

# Genetic Contribution to the Variance of Blood Pressure and Heart Rate: A Systematic Review and Meta-Regression of Twin Studies

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The genetic contribution of blood pressure and heart rate (HR) varied widely between studies. Demographic factors such as ethnicity, age and/or sex might explain some of the heterogeneity. We performed a systematic review focusing on four phenotypes: systolic blood pressure (SBP), diastolic blood pressure (DBP), HR and pulse pressure (PP). Meta-regression was conducted to analyze potential factors in relation to SBP and DBP heritability. A total of 10,613 independent twins that came from 17 studies were included in the analysis. The weighted mean value of heritability for SBP and DBP was 0.54 (95% CIs: 0.48–0.60) and 0.49 (95% CIs: 0.42–0.56). Comparatively, three studies of HR and four studies of PP heritability were limited for the heterogeneity test. Meta-regression showed that, on average, SBP heritability with additive genes/unique environment (AE) model tend to have a higher heritability than additive genes/shared environment/unique environment (ACE) model (coefficient = 0.0947,  $p = .0142$ ). A similar result was found for DBP as well. No other factors such as sex, age, ethnicity, publication year were significantly associated with heritability variance. Our study shows heritability estimates based on twin studies of both SBP and DBP are around 50%, using an AE rather than an ACE model; the variance due to C ended up in A, suggesting that the AE model may overestimate heritability if a small contribution of shared environment exists.

■ **Keywords:** blood pressure, heart rate, heritability, twin study, systematic review, meta-regression

Cardiovascular disease accounts for approximately 17 million deaths a year, nearly one-third of the all-cause mortality. Of note, complications of hypertension accounted for 9.4 million deaths worldwide every year (World Health Organization, 2013). The common measurements of hypertension are SBP and DBP (DBP; Pickering et al., 2005). HR and PP (PP; i.e., the difference between SBP and DBP) serve as an additional predictors for cardiovascular diseases (Cooney et al., 2010; Franklin et al., 1999). In order to better control and prevent related diseases, understanding the etiology behind the blood pressure and HR is critical. Evidence from twin studies and family-based studies suggested that genetic variance might contribute to SBP, DBP, HR, and PP variance (Hottenga et al., 2006; Rice et al., 1989). Traditional twin study is by far the most common approach to calculate the genetic contribution for certain phenotypes by comparing intra-pair concordance, which relies on strong assumptions about the relative environmental similarity of identical (monozygotic, MZ) and fraternal (dizygotic, DZ) twins (Conley et al., 2013).

Heritability, as a measure of balance between genetic and environmental contributions, would naturally vary with the

environmental exposures and genetic lineage and does not have a consistent value (Elks et al., 2012). Earlier twin studies reported that SBP heritability ranged from 0.28 to 0.60 (Rice et al., 1989; Slattery et al., 1988; Wang et al., 1990), DBP ranged from 0.32 to 0.66 (Rice et al., 1989; Slattery et al., 1988; Wang et al., 1990), PP from 0.30 to 0.54 (Snieder et al., 2003; Tarnoki et al., 2012) and HR from 0.50 to 0.69 (Fagard et al., 2003; Snieder et al., 2003). Few of those studies compared and summarized the weighted mean value across different twin registries. Evans published heritability in six Western countries' Caucasian twins to demonstrate a remarkable similarity of blood pressure heritability in European populations (Evans et al., 2003). Snieder calculated heritability between European Americans and

RECEIVED 25 September 2014; ACCEPTED 27 January 2015. First published online 6 March 2015.

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African Americans twins to identify the heterogeneity among Caucasians and Africans (Snieder et al., 2003). Recently, Li reported heritability of 11 metabolic phenotypes in Danish and Chinese twins, including SBP and DBP, to compare heritability between Caucasians and Asians (Li et al., 2013). In addition, there are some other studies looking for age and/or sex differences in twin heritability (Evans et al., 2003; Vinck et al., 2001). However, a systematic analysis for the heritability of SBP, DBP, PP, and HR that accounts for factors such as ethnicity, age and sex is lacking.

Therefore, we aimed to identify the literature that estimated the heritability of blood pressure and HR in twin studies, and to identify and quantify the effects of potential factors that contribute to the heterogeneity of the estimates by meta-regression.

## Materials and Methods

### Literature Search

Selection of relevant twin studies about blood pressure and HR started with a search on electronic database PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>) and Embase (<http://www.elsevier.com/online-tools/embase>) in November, 2013. It was performed using MeSH terms of 'blood pressure' or 'heart rate' combined with the terms 'heritability', and we limited the search to human studies reported in the English language. A supplementary search (e.g., using the term 'genetic contribution' rather than 'heritability') was performed to identify further studies that were not captured by the original search. Abstracts of all these search results ( $n = 641$ ) were examined and relevant articles ( $n = 178$ ) were retrieved for review (Figure 1). Inclusion criteria were twin studies reporting quantitative estimates for blood pressure (SBP, DBP, and PP) and HR heritability.

