Migraine as a cardiovascular risk factor for women

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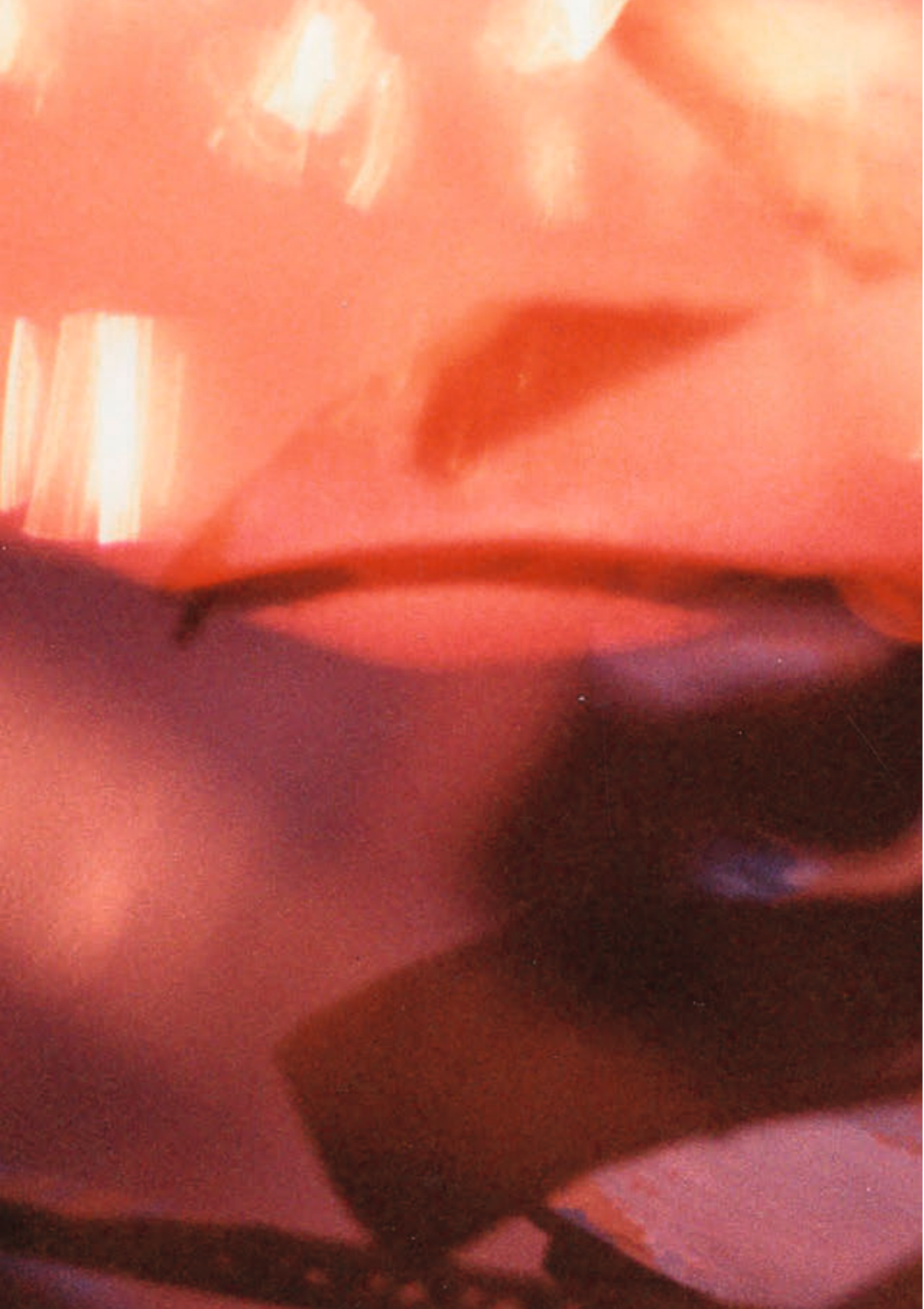

