Advanced MRI in aortic pathology and systemic interactions

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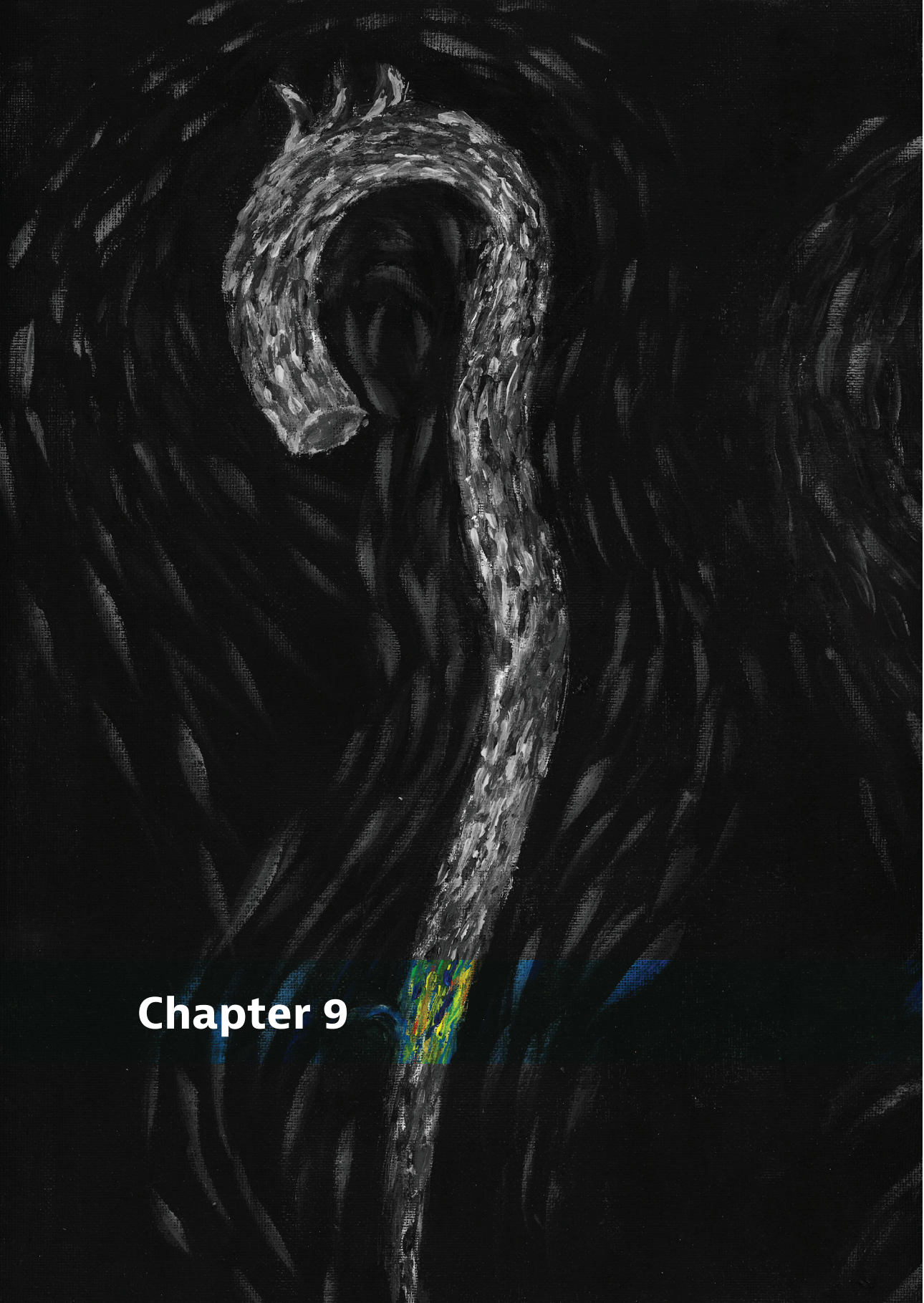

Chapter 9

Summary and perspectives

Cardiovascular disease is the leading cause of death in the world [1]. With the worldwide aging population, cardiovascular disease is likely to become even more prevalent. There is an increasing need for accurate and efficient cardiovascular risk assessment to optimize cardiovascular treatment. The aorta plays a central role in the cardiovascular system. The aorta transports blood to various organ systems while absorbing the pulsatile pressure of the cardiac output. Aortic stiffness is a marker of vascular aging and has shown to be an independent marker for cardiovascular risk [2]. Additionally, enlarged aortic dimensions are linked to an increased risk of rupture [3]. MRI is capable of providing accurate information on aortic morphology, stiffness and blood flow patterns.