Ineligible studies were excluded from the analysis based on four exclusion criteria: (1) the estimates of 27 studies were not conventional blood pressure measurements but some other indexes such as 24-hour SBP, mean SBP or central blood pressure. (2) thirteen studies with extended twin designs (e.g., twins reared apart, twins' blood pressure under stress or heritability measured by multiple time points) were excluded from analysis. (3) to enable a quantitative meta-analysis, measures of uncertainty for the heritability estimates were required; 84 studies without reporting heritability SE or 95% CIs were also excluded. (4) only studies from independent samples could be used for meta-analysis. Some authors used a (sub)sample of the same cohort, or reported more than one estimates under univariate and multivariate models. We selected one estimate with the most covariates included, available for largest sample, and used a variety of sensitivity analyses to address possible over adjustment or under adjustment. Finally, we had 17 studies eligible for further analysis (Figure 1).

### Data Extraction

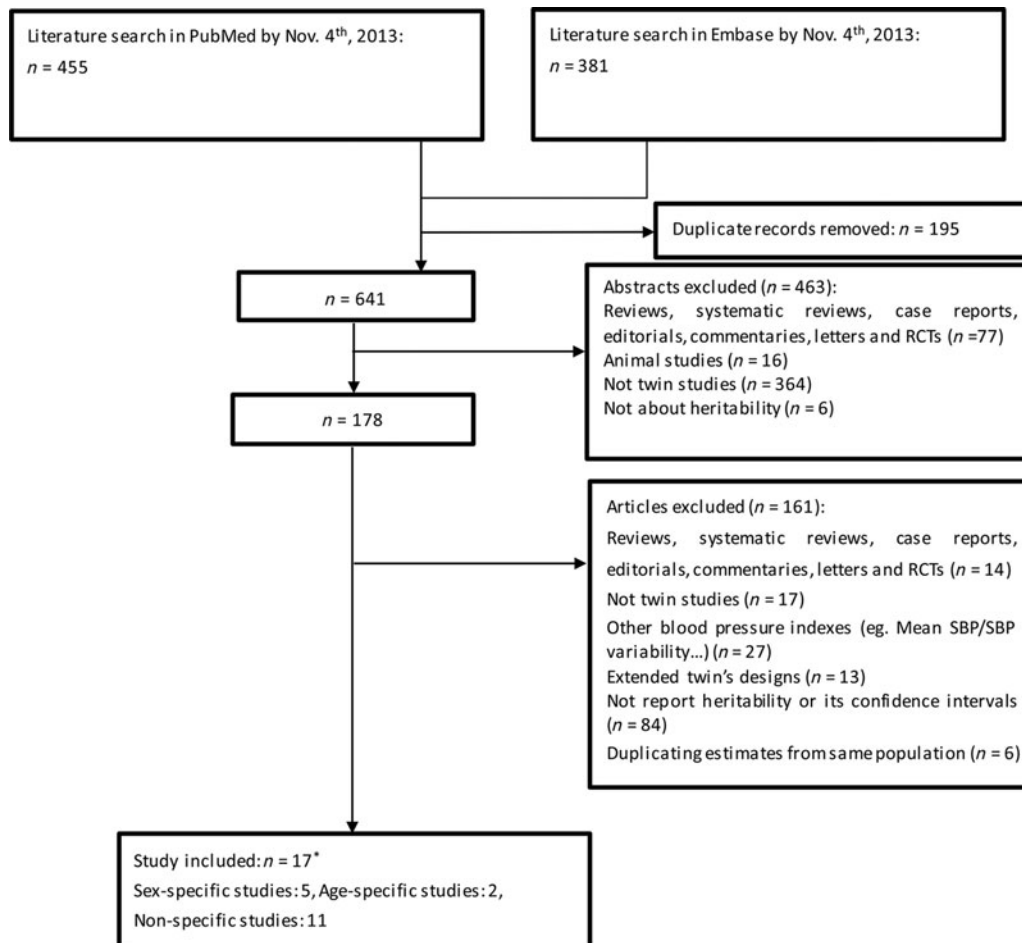
Excel 2010 was used for data extraction and quality assessment. Two trained independent researchers (Liao and Zhou) made qualitative evaluation and data extraction for each literature at the same time. Extraction data included publication information (publication year and authors), demographic characteristics (age, sex, locations and sources), study characteristics (sample size, zygosity determinants, data transformation, best fitting models and whether adjusted variables) and phenotype (SBP, DBP, PP and HR) heritability and its 95% CIs. The results were cross-referenced and any disagreements were resolved by discussion or consultation with a third evaluator (Wang).

The researchers evaluated the quality of all included studies, according to the evaluation criteria of the Agency for Healthcare Research and Quality (AHRQ; <http://www.ncbi.nlm.nih.gov/books/NBK35156/>). We revised the 11 items of cross-sectional prevalent studies criteria to apply in twin studies. Three assessments (items 4, 5, and 11) were removed; the remainder included items to judge the selection bias (indicate source of information, inclusion and exclusion criteria, time period used for identifying twins, explain how missing data were handled and summarize twin response rate), measurement bias (assess for quality assurance like test/retest primary outcome), and confounding bias (describe how confounding was assessed and/or controlled) (Sanderson et al., 2007).

### Statistical Analysis

The heritability of a certain phenotype was meta-analyzed when at least two independent studies were included. We calculated the SE from the reported 95% CIs of each study (Altman & Bland, 2011), then summarized the weighted mean value of heritability and its 95% CIs by the random-effect model and whether the significant heterogeneity was based on a  $P$  value less than 0.05 (Blokland et al., 2012; Borenstein et al., 2011; Li et al., 2003; Verweij et al., 2010). The quantity  $I^2$  was calculated to describe the degree of heterogeneity. Subgroup analysis was performed when the studies specifically reported heritability by sex (male vs. female) or by age groups; otherwise, pooled analysis was applied to all the non-specific studies with both sex, and without any age subgroup classification.