APPENDICES

SUPPLEMENTARY MATERIAL: CHAPTER 3

1. LUMINA BACKGROUND INFORMATION

Dutch migraine patients aged 18-80 years were recruited via nationwide public announcement, advertising in lay press and our research website (www.lumc.nl/hoofdpijn). They were considered eligible after a two-step inclusion process using validated questionnaires via the dedicated Leiden University MIgraine Neuro-Analysis (LUMINA) website. Additionally, patients attending our outpatient headache clinic were invited to participate by a letter. Patients were first asked to fill out a validated web-based screening questionnaire with a sensitivity of 0.93 and specificity of 0.36.[1] Patients who fulfilled the screening criteria, were sent a validated web-based extended migraine questionnaire[2], based on the International Classification of Headache Disorders criteria (previously ICHD-2, now ICHD-3 version) criteria.[3] The specificity of the second questionnaire was 0.95 and sensitivity was 0.45.[2] This questionnaire is accessible for patients via our research website and is described in English in detail by van Oosterhout et al. 2011.[2] We consider the cohort a well-defined web-based cohort. Four percent of subjects were included from our headache outpatient clinic and 87% of the participants were previously diagnosed with migraine by a physician. In addition to questions that were necessary to diagnose migraine accurately, the extended questionnaire also included items on demographic factors, aura and headache characteristics, acute and prophylactic headache medication use, and allodynia. Healthy controls were free of any known neurological or psychiatric disorders and did not have any primary or secondary headaches apart from an occasional episodic tension type headache. Participants unable to use the web-based questionnaires due to lack of the needed internet skills were allowed to fill out the questionnaires on paper.

2. QUESTIONNAIRES AND RATING ON THERMAL DISCOMFORT AND COLD EXTREMITIES (TDCE) AND DIFFICULTIES INITIATING SLEEP (DIS)

To accommodate the participants of this research, the following questionnaires were translated to Dutch. Questionnaire and rating are adapted from Kräuchi et al.[4]

Thermal Discomfort and Cold Extremities (TDCE)

In order to calculate a score, the following two questions were asked:
(A) During the past month, how intensely did you suffer from cold hands?
Answer categories were:1='not at all', 2='a little', 3='quite', 4='extraordinary'.
(B) During the past month, how intensely did you suffer from cold feet?
Answer categories were:1='not at all', 2='a little', 3='quite', 4='extraordinary'.

For categorical analyses TDCE was rated as relevant when the answer to question A or the answer to question B was option 3 or 4.

Difficulties Initiating Sleep (DIS)

(A) During the past month, how often was your sleep onset latency (SOL) longer than 30 min?
Answer categories were:1='never', 2='seldom', 3='1–2 times per week', 4='≥3 times per week'.

(B) During the past month, how long (in minutes) has it usually taken to fall asleep?
Answer: … minutes
(C) During the past month, was it a problem for you to fall asleep?
Answer categories were:1='not at all', 2='a little', 3='quite', 4='extraordinary'.

For categorical analyses, DIS was categorized as relevant when the answer to question A was option 3 or 4 and the answer of question C was option 3 or 4.

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3 Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. 2018;38:1–211.

4 Kräuchi K, Gasio PF, Vollenweider S, Von Arb M, Dubler B, Orgül S, Flammer J, Stutz EZ. Cold extremities and difficulties initiating sleep: evidence of co-morbidity from a random sample of a Swiss urban population. *J Sleep Res.* 2008;17:420-6.

SUPPLEMENTARY MATERIAL: CHAPTER 4

See Supplementary material: Chapter 3, 1. LUMINA background information.

SUPPLEMENTARY MATERIAL: CHAPTER 5

Supplemental Table 1. Additional general, cardiometabolic, gynaecological/obstetric and endocrine characteristics of the total study population, that includes women with and without migraine who were diagnosed with PCOS.

