Twin Research for Everyone

From Biology to Health, Epigenetics, and Psychology

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CHAPTER

24

Twin studies of cardiorespiratory disease, daily cardiovascular activity and imaging

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24.1 Introduction

In 2019, the top three global causes of death consisted of noncommunicable cardiovascular and lung diseases, with ischemic heart disease being the number one cause of death, followed by stroke and chronic obstructive pulmonary disease[1]. Furthermore, cardiovascular diseases and chronic lung diseases, which also include asthma, are among the leading causes of morbidity worldwide.[1] Twin research provides important insights into the underlying causes of cardiorespiratory disease. Twin studies provide information on the degree of heritability for the various diseases and related traits, and may also add to our understanding of the interplay of genetic factors with various environmental risk factors (gene–environment interactions). A large body of twin studies on cardiorespiratory disease already exists. As it is impossible to review the full scope of the literature here, in part A of this chapter we provide examples of twin studies for a wide range of cardiovascular and respiratory diseases focusing on their results for the role of heritability and the interplay with the environment in cardiorespiratory disease. To fully understand disease development it is also important to understand related processes in a nonpatient population during everyday life. In part B of this chapter, an overview is provided of twin studies using ambulatory monitoring to determine the heritability of everyday variation in blood pressure and heart action. Ambulatory monitoring, however, is not the only way to capture disease processes. In the last few decades, imaging has undergone an extensive development and it now plays a crucial role in the detection and

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characterization of most cardiorespiratory phenotypes. In part C of this chapter, we illustrate the opportunities which arise from combining twin research and imaging research.

24.2 Cardiorespiratory twin studies

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24.2.1 Heritability of the most common cardiovascular diseases

24.2.1.1 Hypertension: blood pressure, blood pressure components, and vascular elasticity

Hypertension is a common complex polygenetic trait, traditionally considered to have a moderate genetic component that interacts with various environmental risk factors such as diet, physical activity, and alcohol consumption, which affects ≤1 billion adults globally.[2] Unraveling the multifactorial basis of essential hypertension has been a central question of numerous twin studies, which have demonstrated moderate heritability of 30%–65%, with the remaining variance explained by unique environmental factors. A meta-analysis of 17 studies found that the mean heritability of systolic (SBP) and diastolic (DBP) blood pressure was 54% and 49%, respectively. The effect of common environmental factors was negligible.[3] Gene-environment (GxE) interaction studies have found that several factors, such as education, eating habits, obesity, and the associated gut microbiota, may change the role of genetic factors.[4]

In the last decade, specific blood pressure components, such as the pulsatile component of blood pressure, pulse pressure (PP), and central blood pressure, have also received attention as they have been shown to predict later cardiovascular events.[5] Twin studies confirmed a moderate heritability for these blood pressure components, with a higher inheritance for the central blood pressure variables than the peripheral blood pressure values.[6]

Arterial stiffness is a dynamic property defined by vascular function and vascular wall structure, which is also a good predictor for future cardiovascular events.[5] Pulse wave velocity (PWV), characterizing vascular elasticity, and augmentation index (AIx), an indicator of wave reflection and peripheral vascular resistance have been also studied and a moderate genetic effect was observed for these traits.[7–10]

The genetic origin of the association of hypertension with BMI has also been the focus of a number of studies. These studies have shown that common genetic factors may for a large part explain the correlation of blood pressure components with BMI.[11–14] Blood pressure components were moderately correlated with BMI, largely because of shared genetic factors. However, for the association of BMI with brachial SBP and DBP, aortic SBP, and mean arterial pressure, acquired, modifiable factors were also found to be important.[11]

24.2.1.2 Carotid atherosclerosis

Carotid atherosclerosis, a risk factor of stroke, is one of the most commonly studied atherosclerotic phenotypes as the degree of carotid atherosclerosis can be easily obtained for the carotid artery using ultrasound. The timeline of atherosclerotic progression includes carotid stiffening, increased intima-media thickness (IMT), and plaque development.

Carotid IMT is a reliable marker of subclinical atherosclerosis. Twin studies attributed a moderate role to genetic factors (25%–60%).[15] The Healthy Twin Study provided evidence for segment-specific heritability of carotid IMT (48% for common, 38% for carotid bifurcation, and 45% for internal carotid artery (ICA), respectively) and a shared genetic variation was reported for the three carotid segments.[16]

Plaque formation in the carotid artery has been associated with a number of cardiovascular (e.g., myocardial infarction), retinal, and cerebral ischemia (stroke) complications. Based on the findings of a twin study involving Italian, Hungarian and American twins, heritability was 78% for the presence of carotid plaque, 74% for plaque-type based on its echogenicity, 69% for plaque size, 74% for plaque sidedness, 74% for plaque numerosity, 68% and 66% for the presence of plaque in carotid bulbs and proximal internal carotid arteries. Unique environmental factors were responsible for the remaining variance (22%–34%).[17] An Italian twin study reported additive genetics to be responsible for the variance of carotid plaques in 52%, with unique factors explaining the remaining variance in the trait.[18] Whole-genome association studies confirmed the role of 14 loci on chromosomes 14 loci with at least suggestive significance in the formation of carotid plaques.[19] Numerous single nucleotide polymorphisms (SNPs) have been linked to the increased risk for the development of subclinical or clinical carotid atherosclerosis, though only a minority of these genes seem to be potential future therapeutic targets.

Carotid flow velocities, determinate by ultrasound, showed a moderate and low (63% and 18%) heritability of the ICA peak systolic velocity and ICA/common carotid artery ratio. One of the few twin studies conducted for three traits showed little evidence for the role of genes as common (56%–63%) and individual environmental factors (37%–44%) explained the vast majority of the variance.[20] An Italian twin study showed carotid vascular wall elasticity to be moderately heritable (19%–46%).[21] These findings support the value of the prevention of modifiable environmental factors in case of altered carotid flow velocities.