Meta-regression was conducted to explore potential explanations such as factors regarding study designs and statistical methods for heterogeneity in SBP or DBP estimates across twin studies. Study design factors were publication year (as continuous variable), sample size (as continuous variable), ethnicity (Caucasians, African-Americans or Asians), mean age (as continuous variable) of the population and zygosity determination (DNA-based, questionnaire-based or use both DNA and questionnaire). For statistical methods, it included data transformation (binary variable: yes or no), best fitting model (AE, ACE or other methods) and adjusted covariates (binary

**FIGURE 1**

Literature search and study selection (\*refers to one included study got both sex-specific results and non-specific results).

variable: yes or no). Only one predictor was included in the regression model each time, due to the insufficient power. Funnel plots were made for assessing the publication bias. All analyses were performed with R package metafor (Viechtbauer, 2010).

For sensitivity analyses, we examined the robustness of meta-regression results by: (1) excluding one study that might strongly affect the outcomes, because the study used Sequential Oligogenic Linkage Analysis Routine algorithm (SOLAR) instead of AE/ACE models; (2) testing whether adjusting different covariates might have any effect on meta-analysis results, because one study (Zeegers et al., 2004) reported both adjusted and unadjusted model findings, and two studies (Jermendy et al., 2011; Wu et al., 2011) reported two adjusted models with different covariates.

## Results

### Profile of Included Studies

A total of 23 heritability estimates in SBP, 22 estimates in DBP, 7 in HR and 4 in PP were identified from 17 twin stud-

ies since year 2001 (Baird et al., 2001; Dalageorgou et al., 2008; De Geus et al., 2007; Evans et al., 2003; Fagard et al., 2003; Jermendy et al., 2011; Jiang et al., 2012; Kennedy et al., 2005; Li et al., 2013; Mutikainen et al., 2009; Peeters et al., 2008; Snieder et al., 2003; Tarnoki et al., 2012; Vinck et al., 2001; Wu et al., 2011; Zeegers et al., 2004; Zhang et al., 2009). There were four estimates in SBP, four in DBP, and two in HR reported by sex specifically; five estimates in SBP, five in DBP, and two estimates in HR reported by age subgroup separately. The rest of the estimates were non-specific studies containing both male and female data without any age subgroup classification (Table 1).

In sex-specific studies, the sample size varied from 361 to 3,152 individuals and the mean age ranged from 25.4 to 68.5 years. The majority had data transformation in statistical analysis and they were also mostly conducted with female population and European Caucasians. Two studies used ACE as the best fitting model, and age and sex were common covariates adjusted in the models.

Demographic characters in the non-specific studies were varied among 10 countries (United Kingdom, United States,

**TABLE 1**  
**Details of the Studies Reporting Blood Pressure and Heart Rate Heritability from Twin Studies\***

Year	Reference	Location	Source	Sample size (n)	Age range	Mean age	Zygoty determinant <sup>#</sup>	Phenotype <sup>†</sup>	Data transformation	Best fitting model <sup>‡</sup>	Adjusted for covariates	Heritability estimates		
												Sex <sup>§</sup>	h <sup>2</sup>	95%CI
<b>Sex-specific studies</b>														
2003	Evans et al.	UK	UK adult twin registry	3,152	17–79	46.6	DNA-based	SBP	NA	ACE	Yes <sup>a</sup>	F	0.53	0.48–0.58
2008	Dalageorg et al.	UK	NA	361	NA	49.9	BOTH	DBP	NA	ACE	Yes <sup>a</sup>	F	0.48	0.42–0.53
								HR	Yes	AE	Yes <sup>a</sup>	F	0.55	0.44–0.65
2008	Peeters et al.	Belgian, East Flanders	East Flanders prospective twin survey	768	18–34	25.4	DNA-based	SBP	Yes	AE	Yes <sup>b</sup>	M	0.58	0.448–0.684
								DBP	Yes	AE	Yes <sup>b</sup>	M	0.47	0.317–0.596
								SBP	Yes	AE	Yes <sup>b</sup>	F	0.659	0.56–0.737
2009	Mutikainen et al.	Finland	Finnish twin study on aging	389	63–76	68.5	BOTH	DBP	Yes	AE	Yes <sup>b</sup>	F	0.585	0.464–0.682
								HR	Yes	AE	Yes <sup>b</sup>	F	0.48	0.32–0.60
2009	Zhang et al.	China	Anhui province, community-based twin cohort	1,617	20–60	32.3	DNA-based	SBP	No	ACE	Yes <sup>a</sup>	F	0.42	0.29–0.56
								DBP	No	ACE	Yes <sup>a</sup>	F	0.41	0.25–0.55
<b>Age-specific studies</b>														
2001	Vinck et al.	Belgian	East Flanders prospective twin survey, registry of inhabitants of Leuven, birth registry of cities of Hasselt and Sint-Truiden	176	18–29	23.3	DNA- based	SBP	Yes	AE	Yes <sup>c</sup>	M/F	0.67	0.50–0.78
				152	30–39	32.4	DNA- based	DBP	Yes	AE	Yes <sup>c</sup>	M/F	0.61	0.42–0.75
								SBP	Yes	AE	Yes <sup>c</sup>	M/F	0.56	0.34–0.71
								DBP	Yes	AE	Yes <sup>c</sup>	M/F	0.35	0.10–0.55
				216	40–76	46.2	DNA- based	SBP	Yes	AE	Yes <sup>c</sup>	M/F	0.45	0.21–0.63
2007	De Geus et al.	Netherlands	Netherlands twin registry	160	13–22	16.8	DNA- based	DBP	Yes	AE	Yes <sup>c</sup>	M/F	0.62	0.41–0.76
								SBP	No	AE	Yes <sup>a</sup>	M/F	0.59	0.44–0.71
								DBP	No	AE	Yes <sup>a</sup>	M/F	0.59	0.43–0.71
2007	De Geus et al.	Netherlands	Netherlands twin registry	212	34–63	44.2	DNA- based	HR	No	AE	Yes <sup>a</sup>	M/F	0.68	0.55–0.77
								SBP	No	AE	Yes <sup>a</sup>	M/F	0.49	0.33–0.62
								DBP	No	AE	Yes <sup>a</sup>	M/F	0.51	0.36–0.63
HR	No	AE	Yes <sup>a</sup>	M/F	0.63	0.49–0.72								
<b>Non-specific studies</b>														
2001	Baird et al.	UK	Register of births in Birmingham, UK	396	Born 1950–1954	43.7	Questionnaire	SBP	No	AE	No	M/F	0.48	0.25–0.65

