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Exhaled breath analysis for diagnosis of acute respiratory distress syndrome

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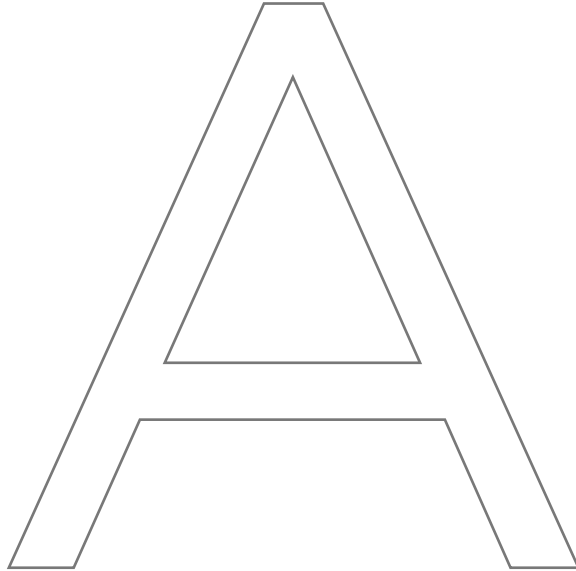
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APPENDICES

Contributing authors and affiliations

Author contributions

Curriculum vitae

List of publications

PhD portfolio

Dankwoord

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AUTHOR CONTRIBUTIONS

Chapter 2

LAH and LDJB designed the study, had full access to all the data in the study, take full responsibility for the integrity of the data, accuracy of the data analysis, and prepared the initial draft of this manuscript. All authors approved the submitted version of this manuscript.

Chapter 3

LDJB and MJS designed the study. LDJB wrote the study protocol. ARMV, NFLH, MRS, DCJJB, RS, TMEN and LAH advised on the study design and participated in the study protocol. All authors approved the study design. LDJB calculated the sample size and designed the statistical analysis plan. LDJB and LAH prepared the initial draft of this manuscript. All authors approved the submitted version of this manuscript.

Chapter 4

LDJB and MJS designed the study. LDJB wrote the study protocol. ARMV, NFLH, MRS, DCJJB, RMS, TMEN, IG and LAH advised on the study design and participated in the study protocol. All authors approved the study design. AL, LAH and MRS participated in data collection. Analysis was performed by LAH. LDJB and LAH prepared the initial draft of this manuscript. All authors approved the submitted version of this manuscript.

Chapter 5

LAH and LDJB designed the study, had full access to all the data in the study, take full responsibility for the integrity of the data, accuracy of the data analysis, and prepared the initial draft of this manuscript. NFLH, MRS, MJS, DCJJB, and RMS advised on the study design and participated in the study protocol. LAH, FLIMV, NFLH, MRS, HAG, SCG, RMS, and LDJB participated in data collection. The analysis was performed by LAH. All authors approved the submitted version of this manuscript.

Chapter 6

LDJB and MJS designed the study. LDJB wrote the study protocol. ARMV, NFLH, MRS, DCJJB, RMS, TMEN, IG and LAH advised on the study design and participated in the study protocol. All authors approved the study design. LAH, NFLH and MRS participated in data collection. Analysis was performed by LAH, CP and RR. LDJB and LAH prepared the initial draft of this manuscript. All authors approved the submitted version of this manuscript.

Chapter 7

SZ, TvdP, MJS and LDJB designed the study. LAH, NFLH, MRS, DWF and LDJB participated in data collection and processing. Analysis was performed by SZ, NFLH and LDJB. SZ, LAH and LDJB prepared the initial draft of this manuscript. All authors approved the submitted version of this manuscript.

CURRICULUM VITAE

Laura Anna Hagens, geboren op 6 oktober 1992 in Enschede, groeide op in het kleine dorpje Rekken in de Achterhoek op een steenworp afstand van de Duitse grens. In 2011 behaalde ze haar VWO diploma in de richting natuur en techniek & natuur en gezondheid aan Het Assink Lyceum te Haaksbergen. Haar brede interesse in bèta vakken en het menselijk lichaam zette ze voort in de opleiding Technische Geneeskunde aan de Universiteit Twente in Enschede. Haar master heeft ze in 2018 afgerond op de intensive care van het Radboud UMC, onder supervisie van professor Hans van der Hoeven en dr. Lianne Roesthuis. In mei 2018 begon ze haar promotietraject om zich te ontwikkelen in het klinisch onderzoek en zich te specialiseren in een specifiek onderwerp. Deze nieuwe uitdaging was helemaal in Amsterdam op de intensive care van het Amsterdam UMC, locatie AMC en gericht op ademgasanalyse voor de diagnose van acute longschade (Acute Respiratory Distress Syndrome, ARDS). Tijdens dit promotietraject heeft Laura van begin tot eind een belangrijke rol gehad in DARTS, een groot observationeel onderzoek. Sinds 2021 is ze daarnaast de uitdaging aangegaan om de kwaliteit van het onderzoek op de intensive care naar een hoger niveau te tillen in de rol van kwaliteit coördinator. Vorig jaar is haar zoon Ilja geboren. Nu, een jaar later, zijn de resultaten van het onderzoek en daarmee van haar promotietraject, te lezen in dit proefschrift.