24.2.1.3 Coronary atherosclerosis

The classic risk factors associated with coronary heart disease (CHD), which may lead to acute myocardial infarction, are well known. Genetic predisposition was shown to play a role in CHD in family studies, but limited information is available from twin studies. A Swedish large twin study involving 51065 same-sex twins showed that during the 40-year follow-up, the heritability of CHD decreased with increasing age, as well as with increasing levels of BMI, in both men and women. Thus, genetic factors may play a more prominent role for CHD development in the

absence of important environmental factors such as BMI.[22] Another Swedish twin study reported that, in general, probandwise concordances and intraclass correlations for angina pectoris (AP) and CHD death were greater in monozygotic (MZ) than dizygotic (DZ) twins among both sexes, indicating moderate heritability estimates for AP in both sexes (39% for males and 43% for females). The correlation between AP and CHD was almost exclusively explained by the influence of familial factors in both sexes, pointing to both shared genetic as shared environmental pathways.[23] Coronary calcification has been found to be moderately heritable in twins (67%, 95% CI: 37%–100%) when adjusted for age and sex, and overlapping genetic factors are largely responsible for the phenotypical resemblance of coronary and carotid or femoral atherosclerotic calcification.[24] These findings are supported by several published case studies where both twin brothers suffered acute myocardial infarction. In those cases, both twins usually have similar comorbidities as well as a similar course of the acute coronary syndrome.[25–26] This emphasizes the need for screening people with a higher risk of future myocardial infarction. GWAS studies of common SNPs already found some genomic regions explaining ~2.4% of coronary artery calcification's heritability.[27]

24.2.1.4 Aortic atherosclerosis and aneurysm

Calcified aortic plaque, assessed by computed tomography (CT), has shown a high heritability (61%), and the association between aortic wall calcification and increased arterial stiffness can be explained by a common genetic background.[28] Aortic atherosclerosis might lead to abdominal aortic aneurysm (AAA) formation, which is an abnormal dilation of the aorta and may progress to rupture and death. The Danish Twin Registry reported that the probandwise concordance rate for AAA was 2.5 times higher in MZ compared with DZ twins indicating a heritability of 77%.[29]

24.2.1.5 Peripheral arterial disease

Peripheral arterial disease (PAD) means the reduction of blood flow to the lower extremities due to slow and progressive narrowing, blockage, or spasms in a blood vessel.[30] The most common risk factors for PAD are well known, and also include genetic predisposition. A Swedish twin study confirmed the role of genetic (58%) and individual environmental factors (42%) in PAD development.[31] A study of 21 discordant twin pairs revealed that the twin with PAD was more likely to be sedentary and a persistent smoker.[31] An ultrasound twin study revealed a heritability of 44%–47% for common and superficial femoral IMT.[32] The variance in femoral plaques was due to genetic factors and the remaining 50% was explained by common (15%) and unique (35%) environmental factors. Sidedness and number of femoral plaques were mainly under genetic control. Femoral plaque composition was explained by genetics (64%) and unique environment (36%). Covariation between the liabilities to carotid and femoral plaques was mainly attributed to shared genes (77%).[18] Recent forays into GWAS and epigenetics studies have suggested an important role of environmental factors in DNA methylation, histone acetylation signatures, and miRNA regulation.[33]

24.2.2 Twin studies in frequent respiratory diseases

24.2.2.1 Lung function

A lung function test is a noninvasive method to investigate how well the lungs are working. Lung function variables (derived from spirometry) are moderately to highly genetically determined based on the results of multiple twin studies.[34–38] GWAS studies identified a number of genes related to respiratory function, such as TMEM132C, UNC93A, and TTLL2, and PPT2 on chromosome 21 in a Korean twin population.[39]

24.3 Twin studies of common chronic lung diseases

24.3.1 Chronic obstructive pulmonary disease (COPD)

COPD is a chronic inflammatory lung disease that causes obstructed airflow from the lungs, leading to airflow limitation by inflammation and destruction of the airways and lung parenchyma. The fast majority of COPD cases (80%–90%) are caused by smoking, which by itself is heritable, as discussed in Chapter 23. The susceptibility to develop severe COPD is strongly influenced by genetic factors (approximately 60%).[40] Heritability was also suggested for specific COPD components in a pilot study of one COPD-concordant and five COPD discordant twin pairs who underwent high resolution CT (HRCT).[41]Lung density and radiological markers of small airway disease (bronchial wall thickening, bronchiectasis, mucus plug formation, air trapping, and emphysema score) were very similar in identical twins, while other components were less similar among MZ twin pairs.[41] Behaviors, such as eating fruit, smoking, and alcohol use may also influence disease risk and those health behaviors are also in part heritable (see other chapters).

24.3.2 Chronic bronchitis

Chronic bronchitis, long-term inflammation of the bronchi, is characterized by chronic cough and sputum from the airways. A Danish twin study found a hereditary predisposition to chronic bronchitis with heritability estimates of 55% in women and 25% in men.[42] The heritability estimate for self-reported chronic bronchitis was a moderate 40% in Swedish samples, with common genetic factors explaining only 14% of the association with smoking.[43] Among twin pairs discordant for smoking, chronic bronchitis was significantly more common in the smoking twin compared with the nonsmoking cotwin.[44]