**TABLE 1**  
Continued.

Year	Reference	Location	Source	Sample size (n)	Age range	Mean age	Zygosity determinant <sup>#</sup>	Phenotype <sup>†</sup>	Data transformation	Best fitting model <sup>‡</sup>	Adjusted for covariates	Heritability estimates									
												Sex <sup>§</sup>	h <sup>2</sup>	95%CI							
2003	Fagard et al.	Belgian, East Flanders	East Flanders prospective twin survey	350	18–34	25.1	DNA- based	HR	No	AE	No	M/F	0.5	0.40–0.58							
2003	Snieder et al.	USA	Georgia cardiovascular twin study—European-Americans	616	10–25.9 for all	14.9	DNA- based	SBP	Yes	AE	Yes <sup>d</sup>	M/F	0.56	0.48–0.62							
															DBP	Yes	AE	Yes <sup>d</sup>	M/F	0.45	0.33–0.55
		USA	Georgia cardiovascular twin study—African-Americans	452	10–25.9 for all	14.6	DNA- based	SBP	Yes	AE	Yes <sup>d</sup>	M/F	0.56	0.48–0.62							
															DBP	Yes	AE	Yes <sup>d</sup>	M/F	0.58	0.46–0.68
2003	Evans et al.	Australia	Australia twin registry	1,066	30–86	45.5	DNA- based	SBP	NA	ACE	Yes <sup>a</sup>	M/F	0.52	0.44–0.59							
															Finland	Finland twin registry	1,328	37–76	58.6	DNA- based	SBP
		DBP	NA	ACE	Yes <sup>a</sup>	M/F	0.47	0.39–0.54													
									SBP	NA	ACE	Yes <sup>a</sup>	M/F	0.54							
		Sweden	Sweden twin registry	598	43–86	65.2	DNA- based	SBP	NA	ACE	Yes <sup>a</sup>	M/F	0.44	0.29–0.56							
															DBP	NA	ACE	Yes <sup>a</sup>	M/F	0.53	0.44–0.61
Netherlands	Netherlands twin registry	798	13–71	32.2	DNA- based	SBP	NA	ACE	Yes <sup>a</sup>	M/F	0.54	0.44–0.62									
													DBP	NA	ACE	Yes <sup>a</sup>	M/F	0.7	0.63–0.75		
2004	Zeegers et al.	Belgian, East Flanders	East Flanders prospective twin survey	424	18–34	25.78	DNA- based	SBP	No	AE	Yes <sup>e</sup>	M/F	0.54	0.44–0.62							
2005	Kennedy et al.	USA	A population birth record-based twin registry and from advertisements	204	15–84	35.5	BOTH	SBP	Yes	AE	Yes <sup>e</sup>	M/F	0.59	0.51–0.67							
															SOLAR algorithm	Yes <sup>a</sup>	M/F	0.276	0.167–0.385		
								DBP	Yes	SOLAR algorithm	Yes <sup>a</sup>	M/F	0.178	0.053–0.303							

