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Understanding hypercoagulability: determinants and impact on cardiometabolic disease

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References

1. Egeberg O. Inherited antithrombin deficiency causing thrombophilia. *Thromb Haemost.* 1965; 13: 516–30.
2. Lee DH, Dane MJ, van den Berg BM, Boels MG, van Teeffelen JW, de Mutsert R, den Heijer M, Rosendaal FR, van der Vlag J, van Zonneveld AJ, Vink H, Rabelink TJ. Deeper penetration of erythrocytes into the endothelial glycocalyx is associated with impaired microvascular perfusion. *PLoS One.* 2014; 9: e96477.
3. Rabelink TJ, de Boer HC, van Zonneveld AJ. Endothelial activation and circulating markers of endothelial activation in kidney disease. *Nat Rev Nephrol.* 2010; 6: 404–14.
4. Dane MJ, van den Berg BM, Avramut MC, Faas FG, van der Vlag J, Rops AL, Ravelli RB, Koster BJ, van Zonneveld AJ, Vink H, Rabelink TJ. Glomerular endothelial surface layer acts as a barrier against albumin filtration. *Am J Pathol.* 2013; 182: 1532–40.
5. de Jongh RT, Serne EH, RG IJ, de Vries G, Stehouwer CD. Impaired microvascular function in obesity: implications for obesity-associated microangiopathy, hypertension, and insulin resistance. *Circulation.* 2004; 109: 2529–35.
6. van der Velden AIM, van den Berg BM, de Mutsert R, van der Vlag J, Jukema JW, Rosendaal FR, Rabelink TJ, Vink H. Microvascular differences in individuals with obesity at risk of developing cardiovascular disease. *Obesity (Silver Spring).* 2021; 29: 1439–44.
7. Lee DH, Dane MJ, van den Berg BM, Boels MG, van Teeffelen JW, de Mutsert R, den Heijer M, Rosendaal FR, van der Vlag J, van Zonneveld AJ, Vink H, Rabelink TJ, group NEOs. Deeper penetration of erythrocytes into the endothelial glycocalyx is associated with impaired microvascular perfusion. *PloS one.* 2014; 9: e96477.
8. Vlahu CA, Lemkes BA, Struijk DG, Koopman MG, Krediet RT, Vink H. Damage of the endothelial glycocalyx in dialysis patients. *J Am Soc Nephrol.* 2012; 23: 1900–8.
9. Morelli VM, Lijfering WM, Bos MHA, Rosendaal FR, Cannegieter SC. Lipid levels and risk of venous thrombosis: results from the MEGA-study. *Eur J Epidemiol.* 2017; 32: 669–81.
10. Huang Y, Ge H, Wang X, Zhang X. Association Between Blood Lipid Levels and Lower Extremity Deep Venous Thrombosis: A Population-Based Cohort Study. *Clin Appl Thromb Hemost.* 2022; 28: 10760296221121282.
11. Deguchi H, Pecheniuk NM, Elias DJ, Averell PM, Griffin JH. High-density lipoprotein deficiency and dyslipoproteinemia associated with venous thrombosis in men. *Circulation.* 2005; 112: 893–9.
12. Ageno W, Becattini C, Brighton T, Selby R, Kamphuisen PW. Cardiovascular risk factors and venous thromboembolism: a meta-analysis. *Circulation.* 2008; 117: 93–102.
13. Chamberlain AM, Folsom AR, Heckbert SR, Rosamond WD, Cushman M. High-density lipoprotein cholesterol and venous thromboembolism in the Longitudinal Investigation of Thromboembolism Etiology (LITE). *Blood.* 2008; 112: 2675–80.
14. Boden G, Vaidyula VR, Homko C, Cheung P, Rao AK. Circulating Tissue Factor Procoagulant Activity and Thrombin Generation in Patients with Type 2 Diabetes: Effects of Insulin and Glucose. *The Journal of Clinical Endocrinology & Metabolism.* 2007; 92: 4352–8.
15. Beijers HJBH, Ferreira I, Spronk HMH, Bravenboer B, Dekker JM, Nijpels G, ten Cate H, Stehouwer CDA. Impaired glucose metabolism and type 2 diabetes are associated with hypercoagulability: potential role of central adiposity and low-grade inflammation – The Hoorn Study. *Thromb Res.* 2012; 129: 557–62.
16. Tripodi A, Branchi A, Chantarangkul V, Clerici M, Merati G, Artoni A, Mannucci PM. Hypercoagulability in patients with type 2 diabetes mellitus detected by a thrombin generation assay. *Journal of Thrombosis and Thrombolysis.* 2011; 31: 165–72.
17. Festa A, D'Agostino R, Jr, Tracy RP, Haffner SM. Elevated Levels of Acute-Phase Proteins and Plasminogen Activator Inhibitor-1 Predict the Development of Type 2 Diabetes: The Insulin Resistance Atherosclerosis Study. *Diabetes.* 2002; 51: 1131–7.