Therefore, the aims of this thesis were to define reference values and standardized methods for essential basic measures of aortic morphology and function using MRI, to expand the clinical applicability, and to assess the relation of MRI based measures of cardiovascular function with various organs in the human body.

In the general introduction (**chapter 1**), we outlined general principles of aortic structure and function, its (patho)physiological changes, as well as the MRI based quantification of aortic morphology and function. **Part 1** of this thesis (**chapters 2 - 3**) outlines standardized methods and reference values for fundamental measures of aortic morphology and function using MRI. **Part 2** (**chapters 4 - 6**), describes different studies that evaluate the prediction of, as well as the predictive value of MRI based measures of aortic function, in order to expand the clinical applicability of these measures. Finally, **part 3** (**chapters 7 - 8**), focusses on the systemic interplay of MRI based measures of cardiovascular function. Below we present the main findings of this thesis, discuss the main implications along with potential future perspectives.

Main findings

Part 1: Defining the basics

In **part 1** we formulated standardized methods and reference values for fundamental measures of aortic morphology and function using MRI.

Chapter 2 provides a consensus-based practical guide on how to measure the aorta using MRI. In this International Society for Magnetic Resonance in Medicine (ISMRM) recommendation paper, a short overview is provided on how, when and where to measure the aorta. The recommendations are based on the most recent international guidelines and literature, and were defined by an expert panel with global representation. In short, it is recommended to use non-contrast enhanced techniques, with ECG gating at end-diastole to measure double-oblique inner-inner diameters at pre-defined anatomical locations. In case of wall thickening or aneurysm formation, additional outer-outer measurements are recommended and if possible direct comparison with a previous scan would be advisable. For the aortic sinus, average cusp-to-commissure and the largest cusp-to-cusp distance should be reported.

In **chapter 3** we established normal and reference values for MRI based pulse wave velocity (PWV), measuring aortic stiffness, in 1,394 participants of the Netherlands Epidemiology of Obesity (NEO) study that were free from cardiovascular disease, smoking, or treatment for diabetes, hypertension of dyslipidaemia. Normal values were specified for participants with a blood pressure < 130/80 mmHg and reference values for untreated elevated blood pressure subgroups (≥ 130/80 and < 140/90 mmHg; and ≥ 140/90 mmHg). We observed that PWV increased with advancing age and blood pressure categories, with also higher variability of PWV with age. Overall, there was no difference between sex in normal PWV. Normal mean PWV was 6.0 m/s [95% CI 5.8–6.1], around 2 m/s lower than normal values reported for carotid-femoral PWV, which likely due to the differences in techniques, illustrating the need for MRI-PWV specific values [4]. Only a few, relatively small, studies have provided age and sex specific normal ranges for MRI-based PWV [5-9]. Our normal and reference values provide incremental information to the limited existing literature and are essential for the clinical application of MRI in the assessment of cardiovascular risk beyond traditional risk factors.

Part 2: Prediction of arterial stiffness and outcome

Part 2 focused on expanding the clinical applicability of MRI based measures of aortic morphology and function through the prediction of as well as assessing the prognostic value of MRI based measures of aortic morphology and function.

In **chapter 4** we developed prediction models using traditional linear regression as well as deep neural networks to estimate MRI-PWV (ePWV) and determined the optimal cut-off to discriminate reliably between lower and higher PWV values. The prediction models used clinical and anthropometric data from 2,254 participants of the Netherlands Epidemiology of Obesity (NEO) study with available MRI-PWV data. External validation was performed using baseline measurements of 114 participants of the MAGNA VICTORIA study [10]. All ePWV models provided an adjusted R^2 of around 0.33, with good discriminative performance with regard to differentiating individuals with lower PWV (< 6.7 m/s) from those with higher PWV values (area under the ROC curve range 0.81–0.89). ePWV could therefore function as gatekeeper in selecting patients who benefit from further MRI-based PWV assessment and thereby could reduce the amount of MRI scans needed, while increasing the availability of accurate cardiovascular risk assessment.