**TABLE 1**  
Continued.

Year	Reference	Location	Source	Sample size (n)	Age range	Mean age	Zygosity determinant <sup>#</sup>	Phenotype <sup>‡</sup>	Data transformation	Best fitting model <sup>‡</sup>	Adjusted for covariates	Heritability estimates		
												Sex <sup>§</sup>	h <sup>2</sup>	95%CI
2011	Jermendy et al.	Hungary	Recruited from national twin meetings and through advertisements published in local newspapers	202	18–81	44.3	Questionnaire	SBP	NA	ACE	Yes <sup>f</sup>	M/F	0.571	0.274–0.735
2011	Wu. et al.	China	Chinese national twin registry	2,076	19.1–81.4	37.81	DNA- based	DBP SBP	NA Yes	ACE ACE	Yes <sup>f</sup> Yes <sup>g</sup>	M/F M/F	0.577 0.41	0.237–0.744 0.26–0.58
2012	Jiang et al.	China	Qingdao twin registry	1,260	NA	36.94	DNA- based	DBP PP	Yes Yes	ACE AE	Yes <sup>g</sup> Yes <sup>h</sup>	M/F M/F	0.27 0.45	0.10–0.45 0.37–0.52
2012	Tarnoki et al.	USA, Hungary	International twin study 2009 project	392	18–82	43.4	BOTH	SBP	NO	ACE	Yes <sup>i</sup>	M/F	0.509	0.302–0.639
2013	Li et al.	Denmark	Danish twin registry	1,512	18–67	38	DNA- based	DBP PP SBP	NO NO YES	ACE ACE AE	Yes <sup>i</sup> Yes <sup>i</sup> Yes <sup>a</sup>	M/F M/F M/F	0.639 0.3 0.71	0.465–0.744 0.000–0.534 0.66–0.75
		China	Qingdao twin registry	650	18–69	40.5	DNA- based	DBP SBP	YES Yes	ACE AE	Yes <sup>a</sup> Yes <sup>a</sup>	M/F M/F	0.52 0.53	0.35–0.69 0.43–0.62
								DBP	Yes	AE	Yes <sup>a</sup>	M/F	0.58	0.49–0.66

Note: \*NA = not available; # BOTH indicated applying the DNA-based zygosity determination and questionnaire zygosity determination at the same time; †SBP = systolic blood pressure; DBP = diastolic blood pressures, HR = heart rate, PP = pulse pressure. ‡SOLAR algorithm: sequential oligogenic linkage analysis routines algorithm.

§M: male, F: female, M/F: male and female data combined.

<sup>a</sup>Adjusted covariates were age and sex.

<sup>b</sup>Adjusted covariate was sex.

<sup>c</sup>Adjusted covariate was age.

<sup>d</sup>Adjusted covariates were age, sex, ethnicity and their interaction.

<sup>e</sup>Adjusted covariates were age, sex, cholesterol ratio and body mass index (BMI).

<sup>f</sup>Adjusted covariates were age, sex, waist circumference and BMI.

<sup>g</sup>Adjusted covariates were age, sex, study site and BMI.

<sup>h</sup>Adjusted covariates were age, sex and BMI.

<sup>i</sup>Adjusted covariates were age, sex and study country.

Australia, Finland, Sweden, Netherlands, Belgian, Hungary, Denmark, and China), and included Caucasians, Asians and African Americans with a mean age ranging from 14.6 to 58.6 years. Two studies stated zygosity determination was based on questionnaire, not DNA. Approximately half the studies used the ACE versus AE model as the best fitting model. One study used a SOLAR algorithm in statistical analysis; 81.2% studies adjusted for covariates commonly age, sex and body mass index (BMI) in analytical models.

### Methodological Quality of the Included Studies

Seven items were used to assess the quality of 17 twin studies (Figure 2). The percentages for not reporting the source of the twins (0%), not assessing confounders (11.11%), and not reporting how to handle missing data (16.67%) were low. However, the percentages of not clearly summarizing response rate and completeness of data collection (72.22%), and not explaining any twins excluded from the study (50%) were relatively high.

### Genetic Contribution to Blood Pressure and Heart Rate

Subgroup analysis of the SBP\DBP heritability by sex was based on four studies, of which only one was conducted in male population. The SBP heritability in men was 0.58 (95% CIs: 0.46–0.70). In three studies conducted among female populations, the pooled heritability of SBP was 0.55 (95% CIs: 0.45–0.64) with significant heterogeneity ( $I^2 = 73.44\%$ ,  $p = .0068$ ). The DBP heritability in men was 0.47 (95% CIs: 0.33–0.61) and it was 0.49 (95% CIs: 0.45–0.54) in female population. Moreover, two female studies calculated the HR heritability and reported 0.55 (95% CIs: 0.44–0.65) and 0.48 (95% CIs: 0.32–0.60) respectively.

Two studies reported five estimates by different age groups. It seemed that heritability of SBP or DBP decreased by age since adolescent, but the test for heterogeneity of all heritability across age groups remained no significance ( $p$ -value was .3459 for SBP, and .308 for DBP). The overall heritability of SBP and DBP was 0.57 (95% CIs: 0.50–0.64) and 0.55 (95% CIs: 0.48–0.62).

Among non-specific studies, 14 estimates of SBP heritability were reported in 10,613 independent twins. Heritability ranged from 0.28 to 0.71, with a weighted mean value of 0.54 (95% CIs: 0.48–0.60). Between studies heterogeneity was substantial ( $I^2 = 82.82\%$ ,  $p < .001$ ; Figure 3a). Similarly, heterogeneity was significant in DBP estimates ( $I^2 = 78.77\%$ ,  $p < .001$ ; Figure 3b) as heritability varied from 0.18 to 0.64 among 10,217 twins; the pooled DBP heritability was 0.49 (95% CIs: 0.42–0.56). Comparatively, studies about HR or PP heritability were limited. The pooled heritability of HR was 0.61 (95% CIs: 0.51–0.70); PP was 0.50 (95% CIs: 0.44–0.55).