24.3.3 Asthma

Asthma is a chronic inflammatory disease of the airways. Its development was linked to genetic factors in around 35%–80%. A study in the Netherlands Twin Register confirmed high heritabilities for asthma (75%) and allergy (66%).[45] Childhood

asthma was also highly heritable (82%) in a Swedish twin study.[46] Nonadditive genetic influences may also be important, which may have consequences for gene hunting strategies. A population-based, cross-sectional Swedish twin study involving 612 MZ and same-sex DZ schoolchildren found that the association between asthma and exhaled nitric oxide level is to a large extent explained by genetics via allergen-specific IgE level and not blood eosinophils which might partly explain the clinical heterogeneity of asthma.[47] Environmental factors play a role in determining individual variations in the severity of asthma symptoms. A retrospective cohort study in twins aged 3–10 years showed that early life antibiotic use, particularly prescribed for respiratory infections, was associated with an increased risk of asthma.[48] In addition, epigenetic changes such as DNA methylation and histone acetylation can be modified by certain environmental factors, such as maternal nutrition, smoking, microbiome, xenobiotic exposure, and stress. Discordant twin studies found DNA methylation differences (HLX gene cg23603194) among asthma patients.[49]

24.3.4 Lung cancer

Smoking is the most important cause of lung cancer. However, genetic effects account for a significant amount of the variation in the liability to develop lung cancer. Heritability of lung cancer among current smokers was 41% and forever smoking pairs 37% according to the Nordic Twin Study of Cancer.[43] GWAS studies found an association with the *CHRNA5* functional D398N (rs16969968) variant, which was identified for smoking as well. This might explain the link with lung cancer.[50]

24.3.5 Exhaled biomarkers

Human-exhaled breath contains a mixture of over 3000 volatile organic compounds (VOCs), this exhaled breath pattern can be distinguished by pattern recognition using electronic noses (e-noses). Most human diseases such as lung cancer are affiliated with multiple chemical compounds. VOC pattern was determined by shared environmental rather than hereditary factors in twins.[51] The bronchodilator response to airway inflammation was studied in healthy twin pairs by measuring FEV1 before and after inhalation of 400 μg salbutamol. A heritability of 14.9% to 44% was found in twin studies.[38,52]

24.3.6 Obstructive sleep apnoea (OSA)

OSA is caused by the repetitive collapse of the upper airway during sleep and one of the major sources of excessive daily sleepiness and cognitive dysfunction. Hereditary factors explained the background of snoring.[53, 54] The heritability of OSA was studied using polysomnography. Heritability estimates for apnoea hypopnea index, respiratory disturbance index (RDI), and oxygen desaturation index ranged from 69% to 83%, while OSA was itself 73% heritable.[55] Genetic factors determinate the co-occurrence of OSA with hypertriglyceridaemia.[56]

24.3.7 In conclusion

Twin research has provided insight into the genetic and environmental factors and gene–environment interactions of cardiorespiratory diseases. Most studies confirmed the relevance of genetic factors and underline the role of screening high-risk individuals. Reducing cardiovascular risk factors is of paramount importance for individuals genetically susceptible to cardiovascular disease. Findings of twin studies may help guide personalized therapy for at-risk patients in the future, as well as prevention strategies, thereby reducing the incidence of chronic cardiovascular and lung diseases.

24.4 Gaining insight into the heritability of everyday cardiovascular function by twin studies

Gonneke Willemsen & Eco de Geus

24.4.1 Introduction

As outlined above, genetic variation plays a large role in the development of cardiovascular diseases. However, to fully understand the pathway from genes to disease, we also need to understand normal everyday functioning of the systems involved, not only in patients but also in the nonpatient population. For this purpose, it may not be sufficient to obtain momentary physiological measurements during a check-up, whether it be at a GP-office or during a large-scale population screening. Such momentary measurements are unlikely to capture all the individual variation in daily life, and the situation may also influence the measurement (think of the white coat effect on blood pressure). Studies have tried to mimic the response to daily challenges within the laboratory, measuring cardiovascular activity while exposing study participants to mental and/or physical challenges. Such laboratory stressors will often be of insufficient intensity and duration to trigger the full set of physiological responses that come into play when stress is "for real."[57] They will thus fail to reveal the slower counter-regulatory responses as well as allostatic adaptations that occur on a time scale of days or weeks. An example is the gradual build-up in resting blood pressure over the course of a stressful work week that subsides in the weekend.[58,59] Laboratory studies also preclude examination of the activities that may have the largest clinical relevance like job-related strain, marital conflict, child care or, at the other end of the spectrum, restful sleep. The solution to increase ecological validity of cardiovascular assessment has been to use ambulatory monitoring of cardiovascular signals in real-life settings, using the increasingly advanced technological solutions that enable this. Superior predictive validity for long term cardiovascular health has repeatedly been shown for ambulatory blood pressure, where full 24-h recordings proved better predictors for cardiovascular morbidity and mortality than laboratory or office measurements.[60–63]

24.4.2 Ambulatory studies of blood pressure and heart rate

Over the last three decades, several ambulatory studies have also been performed in twin families. These studies have focused mostly on the data obtained with an ambulatory blood pressure monitor with blood pressure as well as average heart rate (HR) obtained at intervals over a 24-h period.[64–71] The first twin study on 24-h blood pressure monitoring was published in 1994 and included only 28 MZ and 16 DZ male twin pairs. Participants wore a blood pressure monitor while freely moving around in a hospital, where they slept in the sleep laboratory. No exact heritability estimates were provided but based on the twin comparisons the authors concluded that genetic effects were present for the 24-h profile, in particular the daytime values, of DBP and HR.[64] While this study did not demonstrate genetic effects for SBP, two other small scale studies published in the 1990s,[65, 66] which allowed participants to engage in their normal day life, showed heritability for all three cardiovascular parameters, SBP, DBP, and HR. From 2003 onwards several larger twin studies on ambulatory blood pressure monitoring were conducted.[67–73] As can be seen in Table 24.1, the outcomes of these twin studies are, overall, very much in line with each other and show clear evidence for heritability of SBP (ranging from 32% to 71%) and DBP (ranging from 31% to 70%). Only one of the larger studies[67] included heritability estimates for HR, estimating this to be 70% in men and 51% in women, when including all participants.

