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Epidemiological aspects and complications of congenital hemophilia A in Brazil

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Acknowledgment

This thesis represents not only the culmination of a long academic journey but also the result of a year filled with enriching experiences in the Netherlands — a country so different from my own, yet one that welcomed me with generosity and offered a period of learning and personal growth.

I cherish every moment I spent in Leiden and would like to express my heartfelt thanks to all those who, in one way or another, contributed to making this chapter possible and who helped turn this experience into an unforgettable one.

In particular, I deeply thank my supervisors, Anske, Samantha, and Suely, for their invaluable guidance, clarity and encouragement. You taught me the power of collaboration and how much we can gain by sharing knowledge. You were true facilitators of my work, and I am sincerely thankful.

To Yvonne, thank you for your unwavering support, kindness, and patience throughout this journey. I would also like to thank the families of the participants included in the research for this thesis for believing in the seriousness of our work. Our greatest motivation is to find evidence and better solutions to improve the quality of life for our patients.

To all the friends at the Department of Clinical Epidemiology in Leiden, my sincere and warmest thanks.

Curriculum Vitae

Leticia Lemos Jardim was born on June 25, 1987, in Belo Horizonte, Brazil. She obtained her bachelor's degree in Biomedical Sciences in 2010, followed by a master's degree and her first PhD degree in Sciences Applied to Adult Health from the Federal University of Minas Gerais (Brazil) in 2015 and 2019, respectively. In 2016, she was awarded a scholarship grant for international doctoral internships at the Clinical Epidemiology in Leiden University Medical Center, where she started her second PhD research, supervised by Prof. Dr. Anske van der Bom. During her PhD, she presented her research findings at various national and international conferences. She is currently working as a professor in the Department of Public Health of the Faculty of Medical Sciences of Minas Gerais (Brazil), and she is an epidemiological researcher at the Research Group on Health Policies and Social Protection at the René Rachou Institute (Brazil).

PORTFOLIO

	Year	Hours
Courses		
Leiden University Onboarding Programme Inform & Connect (2 activities) (done)	2025	5
Epidemiology an Introduction	2016	12
Writing course	2016	24
Advanced statistical methods in epidemiology	2019	75
Attended lectures, LUMC presentations, participation in meetings		
Journal Club (thrombosis and haemostasis)	2017	2
Scientific Committee	2017	2
Traineeship abroad		
Immunology laboratory (Amsterdam)	2016	28
Thrombin generation (Maastricht)	2017	30
Other activities		
Organization of the book " <i>Epidemiology and Biostatistics - Transforming data into information for health</i> "	2024	40
Teaching activities		
Epidemiology and biostatistics	2021-2025	40

LIST OF PUBLICATIONS

Publications resulting from this thesis

1. **Jardim LL**, van der Bom JG, Caram-Deelder C, Gouw SC, Leal Cherchiglia M, Meireles Rezende S. Mortality of patients with haemophilia in Brazil: First report. *Haemophilia*. 2019 May;25(3):e146-e152. doi: 10.1111/hae.13730. Epub 2019 Mar 15. PMID: 30875453.
2. **Jardim LL**, Chaves DG, Rezende SM. Development of inhibitors in hemophilia A: An illustrated review. *Res Pract Thromb Haemost*. 2020 May 26;4(5):752-760. doi: 10.1002/rth2.12335. PMID: 32685884; PMCID: PMC7354390.
3. **Jardim LL**, Santana MP, Chaves DG, van der Bom JG, Meireles Rezende S. Risk factors for antibody formation in children with hemophilia. *Blood Coagulation & Fibrinolysis*. 32(7):p 443-450, October 2021.
4. **Jardim LL**, van der Bom J, Brommonschenkel CC, Gouw SC, Rezende SM; on the behalf of the HEMFIL Study Group. Inhibitor incidence in haemophilia A under exclusive use of a third-generation recombinant factor VIII concentrate: results of the HEMFIL Cohort Study. *Br J Haematol*. 2019 Jul;186(1):152-155.
5. **Jardim LL**, Chaves DG, Silveira-Cassette ACO, Simões E Silva AC, Santana MP, Cerqueira MH, Prezotti A, Lorenzato C, Franco V, van der Bom JG, Rezende SM. Immune status of patients with haemophilia A before exposure to factor VIII: first results from the HEMFIL study. *Br J Haematol*.
6. de Oliveira LMM, **Jardim LL**, Santana MAP, Cerqueira MH, Lorenzato CS, Franco VKB, Zuccherato LW, Rezende SM, Chaves DG. Effect of the First Factor VIII Infusions on Immunological Biomarkers in Previously Untreated Patients with Hemophilia A from the HEMFIL Study. *Thromb Haemost*. 2021 Jul;121(7):891-899.
7. **Jardim LL**, Schieber TA, Santana MP, Cerqueira MH, Lorenzato CS, Franco VKB, Zuccherato LW, da Silva Santos BA, Chaves DG, Ravetti MG, Rezende SM. Prediction of inhibitor development in previously untreated and minimally treated children with severe and moderately severe hemophilia A using a machine-learning network. *J Thromb Haemost*. 2024 Sep;22(9):2426-2437.