LIST OF PUBLICATIONS

Smit MR, de Vos J, Pisani L, **Hagens LA**, Almondo C, Heijnen NFL, Schnabel RM, van der Horst ICC, Bergmans DCJJ, Schultz MJ, Bos LDJ; DARTS Consortium.

Comparison of Linear and Sector Array Probe for Handheld Lung Ultrasound in Invasively Ventilated ICU Patients.

Ultrasound Med Biol. 2020 Dec;46(12):3249-3256. doi: 10.1016/j.ultrasmedbio.2020.08.016. Epub 2020 Sep 19.

Aman J, Duijvelaar E, Botros L, Kianzad A, Schippers JR, Smeele PJ, Azhang S, Bartelink IH, Bayoumy AA, Bet PM, Boersma W, Bonta PI, Boomars KAT, Bos LDJ, van Bragt JJMH, Braunstahl GJ, Celant LR, Eger KAB, Geelhoed JJM, van Glabbeek YLE, Grotjohan HP, **Hagens LA**, Happe CM, Hazes BD, Heunks LMA, van den Heuvel M, Hoefsloot W, Hoek RJA, Hoekstra R, Hofstee HMA, Juffermans NP, Kemper EM, Kos R, Kunst PWA, Lammers A, van der Lee I, van der Lee EL, Maitland-van der Zee AH, Mau Asam PFM, Mieras A, Muller M, Neeffes ECW, Nossent EJ, Oswald LMA, Overbeek MJ, Pamplona CC, Paternotte N, Pronk N, de Raaf MA, van Raaij BFM, Reijrink M, Schultz MJ, Serpa Neto A, Slob EMA, Smeenk FWJM, Smit MR, Smits AJ, Stalenhoef JE, Tuinman PR, Vanhove ALEM, Wessels JN, van Wezenbeek JCC, Vonk Noordegraaf A, de Man FS, Bogaard HJ.

Imatinib in patients with severe COVID-19: a randomised, double-blind, placebo-controlled, clinical trial.

Lancet Respir Med. 2021 Sep;9(9):957-968. doi: 10.1016/S2213-2600(21)00237-X. Epub 2021 Jun 18.

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Eur Respir Rev. 2021 Feb 2;30(159):200317. doi: 10.1183/16000617.0317-2020. Print 2021 Mar 31.

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ERJ Open Res. 2021 Jan 18;7(1):00504-2020. doi: 10.1183/23120541.00504-2020. eCollection 2021 Jan.

Hagens LA, Verschueren ARM, Lammers A, Heijnen NFL, Smit MR, Nijsen TME, Geven I, Schultz MJ, Bergmans DCJJ, Schnabel RM, Bos LDJ.

Development and validation of a point-of-care breath test for octane detection.

Analyst. 2021 Jul 12;146(14):4605-4614. doi: 10.1039/d1an00378j.

Heijnen NFL, **Hagens LA**, Smit MR, Cremer OL, Ong DSY, van der Poll T, van Vught LA, Scicluna BP, Schnabel RM, van der Horst ICC, Schultz MJ, Bergmans DCJJ, Bos LDJ.

Biological Subphenotypes of Acute Respiratory Distress Syndrome Show Prognostic Enrichment in Mechanically Ventilated Patients without Acute Respiratory Distress Syndrome.

Am J Respir Crit Care Med. 2021 Jun 15;203(12):1503-1511. doi: 10.1164/rccm.202006-2522OC.

Heijnen NFL, **Hagens LA**, Smit MR, Schultz MJ, van der Poll T, Schnabel RM, van der Horst ICC, Dickson RP, Bergmans DCJJ, Bos LDJ; BASIC consortium.

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Assessment of the Effect of Recruitment Maneuver on Lung Aeration Through Imaging Analysis in Invasively Ventilated Patients: A Systematic Review.

Front Physiol. 2021 Jun 4;12:666941. doi: 10.3389/fphys.2021.666941. eCollection 2021.

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Am J Trop Med Hyg. 2021 Oct 18;105(6):1490-1497. doi: 10.4269/ajtmh.21-0545.