Generally, the estimates for the different quantifications of the blood pressure or HR level (e.g., 24-h average, day-time average, night-time average) do not vary strongly across the larger studies. Differences between studies may be mostly due to choices in design and operationalization of the blood pressure measure. For instance, the lowest estimates for SBP (38% and 32%) were seen by Kupper et al.[68] for the morning and evening average, respectively, when excluding participants on antihypertensive medication (more on this later), while the outcomes for the 24-h average for SBP were closer together at 60%[67] and 70%.[69] Indeed, when Xu et al.[70] compared the heritability using data from two different twin registers (East Flanders Prospective Twin Survey and the Georgia Cardiovascular Twin Study) but with the same operationalization, they found that the estimates could be considered equal. Wang et al.[69] examined whether the same genes may influence daytime levels as night-time levels. The genetic correlation between daytime and nighttime levels was 0.77 for SBP and 0.66 for DBP indicating that common genes underlie the blood pressure levels during the day and night. However, additional unique genetic influences emerged for the nighttime levels. While most studies focused on the levels during the day and night, one study looked at particular aspect during the night, namely dipping.[71] In most individuals blood pressure decreases during the night, and not showing this drop may be related to an increased risk for mortality[74] and morbidity,[75] though being an extreme dipper at night may also be associated with an increased morbidity.[76] Wang et al[71] showed that this trait of having a nocturnal fall in blood pressure was highly heritable with an estimate of 59% for SBP and 81% for DBP.

So far, none of the studies conducting formal twin modeling of ambulatory measured blood pressure showed any evidence for the influence of common environmental factors. Although power may have been low to detect small effects of a shared twin environment, a fair conclusion is that the individual variation in blood pressure is predominantly

TABLE 24.1 Overview of the papers and heritability estimates referred to in the book chapter with regards to ambulatory blood pressure monitoring (ordered by publication date).

First author and year of publication	Sample	Age (years)	Cohort	Measurement	Variable	Heritability estimates[a]
Degaute et al. (1994)[64]	28 MZ & 16 DZ male pairs	Range: 16–36	Recruited via Belgian Twin Registers and university records	25-h measurement using Medilog blood pressure monitor	SBP	No evidence for genetic influences for any of the operationalizations
					DBP	24-hr: genetic effect
						Daytime: genetic effect
						Additional indicators: not clear
					HR	24-h: trend
						Daytime: trend
						Additional indicators: trend
Fagard et al. (1995)[65]	26 MZ & 27 DZ male pairs	Range: 18–38	East Flanders Prospective Twin Survey	Conventional measurement in the morning During the rest of the day and subsequent night measurements using Spacelab blood pressure monitor	SBP	Conventional: 64
						24-hr: 70
						Awake: 63
						Asleep: 72
						Awake crest: 61
						Awake 2pm-8pm: 4[d]
						Nighttime trough: 77
					DBP	Conventional: 73
						24-h: 73
						Awake: 55
						Asleep: 51
						Awake crest: 56
						Awake 2pm-8pm: 1[d]
						Nighttime trough: 57
					HR	24-h: 70
						Awake: 65
						Asleep: 52

(Continued)

TABLE 24.1 Cont'd

First author and year of publication	Sample	Age (years)	Cohort	Measurement	Variable	Heritability estimates[a]
Somes et al. (1995)[66]	38 MZ & 28 DZ pairs	Range: 15–17	The Medical College of Virginia Twin Study	24-h measurement using Accutracker blood pressure monitor	SBP DBP HR	24-h: 22 (incl all DZ pairs) 24-h: 38 (incl all DZ pairs) 24-h: 32 (incl all DZ pairs)
Vinck et al. (2001)[72]	150 MZ & 122 same sex DZ pairs	Range: 18–76 Analyses in all versus 3 age groups	East Flanders Prospective Twin Survey, registers from Leuven, Hasselt and Sint-Truiden	24-h measurement using Spacelab blood pressure monitor Conventional BP during separate visit	SBP DBP	Conventional: 62 (all ages) Daytime: 49 (all ages) Nighttime: 49 (all ages) Conventional 57 (all ages) Daytime 49 (all ages) Nighttime 50 (all ages)
Fagard et al. (2003)[67]	125 DZ, 97 MZ-DC & 128 MZ-MC	Range: 18–34	East Flanders Prospective Twin Survey	24-h measurement using Spacelab blood pressure monitor Conventional BP during separate visit	SBP DBP HR	Conventional 63 24-h average 60 Conventional 55 24-h average 62 Conventional 50 24-h average: 70 (men), 51 (women) Excluding MZ-MC: 66 (no gender difference)
Hottenga et al. (2005)[b,73]	165 MZ twins, 217 DZ twins, 184 singleton siblings	Range: 17–81	Netherlands Twin Register	Ambulatory measurements during the day using Spacelab blood pressure monitor	SBP DBP	Awake: 48 Awake: 44

First author and year of publication	Sample	Age (years)	Cohort	Measurement	Variable	Heritability estimates[a]
Kupper et al. (2005)[68]	230 MZ twins, 305 DZ twins and 257 singleton siblings	Mean = 31.3 (SD =11.2)	Netherlands Twin Register	Measurements during the day using Spacelab blood pressure monitor	SBP	Normotensive only/no antihypertensive medication/correction for antihypertensive medication Morning: 38/49/50 Afternoon: 50/57/57 Evening: 32/42/44
					DBP	Normotensive only/no antihypertensive medication/correction for antihypertensive medication Morning: 40/52/55 Afternoon: 55/61/63 Evening: 31/43/46
Wang et al. (2009)[71]	European Americans: 51 MZ and 54 DZ pairs, 30 singleton twins	Mean = 17.2 (SD = 3.4)	Georgia Cardiovascular Twin Study	24-h measurement using Spacelab blood pressure monitor	SBP	Day: 70 Night: 68 Day-night: 75 Night-specific: 30 Dipping: 59
	African-American: 36 MZ & 46 DZ pairs, 26 singleton twins				DBP	Day: 70 Night: 64 Day-night: 56 Night-specific: 43 Dipping: 81

