WFH aims to address these issues and improve access to care for all PwVWD worldwide.

AUTHOR CONTRIBUTIONS

Ellia Tootoonchian, Donna Coffin collected the data; Jamie M. O'Sullivan, Ellia Tootoonchian, Jeffrey Stonebraker, Michelle Lavin analyzed the data. All authors were involved in writing and reviewing the paper.

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CONFLICT OF INTEREST STATEMENT

Jamie M. O'Sullivan, Baiba Ziemele, Alfonso Iorio, Donna Coffin, Michael Makris, Jeffrey Stonebraker have no conflicts of interest to declare. Ellia Tootoonchian is a salaried employee of the WFH. Augusto B. Federici reported advisory board participation of CSL-Behring, Grifols, Takeda, Octapharma, LFB, and Kedrion and received speaker fees from these pharmaceutical companies. Magdy El Ekiaby is stock holder and serves on the board of directors for the Egyptian Company for Biological Sciences and VIPS Business SA, Switzerland. He has received honoraria from Takeda, CSL and Roche and served on advisory board for Takeda. Magdy El Ekiaby also served as a speaker for and member of the Abbot Transfusion Health Institute. Claudia Khayat Djambas received speaker fees from CSL Behring and LFB. She acted as a principal investigator in studies with LFB and Octapharma.

Dawn Rotellini has acted as a paid consultant to Bayer, BioMarin, Sanofi, Genentech, and Spark, but all payments are made directly to the National Hemophilia Foundation. Dawn Rotellini is the Chief Operating Officer of the National Hemophilia Foundation and serves on the board of directors for the World Federation of Hemophilia—both organizations receive funding from multiple pharmaceutical manufacturers of treatments for bleeding disorders. Robert F. Sidonio has acted as a paid consultant to Guardian Therapeutics, Takeda, Octapharma, Sanofi/Sobi, Genentech/Roche, Pfizer and Bayer. He has received research funding from Takeda, Octapharma and Genentech. Glenn F. Pierce is the Vice President, Medical and serves on the board of directors for the World Federation of Hemophilia, which receives funding from multiple pharmaceutical manufacturers of treatments for bleeding disorders. Paula D. James holds research funding from Bayer and receives royalty payments from UpToDate. Michelle Lavin has served on an advisory board for CSL Behring, as a consultant for Sobi, CSL Behring and Band Therapeutics and received speaker fees from Pfizer, Sobi and Takeda.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The data used in this study is derived from the WFH AGS, a voluntary survey of the 147 WFH national member organisations. The AGS is a reliable source data used to assist with advocacy and program planning leading to improved care of people with bleeding disorders. These data were used with the approval of the WFH and with the specified purpose of improving our understanding of the burden of VWD internationally.

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REFERENCES

1. Connell NT, Flood VH, Brignardello-Petersen R, et al. ASH ISTH NHF WFH 2021 guidelines on the management of von Willebrand disease. *Blood Adv*. 2021;5(1):301-325.
2. James PD, Connell NT, Ameer B, et al. ASH ISTH NHF WFH 2021 guidelines on the diagnosis of von Willebrand disease. *Blood Adv*. 2021;5(1):280-300.
3. Lavin M, Aguila S, Dalton N, et al. Significant gynecological bleeding in women with low von Willebrand factor levels. *Blood Adv*. 2018;2(14):1784-1791.
4. Rodeghiero F, Castaman G, Dini E. Epidemiological investigation of the prevalence of von Willebrand's disease. *Blood*. 1987;69(2):454-459.
5. Bowman M, Hopman WM, Rapson D, et al. The prevalence of symptomatic von Willebrand disease in primary care practice. *J Thromb Haemost*. 2010;8(1):213-216.
6. Noone D, Skouw-Rasmussen N, Lavin M, et al. Barriers and challenges faced by women with congenital bleeding disorders in Europe: results of a patient survey conducted by the European Haemophilia Consortium. *Haemophilia*. 2019;25(3):468-474.
7. van Galen KPM, Lavin M, Skouw-Rasmussen N, et al. Clinical management of woman with bleeding disorders: a survey among European haemophilia treatment centres. *Haemophilia*. 2020;26(4):1-6.
8. Iorio A, Stonebraker JS, Chambost H, et al. Establishing the prevalence and prevalence at birth of hemophilia in males: a meta-analytic approach using national registries. *Ann Intern Med*. 2019;171(8):540-546.
9. Stonebraker JS, Bolton-Maggs PHB, Soucie JM, et al. A study of variations in the reported haemophilia A prevalence around the world. *Haemophilia*. 2010;16(1):20-32.
10. Stonebraker JS, Bolton-Maggs PHB, Michael Soucie J, et al. A study of variations in the reported haemophilia B prevalence around the world. *Haemophilia*. 2012;18(3):e91-4.
11. Lavin M, Aguila S, Schneppenheim S, et al. Novel insights into the clinical phenotype and pathophysiology underlying low VWF levels. *Blood*. 2017;130(21):2344-2353.
12. Atiq F, Saes JL, Punt MC, et al. Major differences in clinical presentation, diagnosis and management of men and women with autosomal inherited bleeding disorders. *EClinicalMedicine*. 2021;32:100726.
13. Sidonio RF, Haley KM, Fallaize D. Impact of diagnosis of von Willebrand disease on patient outcomes: analysis of medical insurance claims data. *Haemophilia*. 2017;23(5):743-749.
14. Federici AB. Towards a more automatic and rapid laboratory diagnosis of von Willebrand disease. *Thromb Res*. 2016;141:198-201.
15. Corrales-Medina FF, Federici AB, Srivastava A, et al. A need to increase von Willebrand disease awareness: vwdtest.com – a global initiative to help address this gap. *Blood Rev*. 2023;58:101018.
16. World Federation of Hemophilia. VWD Call to Action.
17. Stonebraker JS, Bolton-Maggs PHB, Brooker M, et al. The World Federation of Hemophilia annual global survey 1999–2018. *Haemophilia*. 2020;26(4):591-600.
18. Bank World, World Bank Country and Lending Groups classification.
19. World Federation of Hemophilia. Find a haemophilia treatment centre.
20. Escobar MA, Beijlevelt M, Loney A, et al. World Federation of Hemophilia international hemophilia training fellowship program: 50 years of enhancing global care. *Haemophilia*. 2022;28(5):S129-S131.
21. Lavin M, Christopherson P, Grabell J, et al. Longitudinal bleeding assessment in von Willebrand disease utilizing an interim bleeding score. *J Thromb Haemost*. 2022;20(10):2246-2254.
22. Weyand AC, James PD. Sexism in the management of bleeding disorders. *Res Pract Thromb Haemost*. 2021;5(1):51-54.

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