Hagens LA, Van der Ven FLIM, Heijnen NFL, Smit MR, Gietema HA, Gerretsen SC, Schultz MJ, Bergmans DCJJ, Schnabel RM, Bos LDJ.

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Front Med (Lausanne). 2022 Aug 31;9:950827. doi: 10.3389/fmed.2022.950827. eCollection 2022.

Heldeweg MLA, Smit MR, Kramer-Elliott SR, Haaksma ME, Smit JM, **Hagens LA**, Heijnen NFL, Jonkman AH, Paulus F, Schultz MJ, Girbes ARJ, Heunks LMA, Bos LDJ, Tuinman PR. Lung Ultrasound Signs to Diagnose and Discriminate Interstitial Syndromes in ICU Patients: A Diagnostic Accuracy Study in Two Cohorts.

Crit Care Med. 2022 Nov 1;50(11):1607-1617. doi: 10.1097/CCM.0000000000005620. Epub 2022 Jul 21.

Heijnen NFL, **Hagens LA**, van Schooten FJ, Bos LDJ, van der Horst ICC, Mommers A, Schultz MJ, Smit MR, Bergmans DCJJ, Smolinska A, Schnabel RM.

Breath octane and acetaldehyde as markers for acute respiratory distress syndrome in invasively ventilated patients suspected to have ventilator-associated pneumonia.

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Prone Positioning Decreases Inhomogeneity and Improves Dorsal Compliance in Invasively Ventilated Spontaneously Breathing COVID-19 Patients-A Study Using Electrical Impedance Tomography.

Diagnostics (Basel). 2022 Sep 21;12(10):2281. doi: 10.3390/diagnostics12102281.

Atmowihardjo LN, Heijnen NFL, Smit MR, **Hagens LA**, Filippini DFL, Zimatore C, Schultz MJ, Schnabel RM, Bergmans DCJJ, Aman J, Bos LDJ; DARTS Consortium.

Biomarkers of alveolar epithelial injury and endothelial dysfunction are associated with scores of pulmonary edema in invasively ventilated patients.

Am J Physiol Lung Cell Mol Physiol. 2023 Jan 1;324(1):L38-L47. doi: 10.1152/ajplung.00185.2022. Epub 2022 Nov 8.

Smit MR, **Hagens LA**, Heijnen NFL, Pisani L, Cherpanath TGV, Dongelmans DA, de Grooth HS, Pierrakos C, Tuinman PR, Zimatore C, Paulus F, Schnabel RM, Schultz MJ, Bergmans DCJJ, Bos LDJ; DARTS Consortium members.

Lung Ultrasound Prediction Model for Acute Respiratory Distress Syndrome: A Multicenter Prospective Observational Study.

Am J Respir Crit Care Med. 2023 Jun 15;207(12):1591-1601. doi: 10.1164/rccm.202210-1882OC.

Filippini DFL, **Hagens LA**, Heijnen NFL, Zimatore C, Atmowihardjo LN, Schnabel RM, Schultz MJ, Bergmans DCJJ, Bos LDJ, Smit MR.

Prognostic Value of the Radiographic Assessment of Lung Edema Score in Mechanically Ventilated ICU Patients.

J Clin Med. 2023 Feb 4;12(4):1252. doi: 10.3390/jcm12041252.

Fenn D, Lilien TA, **Hagens LA**, Smit MR, Heijnen NFL, Tuip-de Boer AM, Neerinx AH, Golebski K, Bergmans DCJJ, Schnabel RM, Schultz MJ, Maitland-van der Zee AH, Brinkman P, Bos LDJ.

Validation of volatile metabolites of pulmonary oxidative injury: a bench to bedside study.

ERJ Open Res. 2023 Mar 20;9(2):00427-2022. doi: 10.1183/23120541.00427-2022. eCollection 2023 Mar.

Hagens LA, Heijnen NFL, Smit MR, Verschuere ARM, Nijsen TME, Geven I, Presură CN, Rietman R, Fenn DW, Brinkman P, Schultz MJ, Bergmans DCJJ, Schnabel RM, Bos LDJ.

Octane in exhaled breath to diagnose acute respiratory distress syndrome in invasively ventilated

intensive care unit patients.

ERJ Open Res. 2023 Oct 16;9(5):00214-2023. doi: 10.1183/23120541.00214-2023.

Submitted manuscripts

Authors with * contributed equally to the study

Zhang S*, **Hagens LA***, Heijnen NFL, Smit MR, Fenn DW, Brinkman P, Van der Poll T, Schultz MJ, Bergmans DCJJ, Schnabel RM, Bos LDJ.

Development and validation of a diagnostic model for acute respiratory distress syndrome based on volatile organic compounds in exhaled breath.