(Continued)

TABLE 24.1 Cont'd

First author and year of publication	Sample	Age (years)	Cohort	Measurement	Variable	Heritability estimates[a]
Wang et al. (2011)[69]	European Americans: 104 pairs, 30 singleton twins African-American: 78 pairs, 30 singleton twins	Mean = 17.1 (SD = 3.4)	Georgia Cardiovascular Twin Study	24-h measurement using Spacelab blood pressure monitor Conventional Office BP[c]	SBP DBP	Office: 63 24-hr: 71 Office: 59 24-hr: 69
Xu et al. (2015)[70]	703 twins – 308 pairs and 87 singletons Meta-analysis including additional 242 white and 188 black twins	Range 18–34	East Flanders Prospective Twin Survey Meta-analysis including Georgia Cardiovascular Twin Study	24-h measurement using Spacelab blood pressure monitor Conventional BP (Office)	SBP DBP	Daytime: 60; meta: 63 Nighttime: 51; meta: 56 Nighttime-specific: 21; meta: 22 Daytime 54; meta: 59 Nighttime 46; meta: 53 Nighttime-specific 26; meta: 30

[a] *Model fitting results are presented when given.*
[b] *Heritability estimates for three separate laboratory studies were also included in the paper, but not presented here as they involved different participant groups.*
[c] *In addition, two 10-min stress tasks were performed in the laboratory. Data not presented as outside the scope of this chapter.*
[d] *Indicates occasions when common environment could not be excluded from the model.*
Note. Conventional or office BP is the average of several, generally three, sitting BP measurements conducted by or in the presence of the experimenter.

determined by genetic and unique environmental factors. This echoes similar findings for conventional blood pressure.[77] Several twin studies directly compared the heritability of ambulatory and conventional blood pressure measurements (e.g., the average of two or three measurements taken while sitting) obtained in the same individuals,[65,69,72] generally concluding that there were no differences in the extent of heritability of ambulatory and conventionally obtained blood pressure measurements. This was confirmed by Hottenga et al.[73] who compared blood pressure data from three laboratory twin studies and one ambulatory monitoring study. However, Wang et al.[69] suggested that there may be differences in the genes influencing conventional blood pressure measurements versus blood pressure measured over a prolonged period using ambulatory monitoring.

The outcomes of the twin studies on blood pressure heritability seem generalizable to other populations. Two studies[68,73] included in addition to twins also their singleton siblings. No differences in means, variances, and covariances emerged for blood pressure in twins and their singleton siblings, indicating that the results of twin studies may be generalized to nontwin populations. Also, studies exploring sex differences found no evidence for different heritability estimates for men and women in SBP or DBP.[67,69,71,73] Furthermore, Wang et al.[69,71] reported similar heritability estimates for European-American and African-American twins. The one study to examine age differences[72] pointed to a trend for a higher heritability in younger cohorts but this did not reach significance. Finally, Fagard et al.[67] examined whether the chorionicity of MZ twins (whether they were mono- or bichorionic) may influence the heritability of ambulatory blood pressure. Using data from the East Flanders Prospective Twin Study, the authors showed that chorionicity did not influence the heritability estimates for blood pressure. Only for HR gender differences emerged when monochorionic MZ twins were excluded.

Importantly, Kupper et al.[68] replicated previous findings from a family based design,[78] by showing that excluding participants on antihypertensive medication has substantial effects on heritability estimation. Heritability estimates were at its highest when, instead of excluding participants on antihypertensive medication, a correction was made for the average effects of the anti-hypertensive medication used. This correction should thus be applied in genetic investigations of ambulatory blood pressure as it provides the best reflection of the true population variance in blood pressure.

24.4.3 Ambulatory monitoring of other cardiovascular parameters

While the heritability of ambulatory monitored blood pressure and simultaneously measured HR has received much attention, very few heritability studies focused on the ambulatory monitoring of other parameters of cardiovascular function. These parameters are generally obtained by more continuous measurement of the heart function, extracting indicators of HR variability which may reflect parasympathetic or sympathetic influences on the heart. For an extensive explanation of these indicators and a general overview of the heritability of these indicators, the reader is referred to de Geus et al.[79]. The Netherlands Twin Register conducted several studies[80–82,84,85] on ambulatory cardiac parasympathetic nervous system activity using HR variability data obtained in twins and their singleton siblings with an ambulatory monitor of the electro- and impedance cardiogram (see box 24.1). As can be seen in Table 24.2, these studies demonstrated heritability for root mean square

Box 24.1 The monitor was developed for easy wear, allowing for normal everyday activities. To show the size of the monitor, it is here worn outside the clothing. The inset shows the monitor in more detail.

The Netherlands Twin Register has conducted a number of studies on daily life cardiovascular activity. The fast majority of these studies made use of the VU-AMS, which continuously monitors the electrocardiogram and impedance cardiogram. The monitor was developed at the Department of Biological Psychology, Vrije Universiteit to allow participants freedom of movement and enable the measurement of continuous heart action during several days to provide insight into the different factors influencing normal day cardiac action. Since this department also houses the Netherlands Twin Register (www.twinregister.org) this resulted in the largest twin study to date on ambulatory recorded indices of cardiac function. For an overview of the papers including the use of the VU-AMS, see www.vu-ams.nl/research.