18. Festa A, Williams K, Tracy RP, Wagenknecht LE, Haffner SM. Progression of plasminogen activator inhibitor-1 and fibrinogen levels in relation to incident type 2 diabetes. *Circulation*. 2006; 113: 1753–9.
19. Bertoni AG, Burke GL, Owusu JA, Carnethon MR, Vaidya D, Barr RG, Jenny NS, Ouyang P, Rotter JI. Inflammation and the incidence of type 2 diabetes: the Multi-Ethnic Study of Atherosclerosis (MESA). *Diabetes Care*. 2010; 33: 804–10.
20. Duncan BB, Schmidt MI, Offenbacher S, Wu KK, Savage PJ, Heiss G. Factor VIII and other hemostasis variables are related to incident diabetes in adults. The Atherosclerosis Risk in Communities (ARIC) Study. *Diabetes Care*. 1999; 22: 767–72.
21. Yarmolinsky J, Bordin Barbieri N, Weinmann T, Ziegelmann PK, Duncan BB, Schmidt MI. Plasminogen activator inhibitor-1 and type 2 diabetes: a systematic review and meta-analysis of observational studies. *Sci Rep*. 2016; 6: 17714.
22. Frankel DS, Meigs JB, Massaro JM, Wilson PW, O'Donnell CJ, D'Agostino RB, Tofler GH. Von Willebrand factor, type 2 diabetes mellitus, and risk of cardiovascular disease: the framingham offspring study. *Circulation*. 2008; 118: 2533–9.

List of publications

Published articles included in this thesis

Jihee Han, Astrid van Hylckama Vlieg, Renée de Mutsert, Frits R. Rosendaal, Jeroen HPM van der Velde, Sebastiaan C. Boone, Esther Winters-van Eekelen, Saskia le Cessie, and Ruifang Li-Gao. "Associations of coagulation parameters and thrombin generation potential with the incidence of type 2 diabetes: mediating role of glycoprotein acetylation." *European Journal of Epidemiology* (2024)

Jihee Han, Ruifang Li-Gao, Renée de Mutsert, Frits R. Rosendaal, and Astrid van Hylckama Vlieg. "Association between venous thromboembolism-associated genetic variants, coagulation factor levels, and thrombin generation potential." *Ejhaem* (2024).

Jihee Han, Astrid van Hylckama Vlieg, and Frits R. Rosendaal. "Genomic science of risk prediction for venous thromboembolic disease: convenient clarification or compounding complexity." *Journal of Thrombosis and Haemostasis* (2023).

Lushun Yuan, **Jihee Han**, Anouk IM van der Velden, Hans Vink, Renée de Mutsert, Frits R. Rosendaal, Astrid van Hylckama Vlieg, Ruifang Li-Gao, Ton J. Rabelink, and Bernard M. van den Berg. "Sex-specific association between microvascular health and coagulation parameters: the Netherlands Epidemiology of Obesity study." *Journal of Thrombosis and Haemostasis* (2023).

Submitted

Jihee Han, Vincent ten Cate, Ruifang Li-Gao, Alejandro Pallares Robles, Linjun Ao, Raymond Noordam, Frits R. Rosendaal, Philipp S. Wild, Astrid van Hylckama Vlieg. "Genome-wide identification of loci associated with plasma coagulation factor IX activity."

Vincent ten Cate*, **Jihee Han***, Alejandro Pallares Robles*, Marine Germain-Lambert*, Ruifang Li-Gao, Gonneke Willemsen, Frits R. Rosendaal, Henri M.H Spronk, Tilman M Hackeng, Dorret Boomsma, David-Alexandre Trégouët, Pierre Emmanuel Morange, Jouke Jan Hottenga, Hugo ten Cate, Astrid van Hylckama Vlieg, Philipp S. Wild, on behalf of the CROSSLINK consortium "Genome-wide meta-analyses and integrative multi-omics analysis of endogenous thrombin generation potential in the CROSSLINK consortium."

Lushun Yuan*, **Jihee Han***, Renée de Mutsert, Shuzhen Cheng, Frits R. Rosendaal, Dennis O. Mook-Kanamori, J. Wouter Jukema, Hans Vink, Bernard M. van den Berg, Ton J. Rabelink, Astrid van Hylckama Vlieg, Uwe J. F. Tietge, Ko Willems van Dijk, Ruifang Li-Gao. "Association between high-density lipoprotein composition and coagulation factors in the Netherlands Epidemiology of Obesity study."

*Contributed equally

Supplemental Materials are available in the published article or from Jihee Han on request.