	All subjects (N = 49)	**Women with migraine (N = 23)**	**Women without migraine (N = 26)**	***P-value***
General parameters and intoxications[1]				
Education				0.128
Pre-vocational secondary	9 (18.4%)	5 (21.7%)	4 (15.4%)	
Secondary vocational	10 (20.4%)	2 (8.7%)	8 (30.8%)	
Senior general secondary/ Pre-university	5 (10.2%)	3 (13.0%)	2 (7.7%)	
Higher professional	18 (36.7%)	7 (30.4%)	11 (42.3%)	
University/ PhD/ Postdoc	6 (12.2%)	5 (21.7%)	1 (3.8%)	
Unknown	1 (2.0%)	1 (4.3%)	0 (0%)	
Alcohol use of consumers (units/week)	1.0 (0.3–3.8)	1.3 (0.3–5.0)	0.8 (0.1–1.5)	0.415
Practitioner of a sport[2]	21 (43.8%)	6 (27.3%)	15 (57.7%)	0.045*
Anthropometrics				
Waist (cm)	98.0 (87.3–108.3)	95.0 (86.0–109.0)	100.0 (92.3–109.0)	0.312
Hip (cm)	112.0 (104.0–121.0)	109.0 (101.5–116.3)	116.5 (107.8–123.0)	0.055
Cardiometabolic parameters				
Non-fasting glucose (mmol/L)[3]	5.0 (4.0–5.7)	5.0 (4.0–5.5)	4.9 (4.0–6.6)	0.923
Total cholesterol (mmol/L)[3]	5.2 (4.4–6.1)	5.3 (4.5–6.0)	5.1 (4.4–6.4)	0.886
HDL cholesterol (mmol/L)[3]	1.5 (0.4)	1.5 (0.3)	1.5 (0.4)	0.942
Total cholesterol to HDL ratio[3]	3.6 (2.9–4.6)	3.7 (2.7–4.5)	3.5 (3.1–4.7)	0.728
LDL cholesterol (mmol/L)[3]	3.1 (1.0)	3.0 (1.0)	3.2 (1.0)	0.575
Triglycerides (mmol/L)[3]	1.2 (0.8–1.8)	1.0 (0.7–1.8)	1.3 (1.0–1.9)	0.356
ApoA1 (g/L)[3]	1.8 (0.4)	1.7 (0.3)	1.8 (0.5)	0.393
ApoB (g/L)[3]	0.8 (0.7–1.0)	0.8 (0.7–1.0)	0.8 (0.7–1.0)	0.854
Lp(a) (g/L)[3]	0.09 (0.05–0.2)	0.07 (0.04–0.2)	0.10 (0.06–0.2)	0.623
Gynaecological/obstetric parameters				
Age at menarche (years)[4]	13.0 (12.0–14.0)	13.0 (12.0–14.0)	13.5 (12.3–15.0)	0.093
Number of pregnancies in total	2.0 (1.0–3.0)	2.0 (1.0–4.0)	2.0 (1.0–3.0)	0.310
Number of pregnancies that lasted at least 6 months	2.0 (1.0–2.0)	2.0 (1.0–2.0)	2.0 (1.0–2.0)	0.763

Supplemental Table 1. Continued

	All subjects (N = 49)	Women with migraine (N = 23)	Women without migraine (N = 26)	*P-value*
Endocrine parameters[2]				
LH (U/L)	6.4 (1.8–25.4)	3.1 (1.3–17.9)	11.1 (2.0–25.9)	0.230
FSH (U/L)	8.7 (3.4–38.6)	6.7 (2.7–23.6)	11.6 (3.8–42.6)	0.243
AMH (µg/L)[5]	0.1 (0.01–0.7)	0.08 (0.01–0.7)	0.1 (0.01–0.8)	0.913
Androstenedione (nmol/L)	2.2 (1.6–3.7)	2.2 (1.6–4.1)	2.1 (1.6–2.9)	0.515
DHEA (nmol/L)[6]	8.5 (5.4–11.2)	9.1 (5.1–11.6)	8.3 (5.4–11.0)	0.723
DHEA sulfate (µmol/L)	2.7 (1.3)	2.7 (1.2)	2.6 (1.4)	0.682

Values of all subjects are displayed as means (standard deviation) or medians (interquartile range, $Q_3 - Q_1$), or as numbers (percentage). Differences between participants with and without migraine were tested with Student's T-test for variables with a normal distribution, while the Mann-Whitney U test was used for variables with a skewed distribution and for variables with a non-normal distribution in one group. The Fisher's exact test was used for categorical data.
Abbreviations: AMH, Anti-Müllerian hormone; DHEA, dehydroepiandrosterone; FSH, follicle-stimulating hormone; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LH, luteinizing hormone
[1] Self-reported; [2] Data are missing in one migraine patient, that has been excluded from the analyses; [3] Data are missing in one patient without migraine, that has been excluded from the analyses; [4] Data are missing in two patients without migraine, that have been excluded from the analyses; [5] Hormone levels below the detection limit have been considered to be at the detection limit, which is 0.01. This was the case in 6 migraine patients and 8 patients without migraine; [6] Hormone levels below the detection limit have been considered to be at the detection limit, which is 3.6. This was the case in 1 migraine patient and 3 patients without migraine.