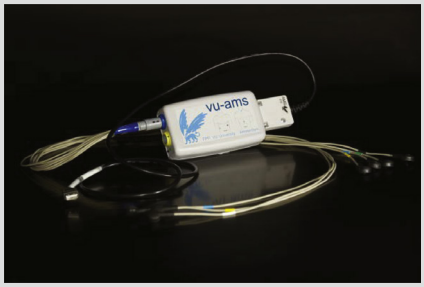

TABLE 24.2 Overview of the papers and heritability estimates with regards to ambulatory monitoring of heart action (as mentioned in the chapter and ordered by publication date).

First author and year of publication	Sample	Age	Cohort	Monitor	Variable	Heritability estimate (%)[a]
Kupper et al. (2004)[81]	218 MZ twins, 301 DZ twins and 253 singleton siblings	Men: mean = 1.3 (SD = 10.6) Women: mean = 30.8 (SD = 10.9)	Netherlands Twin Register	24-h ambulatory electro- and impedance cardiography using the VU-AMS	SDNN	Morning: 35 Afternoon: 36 Evening: 47 Night: 43
					RMSSD	Morning: 41 Afternoon: 48 Evening: 48 Night: 40
Kupper et al. (2005)[84]	222 MZ twins, 305 DZ twins and 253 singleton siblings	Mean = 31.0 (SD = 10.8)	Netherlands Twin Register	24-h ambulatory electro- and impedance cardiography using the VU-AMS	Repiration rate	Morning: 27 Afternoon: 44 Evening: 50 Night: 81
					lnRSA	Morning: 40 Afternoon: 49 Evening: 55 Night: 54
					Heart period	Morning: 37 Afternoon: 45 Evening: 40 Night: 48
Kupper et al. (2006)[80]	215 MZ twins, 296 DZ twins and 244 singleton siblings	Mean = 30.6 (SD = 10.4).	Netherlands Twin Register	24-h ambulatory electro- and impedance cardiography using the VU-AMS	PEP	Morning: 62 Afternoon: 62 Evening: 55 Night: 48
					PEP/LVET ratio	Morning: 58 Afternoon: 56 Evening: 48 Night: 35

(Continued)

TABLE 24.2 Cont'd

First author and year of publication	Sample	Age	Cohort	Monitor	Variable	Heritability estimate (%)[a]
Su et al. (2010)[83]	121 MZ twins and 77 DZ twins	MZ twins: mean = 54.3 (SD = 2.9) DZ twins; mean = 54.9 (SD = 2.7)	The Twins Heart Study, within the Vietnam Era Twin Registry	24-h ECG (Holter) monitor	lnTPow	Univariate: 63 Bivariate with BDI - unadjusted: 64 Bivariate with BDI - adjusted for covariates: 62
					lnULF	Univariate:59 Bivariate with BDI - unadjusted: 61 Bivariate with BDI - adjusted for covariates: 60
					lnVLF	Univariate: 57
					lnLF	Univariate: 43
					lnHF	Univariate: 56
Neijts et al. (2014)[82]	486 MZ twins, 517 DZ twins and 285 nontwin siblings	Mean = 33.5 (SD = 9.2)	Netherlands Twin Register	24-h ambulatory electro- and impedance cardiography using the VU-AMS	pvRSA	Including/excluding participants with a ceiling effect Sleep: 48/53 Sitting: 53/57 Active: 57/57 Max during night: 53 Max during night corrected for ceiling: 55 Daytime RSA-IBI slope: 35
					RMSSD	Including/excluding participants with a ceiling effect Sleep: 53/53 Sitting: 54/52 Active: 49/46
					SDNN	Including/excluding participants with a ceiling effect Sleep: 46/47 Sitting: 48/46 Active: 53/54
					IBImax	52% (corrected for ceiling effects)

First author and year of publication	Sample	Age	Cohort	Monitor	Variable	Heritability estimate (%)[a]
Neijts et al. (2015)[85]	486 MZ twins, 517 DZ twins and 285 nontwin siblings	Mean age 28.5 yrs (SD = 9.6) to 37.2 yrs (SD = 5.4) for the three different waves of data collection	Netherlands Twin Register	24-hr ambulatory electro- and impedance cardiography using the VU-AMS	IBI[a]	Sleep: 52 Leisure: 51 Wake: 52 Work (sitting): 69 Work peak level: 60 5 of 6 reactivity scores were significant: 29–40
					pvRSA[a]	Sleep: 46 Leisure: 43 Wake: 55 Work (sitting): 53 Work peak level: 33 4 of 6 reactivity scores were significant: 34 to 47
					PEP[a]	Sleep average: 38 Leisure average: 25 Wake average: 41 Work (sitting): 44 Work peak level: 39 3 of 6 reactivity scores were significant: 10–19

[a] *Outcomes of different bivariates models differed slightly for the mean level. In case of differences, the lowest value was taken.*

MZ, monozygotic; DZ, dizygotic; SD, standard deviation; SDNN, standard deviations of all normal-to-normal intervals; RMSSD, root mean square of successive differences between adjacent normal-to-normal intervals; ln, logarithm transformation; pvRSA, peak valley respiratory sinus arrhythmia; PEP, pre-ejection period; LVET, left ventricular ejection time; TP, total power; VLF, very low frequency; LF, low frequency; IBI, interbeat interval.

of successive differences between adjacent normal-to-normal intervals (RMSSD, 40%–54%), and for respiratory sinus arrhythmia (RSA, 33%–57%). The NTR also examined ambulatory pre-ejection period (PEP), an indicator of cardiac sympathetic nervous system activity.[80] The heritability for PEP ranged somewhat more than for the parasympathetic indicators, from 25% to 62%, depending on the sample and operationalization. When PEP was corrected for left ventricular ejection time heritability estimates ranged from 35% at night to 58% in the morning. A further indicator of autonomic activity, the standard deviations of all normal-to-normal intervals (SDNN) were also found to be heritable in these studies, with a narrow range from 35% to 48%.[81,82] Additional indicators of HR variability, obtained by spectral analysis were studied by Vaccarino et al.[83] who showed all to be highly heritable. Interestingly, they also found that common genes underlay the association of two indicators total power and ultra-low frequency with the score on the Beck Depression Inventory.