Other publications

1. Santana MSP, Chaves DG, Souza RP, **Jardim LL**, Zuccherato LW, Santos BAS, Cerqueira MH, Lorenzato CS, Franco VKB, Rezende SM. Longitudinal Evaluation of Immunological Biomarkers in Previously Untreated/Minimally Treated Patients With Severe and Moderately Severe Haemophilia A During Exposure to Factor VIII: Results From the HEMFIL Study. *Haemophilia*. 2025 May 25. doi: 10.1111/hae.70048.
2. Zuccherato LW, Souza RP, Camelo RM, Dias MM, **Jardim LL**, Santana MAP, Oliveira AG, Lorenzato CS, Cerqueira MH, Franco VKB, Ribeiro RA, Etto LY, Roberti MDRF, Callado FMA, de Cerqueira MAF, Pinto ISS, Garcia AA, Aneqawa TH, Neves DCF, Tan DM, Tou RP, Chaves DG, van der Bom J, Rezende SM; HEMFIL Study and the Brazilian Immune Tolerance (BrazIT) Study. Large deletions and small insertions and deletions in the factor VIII gene predict unfavorable immune tolerance induction outcome in people with severe hemophilia A and high-responding inhibitors. *Thromb Res*. 2024 Oct;242:109115. doi: 10.1016/j.thromres.2024.109115.
3. **Jardim LL**, Franco MB, de Oliveira NR, de Carvalho BN, Basques F, Ribeiro DD, Lisman T, Pereira LS, Rezende SM. Hypocoagulability in severe yellow fever infection is associated with bleeding: results

- from a cohort study. *Res Pract Thromb Haemost.* 2024 Apr 26;8(4):102427. doi: 10.1016/j.rpth.2024.102427. eCollection 2024 May.
4. Machado AV, Ferreira WE, Vitória MAÁ, Magalhães Júnior HM, **Jardim LL**, Menezes MAC, Santos RPO, Vargas FL, Pereira EJ. COVID-19 and health systems in Brazil and around the world: effects on the working conditions and health of health workers. *Cien Saude Colet.* 2023 Oct;28(10):2965-2978. doi: 10.1590/1413-812320232810.10102023. Epub 2023 Jun 28.
 5. Franco MB, **Jardim LL**, de Carvalho BN, Basques F, Ribeiro DD, Pereira LS, Rezende SM. Deficiency of coagulation factors is associated with the bleeding diathesis of severe yellow fever. *Ann Hematol.* 2023 Jul;102(7):1939-1949. doi: 10.1007/s00277-023-05262-x. Epub 2023 May 24.
 6. Silva GDMD, Souza AA, Castro MSM, Miranda WD, **Jardim LL**, Sousa RP. Influence of socioeconomic inequality on the distribution of COVID-19 hospitalizations and deaths in Brazilian municipalities, 2020: an ecological study. *Epidemiol Serv Saude.* 2023 Feb 10;32(1):e2022303. doi: 10.1590/S2237-96222023000100021. eCollection 2023.
 7. Santana MAP, Chaves DG, Camelo RM, Zuccherato LW, **Jardim LL**, Rezende SM; in behalf of the HEMFIL and BrazIT Study Groups. Prevalence of sporadic haemophilia A. *Haemophilia.* 2023 Mar;29(2):668-670. doi: 10.1111/hae.14742. Epub 2023 Jan 27.
 8. Camelo RM, Dias MM, Caram-Deelder C, Gouw S, de Magalhães LP, Zuccherato LW, **Jardim LL**, de Oliveira AG, de Albuquerque Ribeiro R, Franco VKB, do Rosário Ferraz Roberti M, de Araújo Callado FMR, Etto LY, de Cerqueira MAF, Cerqueira MH, Lorenzato CS, de Souza IS, Serafim ÉSS, Garcia AA, Aneqawa TH, Neves DCF, Tan DM, van der Bom J, Rezende SM; Brazilian Immune Tolerance (BrazIT) Study group. *J Thromb Haemost.* Time between inhibitor detection and start of immune tolerance induction: Association with outcome in the BrazIT study. 2022 Nov;20(11):2526-2537. doi: 10.1111/jth.15878. Epub 2022 Sep 26.
 9. Martins NNN, **Jardim LL**, Pereira LS, Rezende SM, Gonçalves MLP. Blue-green cytoplasmic inclusions in neutrophils/monocytes of patients with yellow fever. *Int J Lab Hematol.* 2022 Aug;44(4):e168-e171. doi: 10.1111/ijlh.13827.
 10. Rezende SM, **Jardim LL**, Lúcia Magalhães V, Teixeira Melo H, Araujo JPB, Genovez G. Building the National Program of Inherited Bleeding Disorders in Brazil. *Blood Adv.* 2019 Dec 6;3(Suppl 1):48-50. doi: 10.1182/bloodadvances.2019GS121559.
 11. Duarte RCF, Rios DRA, Rezende SM, **Jardim LL**, Ferreira CN, Carvalho MDG. Standardization and evaluation of the performance of the thrombin generation test under hypo- and hypercoagulability conditions. *Hematol Transfus Cell Ther.* 2019 Jul-Sep;41(3):244-252. doi: 10.1016/j.htct.2018.08.007. Epub 2018 Dec 31.
 12. Zuccherato LW, Elói-Santos SM, **Jardim LL**, Camelo RM, Chaves DG, Souza RP, Hollox EJ, Rezende SM. Variation of rs3754689 at lactase gene and inhibitors in admixed Brazilian patients with hemophilia A. *Haematologica.* 2019 Nov;104(11):e527-e529. doi: 10.3324/haematol.2019.220608. Epub 2019 Mar 14.
 13. Zuccherato LW, Roberti MRF, **Jardim LL**, Rezende SM. Successful immune tolerance in a young female with inhibitor and severe haemophilia A due to a complex genetic rearrangement. *Haemophilia.* 2018 Jul;24(4):e283-e285. doi: 10.1111/hae.13560. Epub 2018 Jul 13.