### Factors Associated with Blood Pressure Heritability Estimates

Zygosity determinants reached 0.05 significant levels, suggesting a significant association with SBP heritability variance. Besides, no other study design factors (publication year, mean age, ethnicity and sample size) were significantly associated with heritability variance in SBP or DBP estimates (Table 2). Meta-regression results showed that, on average, SBP heritability in DNA-based zygosity determination was 0.2047 higher ( $p = .0057$ ) than in determination combining both DNA and questionnaire methods, however, the association was diminished ( $p = .1824$ ) when comparing questionnaire-based versus both methods (Table 2). Another finding was that the meta-regression that found no effect of mean age on the heritability estimate confirmed the earlier results of age-specific subgroup analysis in terms of no heterogeneity across different age groups.

For the statistical factors, best fitting model was one explanation for SBP heritability variance. The AE model tended to have a higher estimate than the ACE model (coefficient = 0.0947,  $p = .0142$ ), while the SOLAR algorithm estimate was lower than the ACE model (coefficient = -0.2443,  $p = .002$ , Table 2). Similar results were found among DBP heritability estimates (Table 2). Raw twin data transformation and covariates adjustment in the model might not affect the SBP\DBP heritability.

Since only one study applied the SOLAR algorithm, which might strongly affect the results, we conducted a sensitivity analysis by excluding that study. The association between zygosity determinants and SBP heritability was no longer significant after excluding SOLAR algorithm study ( $p = .5643$ , Table 3). Another phenomenon found in the sensitivity analysis was that sample size might affect the DBP heritability as estimates decreased by 0.0001 per individual ( $p = .0006$ , Table 3). But fewer individuals were not nominally associated with SBP heritability in meta-regression analysis ( $p = .7641$ , Table 3). SBP heritability estimates from AE variance component models were on average 0.094 higher than those from ACE models ( $p = .0178$ ) so did the DBP estimates (coefficient = 0.0613,  $p = .0447$ , Table 3).

We conducted another sensitivity analysis testing different adjusted covariates that might affect the meta-regression results. We substituted the initial selected model with the other covariates model and found that best fitting model was one explanation for both SBP (AE vs. ACE model: coefficient = 0.0992,  $p = .0137$ ; SOLAR vs. ACE model: coefficient = -0.2510,  $p = .0022$ ) and DBP heritability variance (coefficient = 0.0777,  $p = .0335$ ; coefficient = -0.3220,  $p < .0001$ ). There were no contradictory results to the initial models with the most covariates included.

### Discussion

In this meta-analysis of published twin studies, we found the pooled heritability of SBP, DBP, HR, and PP were 0.54, 0.49, 0.61, and 0.50 respectively. In addition, we have identified

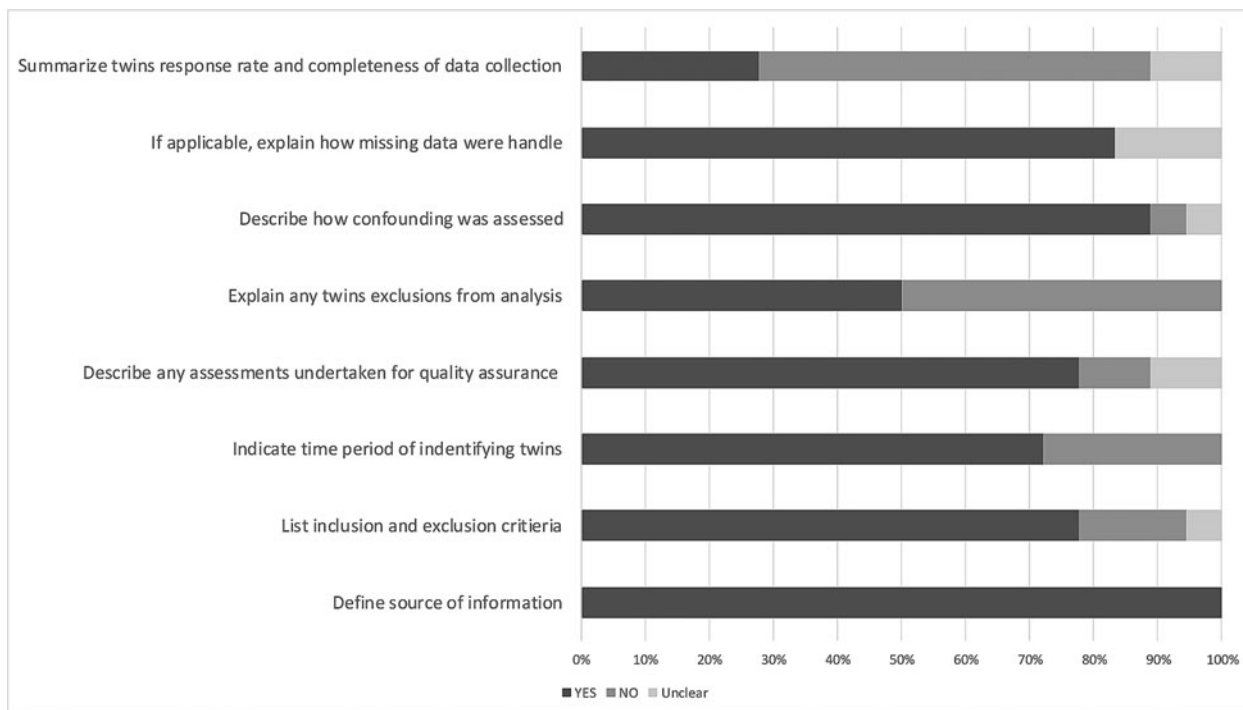


FIGURE 2

The evaluations of the methodological and reporting quality of the included seventeen twin studies.