SUPPLEMENTAL ANALYSES

CARDIOVASCULAR RISK SCORE IN RELATION TO LTH MEASUREMENTS AND ENDOPAT MEASUREMENTS

Furthermore, we examined the correlation between the FRS and outcome measures of the EndoPAT in 42 participants, including 21 migraine patients. We observed no relation between the natural log-transformed FRS (lnFRS) and the lnRHI scores (Pearson's r = 0.17 (95% CI [-0.14–0.45]; $p = 0.279$ and $R^2 = 0.03$). Similarly, no correlation was found between the lnFRS and the AI@75 (Pearson's r = 0.14 (95% CI [-0.17–0.43]; $p = 0.375$ and $R^2 = 0.02$). Further stratification according to the migraine diagnosis did not result in any significant correlations between the lnFRS and the (transformed) lnRHI or AI@75 scores either (data not shown).

Lastly, we examined associations between the FRS and LTH measurements in 47 participants. To capture the total effect of the LTH response, without blockade of any underlying mechanism, we studied the AUC of the entire LTH response, corrected for its baseline, under control conditions.

No association was found between the lnFRS and the natural log-transformed AUC of the total LTH response under control conditions in all participants (Pearson's r = -0.12 (95% CI [-0.40–0.17]; $p = 0.415$ and $R^2 = 0.01$). Further stratification according to the migraine diagnosis did not result in any significant correlations in patients with or without migraine either (data not shown).

SUPPLEMENTARY MATERIAL: CHAPTER 6

ANALYSES OF BASELINE CHARACTERISTICS AMONG MIGRAINEURS VS NON-MIGRAINEURS

Migraine diagnosis was established using the Migraine for Stroke Screener (MISS). See supplementary material: chapter 7.

Table 1. migraine vs no migraine

	Migraine (n=46)	No migraine (n=107)	P-value
Age at event; median (IQR)	59.0 (18.3)	68.0 (19.5)	0.00
BMI; median (IQR)	26.0 (7.4)	26.1 (6.6)	0.82
Penumbra surface; median (IQR)	12184 (12440)	10021 (14726)	0.65
Infarct core; median (IQR)	1405 (3276)	2207 (6487)	0.39
Penumbra/infarct core index; median (IQR)	0.9 (0.2)	0.8 (0.4)	0.56
Infarctvolume; median (IQR)	10.9 (44.6)	16.6 (36.0)	0.84
Toast classification			0.93
Large vessel disease	14 (30)	26 (24)	
Small vessel / lacunar infarct	7 (15)	19 (18)	
Cardial embolic	8 (17)	20 (19)	
Dissection	3 (7)	1 (1)	
Other/unknown	16 (35)	39 (36)	
mRS, pre-admission ≥ 2	2 (4)	9 (10)	0.51
mRS, 3 months FU ≥ 2	20 (43)	50 (47)	0.64
NIHSS ≥ 5	22 (48)	63 (59)	0.21
EQ5D ≥ 6	28 (61)	71 (66)	0.86
BI ≤ 17	2 (4)	11 (10)	0.35

Data are expressed as n (%) unless otherwise stated

SUPPLEMENTARY MATERIAL: CHAPTER 7

MIGRAINE SCREENER FOR STROKE (MISS) QUESTIONNAIRE

Migraine Screener for Stroke (MISS) is a 5 question reliable screening tool for migraine diagnosis in patients with transient ischemic attack or stroke. The screener was validated through semi-structured telephone interviews with the International Classification of Headache Disorders, second-edition criteria as gold standard. The sensitivity of all questions combined was 0.47 (95% CI 0.31-0.62), the specificity was 0.97 (95% CI 0.93-0.99), the positive predictive value (PPV) was 0.80 (95% CI 0.59-0.93) and the negative predictive value (NPV) was 0.87 (95% CI 0.82-0.92). For assessing migraine with aura, the question about visual disturbances had a good NPV (0.99, 95% CI 0.96-1.00), but a low PPV (0.38, 95% CI 0.24-0.53). To prevent misclassification, especially for the aura symptoms, patients with a positive screener should be interviewed more extensively to confirm the migraine diagnosis.[1]