PhD Portfolio

Courses	Hours	Year
Scientific Conduct for PhDs	5	2021
PhD Introductory Meeting	5	2022
Basic Methods and Reasoning in Biostatistics	42	2022
BROK (exemption)	-	-
Epidemiology - The First Round	84	2021
Gene Finding: Genome-Wide Association Studies and Beyond	21	2021
Causal Inference	84	2022
Prediction Modeling and Intervention Research	84	2022
Statistical Aspects of Clinical Trials	28	2023
Meta-Analysis	42	2023
Survival Analysis	42	2023
Study Design and Analysis (Schiermonnikoog)	56	2023
Capita Selecta	56	2024
Regression Analysis	42	2024
Skill for the Practicing Epidemiologist	28	2024
Advanced Epidemiology Methods	56	2024
Congress attendance and presentations	Year	
NVTH symposium and PhD course	2022	
Oral presentation, Annual Dutch Diabetes Research Meeting	2022	
Oral and poster presentations, NVTH symposium and PhD course	2023	
Oral (2x) and poster presentations, ISTH congress	2023	
Oral and poster presentations, ECTH congress	2023	
Poster presentation, NVTH symposium and PhD course	2024	
Poster (2x) presentations, ISTH congress	2024	
Oral presentation, CHARGE consortium meeting	2024	
Oral presentation, HDHL NUTRIMMUNE midterm symposium	2025	
Oral (2x) presentations, Annual WEON conference	2025	
Teaching activities	Year	
Academic and Scientific Training Year 2 (BSc Medicine)	2023	
Clinical Research in Practice (MSc Biomedical Sciences)	2024	
Academic and Scientific Training Year 2 (BSc Medicine)	2025	
Academic and Scientific Training Year 1 (BSc Medicine)	2025	
Academic and Scientific Training Year 3 (BSc Medicine)	2025	
Student supervision	Year	
Shirley Bao, biomedical sciences, BS Internship	2024	
Sophie Matthijssen, biomedical sciences, MS Internship	2024	
Awards and prizes	Year	
NVTH 2023 Award for Scientific Excellence	2023	
ISTH 2023 Early Career Award	2023	
ECTH 2023 Prix D'Honneur de la Jeunesse	2023	

Curriculum Vitae

Jihee Han was born on the 1st of June 1992 in Boryeong, Republic of Korea. She completed her pre-university education at Daechon Girls' High School in Boryeong, Republic of Korea, between 2008 and February 2011. She majored in nutrition science and food management and minored in convergence design at Ewha Womans University, Seoul, Republic of Korea, between 2011 and 2016. After obtaining her bachelor's degree, she started her master's program in nutrition science and food management at the same university. She focused on epigenetic and genetic risk factors of metabolic diseases under the supervision of Prof. dr. Yoon Jung Park. In 2018, she received her master's degree with distinction. She worked as a researcher at Korea National Cancer Center in 2018, at a gene-based personalized healthcare company in 2019, and at a pharmaceutical company between 2020 and 2021.

In 2021, she received a scholarship from Chungcheongnam-do Human Resources Development Foundation to start her PhD program at the Department of Clinical Epidemiology at Leiden University Medical Center, Netherlands, under the supervision of Prof. dr. Frits R. Rosendaal, Dr. Astrid van Hylckama Vlieg, and Dr. Ruifang Li-Gao. During her PhD, she studied the genetic and clinical determinants of coagulation factors levels and the effect of a disturbed coagulation system on cardiometabolic diseases with a focus on venous thromboembolism. She published her research in peer-reviewed journals and presented at national and international conferences where she received multiple awards for her research. With the completion of her PhD, she also completed her training as a clinical epidemiologist (Epidemiologist B).

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To all my colleagues at the Department of Clinical Epidemiology, thank you for the enjoyable and intellectually enriching time we shared. I thank Dr. Renée de Mutsert, Ingeborg, and Petra for their generous support with the NEO cohort. Your patience in answering my many questions and responding to all my requests with kindness truly made my work possible. A special thank you to Yvonne Souverein, whose administrative support helped me navigate all the practical challenges of living and working here. I am especially grateful to my office mates (Louise, Martha, Qinqu, and Jamilla). Our coffee breaks, snacks, and chats were a great source of comfort and joy. To the Epi VTE group and T&H group, thank you for the great times and helpful discussions during the meetings and conferences. To my coffee and drink mates, Eleonora, Marieke, and Ruben, our conversations were always delightful and provided exactly the boost I needed.

To my dear paranympths, Keyong Deng and Lodewijk Pet, thank you from the bottom of my heart. Keyong, your dedication and passion for research have always inspired me. Lodewijk, I wish I had discovered your brilliance and sense of humor earlier. You made my PhD journey so much more enjoyable.

Lastly and most importantly, I want to thank my family in Korea, who have always cared for me more than I care for myself, despite the distance. To my parents, your endless belief in me gave me the courage to pursue anything. Thank you always, and I love you. And to my beloved husband, Woojun, thank you for believing in me when I couldn't believe in myself. Your support made me a stronger and better version of who I am. I am endlessly grateful.