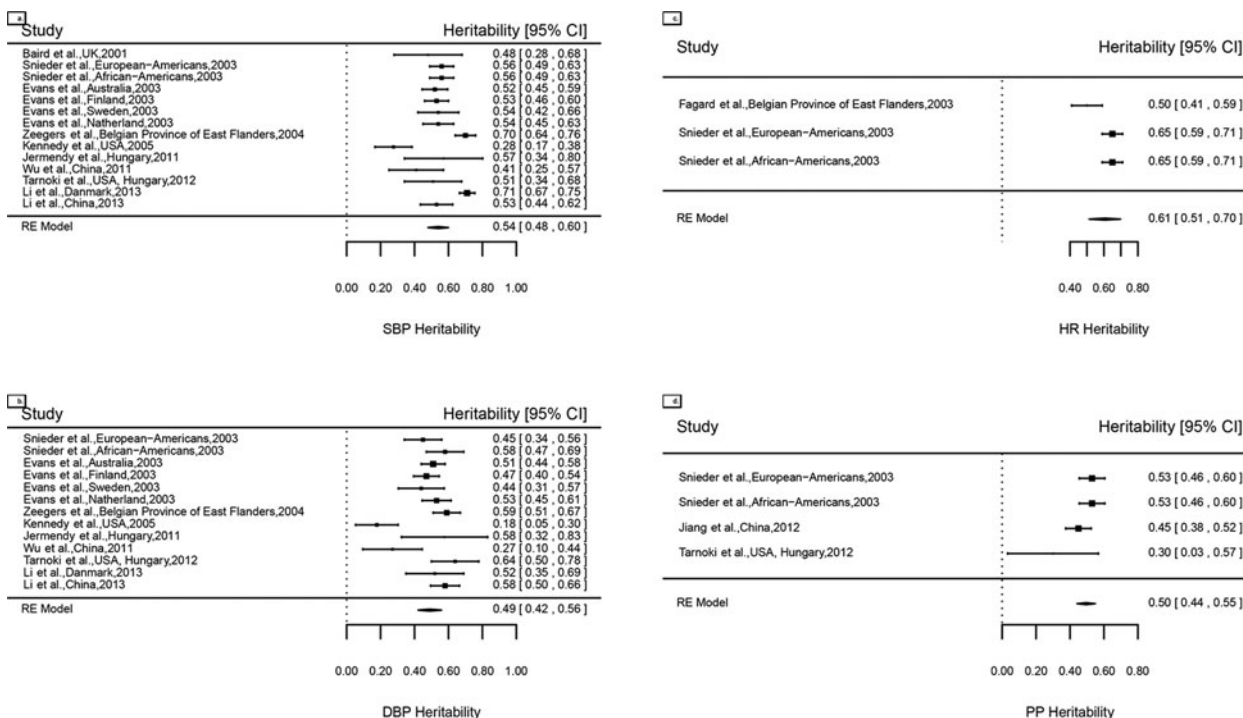


FIGURE 3

Heritability estimates of blood pressure and heart rate in non-specific twin studies (SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate, PP: pulse pressure).



**TABLE 2**  
**Meta-Regression of Univariate Analyses to Identify Factors Associated with Reported SBP and DBP Heritability Estimates in Non-Specific Twin Studies**

Covariates	SBP heritability				DBP heritability				
	Coefficient	SE	Z	P-value	Coefficient	SE	Z	P-value	
<b>Study designs</b>									
Publication year	per +1 year	0.0036	0.0068	0.5287	0.5970	0.0045	0.0079	0.5683	0.5699
Sample size	per +1 individual	0.0000	0.0001	0.4947	0.6208	-0.0001	0.0001	-0.8807	0.3785
Mean age	per +1 year	-0.0012	0.0020	-0.6044	0.5456	-0.0009	0.0023	-0.3995	0.6895
<b>Ethnicity</b>									
	Asian versus African	-0.0801	0.1270	-0.6304	0.5284	-0.1231	0.1419	-0.8679	0.3855
	Caucasian versus African	-0.0112	0.1042	-0.1078	0.9141	-0.0925	0.1200	-0.7704	0.4411
<b>Zygosity determinants*</b>									
	DNA based versus Both	0.2047	0.0740	2.7651	<b>0.0057</b>	0.1035	0.0876	1.1813	0.2375
	Questionnaire versus Both	0.1532	0.1149	1.3335	0.1824	0.1773	0.1782	0.9950	0.3197
<b>Statistical methods</b>									
<b>Data transformation</b>									
	Yes versus No	-0.0328	0.0587	-0.5581	0.5767	-0.0916	0.0627	-1.4601	0.1443
<b>Model fitting</b>									
	AE versus ACE	0.0947	0.0386	2.4514	<b>0.0142</b>	0.0613	0.0306	2.0069	<b>0.0448</b>
	SOLAR algorithm versus ACE	-0.2443	0.0790	-3.0910	<b>0.0020</b>	-0.3207	0.0666	-4.8155	<b>&lt; 0.0001</b>
<b>Adjusting covariates#</b>									
	Yes versus No	0.0632	0.1420	0.4453	0.6561	-	-	-	-

Note: SBP = systolic blood pressure; DBP = diastolic blood pressures; SOLAR algorithm = sequential oligogenic linkage analysis routines algorithm; Bold type represents  $p < .05$ ; \* Indicates applying both the DNA-based zygosity determination and questionnaire zygosity determination at the same time; #All the studies in the DBP estimates were adjusted at least one covariate.