The NTR studies further showed that common genes influenced the parameters across the different periods of the day though at night new specific genes may also emerge.[80,81] Common genes also explain a large part of the association between closely related variables such as RSA with respiration rate and heart period[84] and SDNN, RSA, and RMSSD.[82] To gain more insight into the response to challenges during the day, Neijts et al.[85] expanded upon the findings by Kupper et al.[80] by operationalizing several definitions of reactivity (e.g., work levels while sitting versus average sleep or leisure levels). Significant heritability was seen for HR and parasympathetic reactivity (here indexed by RSA) and to a lesser extent for sympathetic reactivity (indexed by PEP). Further analyses showed that the response to the challenging periods of the day compared to resting levels was due to the emergence of additional genes influencing the response.

24.4.4 In conclusion

Overall, twin studies of ambulatory monitored cardiovascular activity show the importance of genetic factors for cardiovascular activity during the day and night. In addition, by studying cardiovascular function for prolonged periods of time valuable insights can be obtained in specific phenomena relevant to cardiovascular morbidity and mortality. Further studies are expected to provide more insight into the interplay of genetic and environmental factors on daily cardiovascular function and cardiovascular risk.

25.5 Imaging of twins

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Imaging has developed rapidly in recent decades, with the emergence of new techniques. X-ray, mammography, and CT involve ionizing radiation. Therefore, most of these twin studies are mainly retrospective. Ultrasound propagates by sound waves, while magnetic resonance imaging (MRI) operates through a magnetic field.

Given their lack of harmful effect, these imaging modalities are frequently applied in twin studies. Here we briefly describe the techniques and present some examples to illustrate the enormous potential of imaging twin studies for gaining insight into disease processes.

25.5.1 X-ray

The use of X-ray has become the gold standard, among others, to analyze bone structure and abnormalities as well as certain thoracic abnormalities. There are some case studies with radiographs on twins, including a case study of a Scottish identical twin pair with recurrent right elbow dislocation[86] and a case of conjoined twins.[87]

Taking into account the effects of ionizing radiation, most twin studies analyze X-ray image data that were obtained in hospitals as part of the screening of potentially affected twins. A UK twin study examined the heritability of osteoarthritis of the hip joint which was between 58% and 64%.[88] Genetic determinants of hip joint morphometry and their relationship to hip cartilage thickness were also studied, and genetic factors accounted for most of the variation in minimal joint space and acetabular anatomy.[89]

Additional radiography studies analyzed the spine in the development of idiopathic scoliosis. Twin studies have shown that MZ twins are more often concordant for idiopathic adult scoliosis than DZ twin pairs. Phenotypic differences between MZ twins may also be the result of epigenetic differences. Genetic factors contributing to the spine curvature were also raised, as well as the severity of the curvature of scoliosis.[90, 91]

A population-based Korean twin study examined the origin of a common foot deformity, hallux valgus, in twins and their families with X-Ray. Heritability was estimated at 51% for hallux valgus and 47% for hallux valgus angle, and it was suggested that genetic vulnerability may be reinforced by lifestyle factors, such as shoe wearing habits or preference.[92]

Dual-energy X-ray absorptiometry (DEXA) was used for measuring bone mineral density and body composition in twins which indicated that 20% of adult hip axis length is associated with environmental factors. Accordingly, any environmental effects of physical activity or nutrition on hip geometry must occur before early teenage years.[93] Bone mineral density was strongly heritable in twins, especially in females at all locations using both DEXA and quantitative bone ultrasound (QUS), which may explain the importance of family history as a risk factor for bone fractures. Unshared environmental effects accounted for the rest of the variance with slight differences in magnitude across various bone regions, supporting the role of lifestyle in preventing osteoporotic fractures with various efficacy in different bone regions.[94]

25.5.2 Breast mammography

Compared to the traditional X-ray, breast mammography is performed with different physical parameters and photographic techniques. It is therefore suitable for detecting

subtle structural differences in the soft parts of the breast. For women of equivalent age, those whose breasts display greater white or bright areas on a mammogram—i.e. greater mammographic density—are at 1.8–6 times greater risk of developing breast cancer. Twin studies have reported that, under the assumptions of the classic twin model and after adjusting for age, BMI, and other determinants, the patterns of twin correlations for mammographic density measures are consistent with additive genetic factors explaining ~60% of their residual variances.[95,96] An Australian twin study also revealed that at least two common breast cancer susceptibility genetic variants were associated with mammographic density measures that predict breast cancer. These findings could help elucidate how those variants and mammographic density measures are associated with breast cancer susceptibility.[97] The heritability of the extent of dense and nondense areas within the dense breasts was also examined, and a negative genetic correlation was found between these two parameters. This may mean that the same genetic factors affect both parameters, but in different ways.[96] In a Korean twin study, the same high heritability of mammographic density was found as in Western women indicating that environmental factors are responsible for the differences in the risk of breast cancer across populations. An inverse additive genetic correlation was reported between dense and nondense mammographic area predicting that genes positively associated with dense area may have the opposite effect on nondense area.[98]