Question 1. Have you ever had a migraine attack or do you still have migraine attacks?
Never
1–4 times
≥5 times
Unknown

Question 2. Have you ever been diagnosed with migraine by a physician?
Yes
No
Unknown

Question 3. Have you ever had severe headache attacks accompanied by nausea or vomiting?
Never
1–4 times
≥5 times
Unknown

Question 4. Have you ever had severe headache attacks accompanied by hypersensitivity to lights and sounds?
Never
1–4 times
≥5 times
Unknown

Question 5. Have you ever had visual disturbances lasting 5–60 min followed by headache?
Never
1–2 times
≥3 times
Unknown

Table 3. a Screener versus final ICHD-II diagnosis of migraine as gold standard

Screener question	Answer to screener question	Final diagnosis		Test characteristics (95% CI)
		migraine	no migraine	
(1) Self-reported migraine	Yes, ever (n) No, never (n)	43 5 Sens 0.90 (0.77–0.97)	19 149 Spec 0.89 (0.84–0.94)	PPV 0.69 (0.57–0.82) NPV 0.97 (0.93–0.99)
(2) Diagnosed with migraine by a physician	Yes, ever (n) No, never (n)	26 20 Sens 0.57 (0.41–0.71)	8 160 Spec 0.95 (0.91–0.98)	PPV 0.76 (0.59–0.89) NPV 0.89 (0.84–0.94)
(3) Severe headache with nausea	Yes, ever (n) No, never (n)	42 5 Sens 0.89 (0.77–0.97)	17 148 Spec 0.90 (0.85–0.94)	PPV 0.71 (0.58–0.82) NPV 0.97 (0.93–0.99)
(4) Severe headache accompanied by hypersensitivity to light and sound	Yes, ever (n) No, never (n)	44 2 Sens 0.96 (0.85–1.00)	18 149 Spec 0.89 (0.85–0.94)	PPV 0.71 (0.58–0.82) NPV 0.99 (0.95–1.00)
(5) Visual disturbances followed by headache	Yes, ever (n) No, never (n)	28 15 Sens 0.65 (0.49–0.79)	20 144 Spec 0.88 (0.83–0.93)	PPV 0.58 (0.43–0.72) NPV 0.91 (0.85–0.95)
All questions combined	Yes, ever (n) No, never (n)	20 23 Sens 0.47 (0.31–0.62)	5 156 Spec 0.97 (0.93–0.99)	PPV 0.80 (0.59–0.93) NPV 0.87 (0.82–0.92)

Sens = Sensitivity; Spec = specificity; missing data <5%.

b Visual disturbances followed by headache versus final ICHD-II diagnosis of migraine with aura as gold standard

Screener question	Answer to screener question	Final diagnosis		Test characteristics (95% CI)
		migraine with aura	no migraine with aura	
(5) Visual disturbances followed by headache	Yes, ever (n) No, never (n)	18 2 Sens 0.90 (0.68–0.99)	30 157 Spec 0.90 (0.68–0.99)	PPV 0.38 (0.24–0.53) NPV 0.99 (0.96–1.00)

Sens = Sensitivity; Spec = specificity; missing data <7%.

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SUPPLEMENTARY MATERIAL: CHAPTER 8

SEE SUPPLEMENTARY MATERIAL: CHAPTER 7: MISS QUESTIONNAIRE.

In the present study, migraine diagnosis was considered positive when participants answered confirmatively to a combination of the three questions selected to obtain the highest possible predictive value (ever migraine attack, ever severe headache with nausea/vomiting or ever severe headache with photo- and/or photophobia, positive predictive value: 0.80 (0.66-0.90) negative predictive value: 0.96 (0.91-0.98))[5] or in case of migraine diagnosis by physician's report.