AWARDS

1. "Best Hemostasis Work" Award - Brazilian Congress of Hematology, Hemotherapy and Cell Therapy - HEMO 2023 with the study 'Prediction of inhibitor development in children with severe hemophilia A: artificial intelligence analysis of the Hemfil study'. HEMO Congress in São Paulo.
2. 'Reach the World Travel Grant' by the International Society on Thrombosis and Haemostasis (ISTH) to present the study 'Prediction of Inhibitor Development in Previously Untreated Children with Hemophilia A using a Machine-Learning Network and Information Theory Quantifiers: Results from the HEMFIL Cohort Study.' at the ISTH 2023 Congress in Montreal.
3. 'Reach the World Travel Grant' by the International Society on Thrombosis and Haemostasis (ISTH) to present the study 'Prevalence of sporadic haemophilia A: An updated analysis of two cohort studies. In: International Society on Thrombosis and Haemostasis ' at the ISTH 2022 Congress in London.
4. 'Reach the World Travel Grant' by the International Society on Thrombosis and Haemostasis (ISTH) to present the study 'Clinical Characteristics and Incidence of Inhibitors in Previously Untreated Children with Haemophilia: An Update of the Hemfil Cohort Study.' at the ISTH 2021 Congress in Philadelphia.
5. 'Reach the World Travel Grant' by the International Society on Thrombosis and Haemostasis (ISTH) to present the study 'Clinical Characteristics and Incidence of Inhibitors in Patients with Haemophilia: Results of the HEMIL Cohort Study' at the ISTH 2019 Congress in Melbourne.
6. 'Reach the World Travel Grant' by the International Society on Thrombosis and Haemostasis (ISTH) to present the study 'Incidence in Hemophilia A under Exclusive Use of a Third-generation Recombinant Factor VIII Concentrate: Results of the HEMFIL Cohort Study.' at the ISTH 2018 Congress in Dublin.
7. Milwaukee SSC Award (The highest scored Reach the World abstracts), The Scientific and Standardization Committee (SSC) ISTH – Montpellier and the study: 'Immunological Profile of Previously Untreated Patients with Haemophilia A: Results from the HEMFIL Study.' at the ISTH 2016 Congress in Montpellier.

Images of the Thesis

The tree on the cover of this book is called the Yellow Ipê. It is native to Brazil and is one of the country's most iconic trees. It blooms even in times of drought, symbolizing strength, resilience, and the ability to overcome challenges, as well as the beauty that can emerge even in the face of adversity.

The “Graúna”, presented in all the chapters of this book, is a Portuguese denomination for a black bird. It is considered the most striking and popular drawing by cartoonist Henfil.

The HEMFIL is a Brazilian cohort study named to honor Mr. Henrique de Souza Filho (1944 - 1988), also known as Henfil. Henrique was one of the greatest Brazilian cartoonists, also a journalist and writer, and the creator of characters with great popularity in the country. Henfil had severe hemophilia A and died from AIDS, after contamination with clotting factor concentrates.