25.5.3 Ultrasound

Ultrasound is one of the most commonly involved imaging modality in twin research. The first twin studies using ultrasound began in the mid-1990s and have examined a wide variety of disorders. To name a few, in 1995, a study of twin pairs with polycystic ovary syndrome (PCOS, a disease where numerous small cysts are seen in the ovaries together with an abnormal amount of androgen production) showed that 5 of 19 pairs of MZ twins were discordant for PCOS. Accordingly, the authors concluded that PCOS may be a polygenic condition, an X-linked disorder, the result of an intrauterine or a postnatal event, or the result of an interaction between genetic and environmental factors.[99] In a Finnish twin study, transvaginal ultrasound was applied, and heritability of the number of uterine fibriods (myomas, benign tumors) was found to be 26%. The incidence of myomas was associated with a higher BMI, which is known to be a highly hereditary trait[100] (see Cancer and Twin Research chapter). A Hungarian twin study analyzed the background of the common liver lesion of nonalcoholic fatty liver disease and found this to have no genetic background, that is, common (74.2%) and individual (25.8%) environmental factors accounted for the variance of the disease.[101] Thyroid gland is easily examinable with ultrasound, therefore, various twin studies analyzed this endocrin organ. Based on a Danish twin study, genetic factors accounted for 71% of the individual differences in thyroid volume. This fits the observation that not all individuals develop goiter even in iodine-deficient areas.[102]

25.5.4 Computed tomography (CT)

CT is a diagnostic imaging procedure that involves rotating X-ray beams around the body to build cross-sectional images. In most cases, intravenous contrast material is administered in order to observe enhancement of certain organs or lesions for better characterization. Given the invasive nature and the ionizing radiation exposure, most twin studies are retrospective or case studies in this field or in the case of prospective study conducted with low or ultralow radiation.

A CT study on twin pairs found no significant differences between MZ and DZ twins in the development of paranasal sinuses which was mainly influenced by environmental factors, while the development of one common normal anatomical variant, the concha bullosa was partly genetically influenced.[103]

Since CT is the best choice for imaging the bone structure, several twin studies analyzed heritability of bone structures. To understand the genetic background of the microarchitecture of the distal tibia and distal radius and remodeling markers, female twin pairs aged 40 to 61 years underwent high-resolution peripheral quantitative CT. A substantial genetic component has been found, which indicates that middle-aged women differ in their bone microarchitecture and remodeling markers more because of differences in their genetic factors than differences in their environment.[104] The same group reported that a larger within twin pair difference in cortical porosity of the distal tibia was associated with a larger within twin pair differences in height. Accordingly, taller women assemble wider bones with relatively thinner and more porous cortices predisposing to fracture.[105]

25.5.5 Magnetic resonance imaging (MRI)

MRI is a noninvasive imaging technology that produces three-dimensional detailed anatomical images based on the detection of change in the direction of the rotational axis of hydrogene protons. Based on its noninvasive nature and lack of ionizing radiation, MRI is a popular multiparametric imaging modality in prospective study of twins.

Obesity is a common trait in the field of MRI twin research. Finnish twin researchers have shown by MR examination of long-term discordant twin pairs in terms of physical activity that regular physical activity is an important factor in preventing the deposition of high-risk adipose tissue, even though genetic determinants and childhood environmental factors play a role.[106,107] Australian researchers used MR to show a link between low birth weight and abdominal visceral and subcutaneous adipose tissue volume, which means that low birth weight is a high risk for abdominal obesity.[108] This is consistent with the results of epigenetic studies, as it reflects abnormal programming during pregnancy. An interesting example of high-risk adipose tissue accumulation was presented in 16 middle-aged (50–74 years) same-sex twin pairs with long-term discordance in physical activity habits. The inactive twins had 50% more visceral adipose tissue, 54% higher intramuscular adipose tissue, and 170% higher liver fat score compared to the physically active twins.[106]

The same Finnish research group also found a link between pancreatic fat content, insulin resistance and liver fat content.[109]

25.5.6 Neuroimaging

Neuroimaging is the other field where numerous twin studies have been conducted. To name a few, structural MRI data from the Human Connectome Project was used to investigate body mass index (BMI) associated differences in gray matter volume (GMV) within MZ twin pairs discordant for BMI. Heavier MZ twin siblings demonstrated less GMV within certain brain cortical areas. These results indicated that nongenetic influences and the mere presence of a higher BMI constitute relevant factors in the context of body weight-related structural brain alterations.[110]

A quantitative neuroimaging study in twins between 13 and 24 years of age using diffusion tensor imaging confirmed that genetic factors play a key role in the development of white matter microstructure.[111] MRI-visible dilated perivascular spaces (dPVS) in brain are common findings even in healthy young persons. A study on healthy young adult twins and nontwin siblings confirmed that dPVS volumes within basal ganglia and white matter were highly determined by genetic factors, especially in white matter.[112]

25.6 Future directions: radiogenomics and imaging epigenetics

The radiological and pathological sciences have developed closely together in recent decades, leading to the emergence of radiogenomics (or imaging genomics), a new branch of research that examines the relationships between radiological and histological features. Radiological tumor phenotypes can be used to provide noninvasive information on gene expression patterns, tumor subtypes, and even molecular biology data.[113] Radiogenomics has not yet been applied to discordant twins. However, valuable studies could be performed involving twins, investigating not only the radiomorphology but also the underlying epigenetic or environmental factors in the affected sibling compared to the healthy twin.[114]

The combination of epigenetics with imaging can answer questions whether various imaging phenotypes can predict epigenetic modification, that are related to organ (such as brain) structure, function, and metabolism, which impact disease risk and progression. The integration of genetic imaging methods with epigenetic markers in humans appears promising, especially in neuroimaging.[115] Imaging epigenetics will provide deeper insight into the causative pathogenetic and pathophysiological pathways through which genes and environment interrelate during life and impact physiology, pathophysiology, aging, and disease, especially in MZ twins discordant for a chronic disease.[114] This knowledge may open doors for the development of novel biomarkers and preventive and disease-modifying treatments.

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