Chapter 5 assessed the long-term prognostic value of ascending aorta curvature radius, regional PWV and flow displacement on aortic dilatation and elongation in 21 Marfan and 40 non-syndromic thoracic aortic aneurysm patients. We found that a smaller aortic curvature is associated with an increased ascending aorta dilatation rate and flow displacement is associated with ascending aorta elongation at long-term follow-up (8.0 [7.3–10.7] years). Since both aortic dilatation and elongation are associated with increased risk of dissection, markers that are able to predict either dilatation or elongation could aid in risk assessment of aortic pathology. Interestingly, in a previous study in this population, normal regional PWV was associated with absence of aortic growth at 2-year follow-up, whereas in our study at long-term follow-up PWV was not associated with (absence of) aortic growth [11]. This may indicate that PWV is a less important marker for aortic growth than previously thought and suggests that ascending aorta curvature radius and flow displacement may be more useful in the risk stratification of ascending aorta elongation and aneurysm formation.

In **chapter 6** we continued to illustrate the potential of MRI derived flow in prediction of aortic growth and progression of dissection in a case report of a 31-year-old male with Marfan syndrome and a recent uncomplicated type B dissection from the left subclavian to the right common iliac artery who underwent 4D flow MRI. The MRI was performed just two weeks before retrograde progression to a type A dissection, requiring urgent surgical valve-sparing root, ascending and arch replacement. On MRI, the type B dissection had a large proximal intimal tear just distal to the left subclavian artery (15 mm). Aortic blood flow (3.6 L/min) was split disproportionately into the true (0.8 L/min, 22%) and false lumen (2.8 L/min, 78%), which has been shown to be a prognostic factor for false lumen dilatation [12]. 4D flow streamlines revealed vortical flow in the proximal false lumen, which has been linked to aortic dilatation in Marfan patients [13]. Elevated wall shear stress (WSS) was observed at the sinotubular junction, inner wall of the ascending aorta and around the subclavian artery, of which elevated WSS just distal to the subclavian artery in a type B dissection has been associated with retrograde type A dissection [14]. In addition, elevated WSS has also been shown to corresponded to the site of the future dissection entry tear of a retrograde type A dissection [14]. Interestingly, in our case elevated WSS was observed at the location of the sinotubular junction which seems to correspond to the future entry tear location. Our case illustrates that besides clinical and morphological parameters, flow derived parameters may contribute to improved risk assessment of retrograde progression of type B dissection to acute type A dissection.

Part 3: Systemic interactions of cardiovascular function

Besides the local impact of aortic morphology and function, in **part 3** we also investigated the systemic interaction of cardiovascular function using MRI. For these studies we used data from the UK Biobank; a large middle-aged population-based imaging study.

In **chapter 7** we studied the impact of visceral and general obesity on vascular and left ventricular function and geometry in 4,590 participants of the UK Biobank. MRI was used for assessment of left ventricular (LV) parameters [end-diastolic volume (EDV), ejection fraction (EF), cardiac output (CO), and index (CI)] and for body composition analysis [subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT)]. Arterial stiffness was assessed by the augmentation index, which is derived from the central pressure waveform and is defined as the percentage

of increase in pulse pressure from the reflected waveform. Overall, all obesity measures were positively associated with vascular stiffness, of which visceral obesity in women showed the strongest association with vascular stiffness. Visceral obesity was associated with a smaller EDV, lower EF and the strongest negative association with CI. In contrast, general obesity (SAT) was associated with a larger EDV and a higher CO, possibly due to the expansion of intravascular volume associated with general obesity [15, 16]. In the gender-specific analysis, only men showed a significant association between VAT and EF. Since men have larger volumes of VAT, the negative association between VAT and EF in men supports the suggestion that VAT is an independent risk factor for cardiac dysfunction, possibly exerted through a direct metabolic effect of adipokines released from VAT [17]. In conclusion, visceral obesity was associated with a smaller LV EDV and subclinical lower LV systolic function in men, suggesting that visceral obesity might play a more important role compared to general obesity in LV remodeling.