ABBREVIATIONS

ACOG	american congress of obstetricians and gynecologists
ADMA	asymmetric dimethylarginine
ASCO	atherosclerosis small-vessel disease cardiac pathology other causes
ATC	anatomical therapeutic chemical
AUC	area under curve
BMI	body mass index
BP	blood pressure
CADASIL	cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CI	confidence interval
CGRP	calcitonin gene related peptide
CSD	cortical spreading depolarization
CVD	cardiovascular disease
COC	combined oral contraceptives
COX-1	cyclooxygenase-1
CREW	cardiovascular healthy aging in women
CREW-MIST	cardiovascular healthy aging in women microvascular status
CT	computed tomography
DBF	dermal blood flow
DM	diabetes mellitus
DIS	difficulty initiating sleep
DUST	dutch acute stroke study
EDHF	endothelium derived hyperpolarizing factor
EMLA	eutectic mixture of local anesthetics
EPC	endothelial precursor cells
ET-1	endothelin-1
FAI	free androgen index
FHM	familial hemiplegic migraine
FMD	flow mediated dilation
FRS	framingham risk score
GABA	gamma-aminobutyric acid
GWAS	genome wide association study
HDL	high density lipoprotein
lHR	hazard ratio
HRT	hormone replacement therapy
ICD	internation classification of diseases
ICHD	international classification of headache disorders
ICPC	international classification of primary care
IHS	international headache society
LAA	large artery atherosclerosis
LACI	lacunar infarct

LH	luteinizing hormone
LTH	local thermal hyperaemia
LNMMA	ng-monomethyl-l-arginine
LUMINA	leiden university migraine neuro-analysis
MA	migraine with aura
MI	myocardial infarction
MISS	migraine screener for stroke
MO	migraine without aura
MRI	magnetic resonance imaging
MRM	menstrually related migraine
mRS	modified rankin scale
NIHSS	national institutes of health stroke scale
NO	nitric oxide
NPRS	numeric pain rating scale
OCP	oral contraceptives
OR	odds ratio
PACAP	pituitary adenylate cyclase activating peptide
PACI	partial anterior circulation infarct
PE	preeclampsia
PCOS	polycystic ovary syndrome
PFO	patent foramen ovale
POCI	posterior circulation infarct
PSI-CVA	parelsnoer institute cerebrovascular accident initiative
PVD	peripheral vessel disease
RR	relative risk
RHI	reactive hyperaemia index
RVCL-S	retinal vasculopathy with cerebral leukodystrophy and systemic manifestations
SHBG	sex hormone-binding globulin
STIZON	stichting informatievoorziening voor zorg en onderzoek
SVD	small vessel disease
TACI	total anterior circulation infarct
TIA	transient ischemic attack
TDCE	thermal discomfort and cold extremities
TOAST	trial of org 10172 in acute stroke treatment
TRPV-1	transient receptor potential vanilloid 1
WHO	world health organization
WML	white matter lesions

LIST OF PUBLICATIONS

Linstra KM, Ibrahimi K, Terwindt GM, Wermer MJH, MaassenVanDenBrink A. Migraine and cardiovascular disease in women. *Maturitas.* 2017;97:28-31

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CURRICULUM VITAE

Katie Linstra was born on the 13th of February, 1987 in Gouda, the Netherlands. She attended secondary school at the bilingual department of the “Wolfert van Borselen” in Rotterdam. In 2005 she was accepted at University College Utrecht, where she graduated cum laude with a premedical science major. During her bachelor, she participated in an exchange semester at the National University of Singapore in 2007, following courses in Pharmacology, Nanotechnology and Health psychology. Her bachelor thesis research concerned painful diabetic neuropathy. In 2008 she started a master in medicine at the Selective Utrecht Medical Masters (SUMMA) programme at the University Medical Centre in Utrecht. As part of her research traineeship, she investigated a new method of spinal cord stimulation for chronic pain at the department of Neurosurgery, Anaesthesiology and Medical Technology. After obtaining her medical degree in 2012, she worked as a resident (ANIOS) at the Department of Neurology of the Tergooi ziekenhuis in Blaricum. In 2014, she started her PhD research at the Neurology department of the Leiden University Medical Center and at the department of Internal Medicine, Division of Vascular Medicine and Pharmacology at the Erasmus Medical Centre in Rotterdam, under the guidance of prof.dr. M.J.H. Wermer, prof. dr. A. MaassenvandenBrink and prof. dr. G. M. Terwindt. Katie is currently working at a.s.r. as medical advisor.

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