Submitted

Publications as part of collaborative study groups

18 publications as member of the Amsterdam UMC COVID-19 Biobank Study Group

17 publications as member of the PRoVENT-COVID Collaborative Group

PHD PORTFOLIO

PhD student: *Laura A. Hagens*
 PhD period: *2018 - 2023*
 PhD supervisors: *prof. dr. M.J. Schultz, dr. L.D.J. Bos,
 dr. D.C.J.J. Bergmans*

COURSES

Doctoral School courses	Year	ECTS
eBrok	2018	1.0
Practical biostatistics	2018	1.1
AMC World of Science	2018	0.7
Advanced topics in biostatistics	2020	2.1
E-science (Big Data)	2019	0.7
Scientific writing	2020	1.5
Research Data Management	2019	0.5

External courses	Year	ECTS
NRS Lung Course	2019	1.3
ESAIC Masterclass ARDS	2021	0.5

PRESENTATIONS

	Year	ECTS
Inspires	2018	0.5
ESICM (online)	2020	0.5
ERS (online)	2021	0.5
ESAIC masterclass	2021	0.5
ESICM (live)	2022	0.5

CONFERENCES

	Year	ECTS
Breath Summit - Maastricht	2018	0.75
INSPIREs International Symposium on Acute Lung Injury, Amsterdam	2018	0.5
European Respiratory Society Congress - Madrid, Spanje	2019	0.75
Precision Medicine in ARDS seminar - European Respiratory Society ARDS symposium - Barcelona, Spanje	2020	0.75
ESICM lives - Online version	2020	0.75
ERS - Online version	2021	0.75
Symposium Translationele Intensive Care Geneeskunde	2021	0.2
European Society of Intensive Care Medicine International Congress - Parijs, Frankrijk	2022	0.75
Symposium Translationele Intensive Care Geneeskunde	2022	0.2

TUTORING AND MENTORING

	Year	ECTS
Melissa de Bie	2021	1.0
Peter van 't Ooster	2021	1.0
Sabine van Mierlo	2021	1.0

OTHER ACTIVITIES

	Year	ECTS
Intensive care research meeting (weekly)	2018-2023	8.0
Laboratory of Experimental Intensive Care and Anesthesiology (LEICA) research meeting (weekly)	2018-2021	6.0
Journal club (monthly)	2018-2023	4.0

DANKWOORD

Het laatste stukje van mijn proefschrift dat ik schrijf en het eerste wat iedereen leest.

Voor mij geen klassiek dankwoord, ik ben bang dat ik iemand zou vergeten. Laat ik vooropstellen: mijn onderzoek deed ik niet alleen, maar samen en ik werd gesteund door velen. Daarom aan iedereen die op enige wijze heeft bijgedragen aan het tot stand komen van dit proefschrift: ik ben je dankbaar!

In het bijzonder wil ik mijn promotieteam bedanken.

Lieuwe, drijvende spil achter de onderzoekslijn. Jij hebt mij de kans gegeven om mijn promotietraject te doen op de intensive care van locatie AMC. Van jou heb ik de ins-and-outs geleerd van het onderzoek doen. Vol enthousiasme heb je mij wegwijs gemaakt binnen de wetenschap en opgeleid tot onderzoeker. Ik ben trots op wat ik met dank aan jou heb mogen leren!

Marcus, altijd heb jij ideeën en een visie over hoe onderzoek opgezet, uitgevoerd en gepresenteerd zou moeten worden. Door je jarenlange ervaring heb je mij waardevolle inzichten gegeven. Ook hier heb ik enorm van kunnen leren, waarvoor hartelijk dank.

Dennis, dank dat jij hebt meegedacht en mede ervoor gezorgd hebt dat de DARTS studie in Maastricht kon lopen.

Aan dr. Agnes Boots, dr. Paul Brinkman, prof. dr. Frederique Paulus, prof. dr. Ignacio Martin-Loeches en prof. dr. Iwan van der Horst: dank voor de moeite die u genomen heeft om mijn proefschrift te beoordelen en voor uw aanwezigheid tijdens mijn promotie in Amsterdam als lid van mijn promotiecommissie.

Team DARTS en de IC onderzoeksgroep, jullie wil ik toch graag even noemen. Jullie hebben mij gedurende mijn hele promotietraject geholpen, gesteund en geïnspireerd. Jullie hebben mijn promotietijd fantastisch en onvergetelijk gemaakt, ik ben jullie allemaal heel erg dankbaar!

Als laatste natuurlijk Mart, jij bent met mij meeverhuisd, hebt me altijd gesteund, samen vormen wij een team! En inmiddels met Ilja erbij een gezin, waar we ook gaan, we gaan samen.