Chapter 8 investigated the associations between left ventricular function, vascular function and measures of cerebral small vessel disease in 4,366 participants of the UK Biobank. MRI was used to asses LV function and cerebral small vessel disease (cSVD) measures (total brain volume, grey and white matter volumes, hippocampal volume and white matter hyperintensities). Again, the augmentation index was used as a measure of arterial stiffness. To acquire a more detailed insight into the complex interaction between cardiovascular function and the brain, we assessed linear as well as non-linear associations using polynomial splines. We found that EF is non-linearly associated with cSVD measures (with the largest brain volume for an EF between 55 and 60%) and that lower cardiac index is linearly associated with a larger burden of cSVD. These associations between lower cardiac function and cSVD are possibly explained by chronically reduced cerebral perfusion [18]. In accordance with previous research no associations were found for augmentation index with cSVD imaging measures [19, 20]. A possible explanation the lack of association is the use of augmentation index for assessment of arterial stiffness, which is based on the principle of wave reflection. In elderly patients, in whom the aorta is likely stiffer due to aging, the wave reflection may actually be reduced because of increased compliance between the stiffened aorta and the stiffer peripheral arteries. In conclusion, this study provides novel insights into the complex associations between the heart and the brain, which could potentially guide early interventions aimed at improving cardiovascular function and the prevention of cSVD.

Conclusion, implications and future perspectives

In this thesis we expanded the potential clinical utility of MRI-based measures of aortic morphology and function in the assessment of cardiovascular risk and further unraveled complex cardiovascular systemic interactions using MRI. We provided much needed standardized methods and reference values for fundamental MRI-based measures of aortic morphology and function, explored new methods to make PWV more accessible, evaluated the prognostic value of MRI-based measures of aortic morphology and function and explored systemic interactions of cardiovascular function with obesity as well as the brain.

Our recommendation paper on how to measure the aorta using MRI, a recommendation endorsed by the International Society for Magnetic Resonance in Medicine (ISMRM), emphasizes the importance of international collaboration and consistency of acquisition and analysis of MRI scans of the aorta. Accurate follow-up measurements are crucial as patients with aortic diameter of ≥5.5 cm or growth rate of >0.5 cm/year should be considered for aortic surgery according to international guidelines, due to the increased risk of aortic dissection [3, 21]. Besides consistent and accurate measurements of aortic diameters, better predictors for aortic dissection are also needed. The International Registry of the Aortic Dissection showed that >50% of dissections occurred at diameters below the cut-off for pre-emptive surgery [22]. Other geometric and functional parameters like aortic length, curvature, strain, volumetric measurements and flow derived parameters such as wall shear stress have been proposed as potentially more sensitive risk factors for aortic dissection, as was illustrated in our case report. It is therefore likely that MRI will take a predominant place in the diagnostic assessment of aortic pathology, since it is the only technique available to image the entire aorta with additional information on physical properties like strain, stiffness, wall shear stress and blood flow patterns. As artificial intelligence further develops it is expected that these parameters can be generated with minimal input required, which would create vast amounts of useful clinical data to develop new biomarkers for aortic dissection. However, first a clear uniform definition of how these parameters should be acquired is needed to create reliable input for deep-learning training. Nonetheless, creating a clear uniform definition can be challenging due to the continuous development of new scanning techniques. This is also true for PWV. Different MRI scanning techniques such as techniques based on 2D through-plane or in-plane phase-contrast and more

recently 4D flow have been used to describe normal PWV values, in which 4D flow has the advantage of providing local PWV and additional parameters as wall shear stress at the cost of temporal resolution [23]. Despite their differences, however, these techniques have shown good agreement with invasive intra-aortic pressure measurements and overall showed comparable normal PWV values as our study [5, 6, 8, 9, 23].

Along with the rapid technological developments in the 21st century, healthcare expenses have risen to an all-time high [24]. Therefore, we need to look at inventive ways to improve risk stratification and thereby optimize treatment efficiency without making excess costs. New technologies such as artificial intelligence can aid in this process. However, artificial intelligence does not come without its limitations and can even cause harm if not used correctly. As stated above, the success of artificial intelligence algorithms hinges on the integrity of the data put into the model. Biased input will lead to a biased model, as was painfully illustrated in the recent Dutch childcare benefits scandal in which biased input of the artificial intelligence algorithm lead to falsely accusing thousands of parents with a foreign ethnicity of fraud [25]. Furthermore, these algorithms are often viewed as a ''black box'', in which it is unclear how the machine came to the conclusion that it did, making standardization and reproducibility difficult or even impossible [26]. We developed equally functioning prediction models using both traditional as well as deep neural networks for MRI-based PWV that could function as gatekeeper in selecting patients who benefit from further MRI assessment and provided a suggestion for cardiovascular risk management using ePWV. A combination of ePWV with MRI-assessed PWV might be a safe and cost effective strategy for more widely available accurate cardiovascular risk assessment beyond traditional risk factors, however this remains area for future research. A previous ePWV model has been developed based solely on blood pressure and age to predict carotid-femoral PWV, which showed similar predictive performance as compared to our model [27]. Recent studies have demonstrated the potential of carotid-femoral ePWV as it was independently associated with stroke risk in middle aged men as well as a predictor of cardiovascular mortality in acute myocardial infarction patients [28, 29]. Taken these studies into account as well as the fact that MRI is a more accurate technique as compared to carotid-femoral tonometry to establish PWV [30], suggests a potential clinical relevance for MRI-based ePWV as a stratification tool for cardiovascular risk management.

Even though PWV is an independent marker for cardiovascular risk, we found no prognostic value of PWV for aortic growth. The prognostic value of ascending aortic curvature and flow displacement on aortic growth on the other hand, may provide new opportunities in the risk assessment of aortic growth and possibly even risk of dissection. Assessment of prognostic factors for adverse events such as aortic dissection using advanced MRI parameters is challenging, given the need for a large group of patients with extensive baseline MRI assessment in combination with long term follow-up. However, with new large population based imaging studies arising, such as the NEO and UK Biobank (aiming to re-scan 100.000 participants with cardiac, brain and abdominal MRI), this will change in the near future [31]. These large scale population imaging studies can furthermore be used to investigate complex systemic (cardiovascular) interactions and may provide new insight into possible treatment and/or preventive strategies. The non-linear association between cardiac function and cerebral small vessel disease further contributes to the complex puzzle of the heart brain axis, in which the Framingham Heart Study has demonstrated the potential benefit of early diagnosis and treatment of cardiovascular disease in prevention of cognitive decline [32]. In the current worldwide obesity epidemic, the negative association between visceral obesity and cardiac function provides insight into the diverse impact of body fat distribution on cardiovascular function and further supports the benefit of early preventive strategies aimed at reducing obesity. However, the complexity of these pathophysiological processes and interventions should not be underestimated.

References

1. WHO Cardiovascular diseases (CVDs) Fact sheet. Available at: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds) Accessed 26 February 2021.
2. Maroules CD, Khera A, Ayers C, et al. Cardiovascular outcome associations among cardiovascular magnetic resonance measures of arterial stiffness: the Dallas heart study. Journal of cardiovascular magnetic resonance : official journal of the Society for Cardiovascular Magnetic Resonance. 2014;16:33.
3. Erbel R, Aboyans V, Boileau C, et al. 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases: Document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). European heart journal. 2014;35:2873-926.
4. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values'. European heart journal. 2010;31:2338-50.
5. Nethononda RM, Lewandowski AJ, Stewart R, et al. Gender specific patterns of age-related decline in aortic stiffness: a cardiovascular magnetic resonance study including normal ranges. Journal of cardiovascular magnetic resonance : official journal of the Society for Cardiovascular Magnetic Resonance. 2015;17:20.
6. Kim EK, Chang SA, Jang SY, et al. Assessment of regional aortic stiffness with cardiac magnetic resonance imaging in a healthy Asian population. The international journal of cardiovascular imaging. 2013;29 Suppl 1:57-64.
7. Voges I, Jerosch-Herold M, Hedderich J, et al. Normal values of aortic dimensions, distensibility, and pulse wave velocity in children and young adults: a cross-sectional study. Journal of cardiovascular magnetic resonance : official journal of the Society for Cardiovascular Magnetic Resonance. 2012;14:77.
8. Westenberg JJ, Scholte AJ, Vaskova Z, et al. Age-related and regional changes of aortic stiffness in the Marfan syndrome: assessment with velocity-encoded MRI. Journal of magnetic resonance imaging : JMRI. 2011;34:526-31.
9. Harloff A, Mirzaee H, Lodemann T, et al. Determination of aortic stiffness using 4D flow cardiovascular magnetic resonance - a population-based study. Journal of cardiovascular magnetic resonance : official journal of the Society for Cardiovascular Magnetic Resonance. 2018;20:43.
10. Paiman EHM, van Eyk HJ, Bizino MB, et al. Phenotyping diabetic cardiomyopathy in Europeans and South Asians. Cardiovascular diabetology. 2019;18:133.
11. Kroner ES, Scholte AJ, de Koning PJ, et al. MRI-assessed regional pulse wave velocity for predicting absence of regional aorta luminal growth in marfan syndrome. International journal of cardiology. 2013;167:2977-82.
12. Clough RE, Waltham M, Giese D, et al. A new imaging method for assessment of aortic dissection using four-dimensional phase contrast magnetic resonance imaging. Journal of vascular surgery. 2012;55:914-23.

13. van der Palen RL, Barker AJ, Bollache E, et al. Altered aortic 3D hemodynamics and geometry in pediatric Marfan syndrome patients. Journal of cardiovascular magnetic resonance : official journal of the Society for Cardiovascular Magnetic Resonance. 2017;19:30.

14. Osswald A, Karmonik C, Anderson JR, et al. Elevated Wall Shear Stress in Aortic Type B Dissection May Relate to Retrograde Aortic Type A Dissection: A Computational Fluid Dynamics Pilot Study. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery. 2017;54:324-330.

15. Messerli FH. Cardiopathy of obesity--a not-so-Victorian disease. The New England journal of medicine. 1986;314:378-80.

16. Wade K, Chiesa S, Hughes A, et al. Assessing the Causal Role of Body Mass Index on Cardiovascular Health in Young Adults: Mendelian Randomization and Recall-by-Genotype Analyses; 2018.

17. Sawaki D, Czibik G, Pini M, et al. Visceral Adipose Tissue Drives Cardiac Aging Through Modulation of Fibroblast Senescence by Osteopontin Production. Circulation. 2018.

18. Chen YJ, Wang JS, Hsu CC, et al. Cerebral desaturation in heart failure: Potential prognostic value and physiologic basis. PloS one. 2018;13:e0196299.

19. Mitchell GF, van Buchem MA, Sigurdsson S, et al. Arterial stiffness, pressure and flow pulsatility and brain structure and function: the Age, Gene/Environment Susceptibility--Reykjavik study. Brain : a journal of neurology. 2011;134:3398-407.

20. Maillard P, Mitchell GF, Himali JJ, et al. Effects of Arterial Stiffness on Brain Integrity in Young Adults From the Framingham Heart Study. Stroke. 2016;47:1030-6.

21. Hiratzka LF, Bakris GL, Beckman JA, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with Thoracic Aortic Disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. Circulation. 2010;121:e266-369.

22. Pape LA, Tsai TT, Isselbacher EM, et al. Aortic diameter >or = 5.5 cm is not a good predictor of type A aortic dissection: observations from the International Registry of Acute Aortic Dissection (IRAD). Circulation. 2007;116:1120-7.

23. Wentland AL, Grist TM and Wieben O. Review of MRI-based measurements of pulse wave velocity: a biomarker of arterial stiffness. Cardiovascular diagnosis and therapy. 2014;4:193-206.

24. Marino A and Lorenzoni L. The impact of technological advancements on health spending. 2019.

25. Amnesty International. Xenofobe machines – Discriminatie door ongereguleerd gebruik van algoritmen in het Nederlandse toeslagenschandaal. Available at: https://www.amnesty.nl/wat-we-doen/tech-en-mensenrechten/algoritmes-big-data-overheid Accessed 23 March 2022.

26. Mathur P, Srivastava S, Xu X, et al. Artificial Intelligence, Machine Learning, and Cardiovascular Disease. Clin Med Insights Cardiol. 2020;14:1179546820927404.

27. Greve SV, Blicher MK, Kruger R, et al. Estimated carotid-femoral pulse wave velocity has similar predictive value as measured carotid-femoral pulse wave velocity. Journal of hypertension. 2016;34:1279-89.

28. Hsu PC, Lee WH, Tsai WC, et al. Usefulness of Estimated Pulse Wave Velocity in Prediction of Cardiovascular Mortality in Patients With Acute Myocardial Infarction. The American journal of the medical sciences. 2021;361:479-484.

29. Jae SY, Heffernan KS, Kurl S, et al. Association between estimated pulse wave velocity and the risk of stroke in middle-aged men. Int J Stroke. 2021;16:551-555.

30. Pereira T, Correia C and Cardoso J. Novel Methods for Pulse Wave Velocity Measurement. Journal of medical and biological engineering. 2015;35:555-565.

31. Littlejohns TJ, Holliday J, Gibson LM, et al. The UK Biobank imaging enhancement of 100,000 participants: rationale, data collection, management and future directions. Nature communications. 2020;11:2624.

32. Satizabal C, Beiser AS and Seshadri S. Incidence of Dementia over Three Decades in the Framingham Heart Study. The New England journal of medicine. 2016;375:93-4.