**TABLE 3**  
**Sensitivity Analysis for Meta-Regression of Univariate Analyses to Identify Factors Associated with Reported SBP and DBP Heritability Estimates in Non-Specific Twin Studies (Excluded Kennedy Study)**

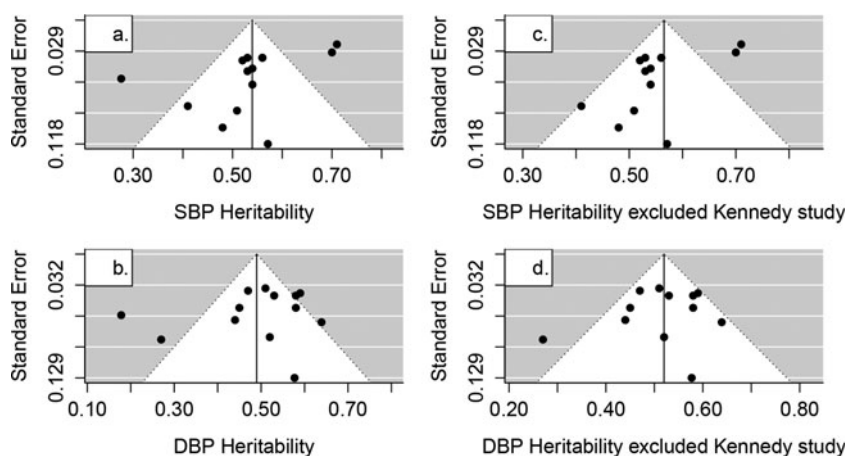
Covariates	SBP heritability				DBP heritability				
	Coefficient	SE	Z	P-value	Coefficient	SE	Z	P-value	
<b>Study designs</b>									
Publication year	per +1 year	0.0035	0.0053	0.6579	0.5106	0.0040	0.0045	0.8945	0.3711
Sample size	per +1 individual	0.0000	0.0000	-0.3002	0.7641	-0.0001	0.0000	-3.4250	<b>0.0006</b>
Mean age	per +1 year	-0.0014	0.0016	-0.9171	0.3591	-0.0014	0.0012	-1.2465	0.2126
<b>Ethnicity</b>									
	Asian versus African	-0.0746	0.0952	-0.7833	0.4335	-0.0834	0.0861	-0.9689	0.3326
	Caucasian versus African	0.0226	0.0762	0.2962	0.7671	-0.0609	0.0731	-0.8339	0.4044
<b>Zygosity determinants*</b>									
	DNA based versus Both	0.0642	0.1113	0.5764	0.5643	-0.1259	0.0809	-1.5554	0.1198
	Questionnaire versus Both	0.0118	0.1412	0.0835	0.9335	-0.0620	0.1550	-0.4001	0.6891
<b>Statistical methods</b>									
<b>Data transformation</b>									
	Yes versus No	0.0160	0.0478	0.3347	0.7379	-0.0212	0.0424	-0.4994	0.6175
<b>Model fitting</b>									
	AE versus ACE	0.0940	0.0397	2.3701	<b>0.0178</b>	0.0613	0.0305	2.0073	<b>0.0447</b>
<b>Adjusting covariates#</b>									
	Yes versus No	0.0898	0.1243	0.7222	0.4702	-	-	-	-

Note: SBP = systolic blood pressure; DBP = diastolic blood pressures; bold type represents  $p < .05$ . \*Indicates applying both the DNA-based zygosity determination and questionnaire zygosity determination at the same time. #All the studies in the DBP estimates were adjusted at least one covariate.

and quantified the possible effects of one main potential factor: the choice of final variance component model or other statistical methods, which might explain the heterogeneity in twin studies.

From the results of methodological quality assessment, the low percentage of response rate description and the rationale for exclusion might indicate a probable selection bias in most studies. This would affect the heritability estimates. Selection bias in the original study might influence the correlation coefficient estimates of MZ and DZ, thus generating biased estimates of heritability (Martin &

Wilson, 1982). Another issue in the current meta-analysis that merits discussion was publication bias for which results were subject to experimenters' preference, a sponsor's interests, or community expectations. Publication bias test was conducted among the literature of non-specific studies reporting of SBP and DBP heritability estimates (Figure 4); however, the number of HR and PP estimates was too small to accurately evaluate this. Test for funnel plot asymmetry of SBP estimates was -2.8768 ( $p = .0139$ ). Since asymmetry might be caused by one outlier study (Kennedy et al., 2005), we excluded that study to test the funnel plot asymmetry.



**FIGURE 4**

Funnel plots of the reported SBP and DBP heritability estimates in non-specific twin studies (SBP: systolic blood pressure, DBP: diastolic blood pressure).

Publication bias remained significant (estimate =  $-2.8969$ ,  $p = .0145$ ) for SBP estimates. However, the  $p$  values of DBP heritability were 0.3910 and 0.5915, suggesting a low probability of bias (Viechtbauer, 2010). Ioannidis offered several suggestions to remedy the publication bias, including use of large-scale studies, enhanced research standards and precaution to test chance of finding the true results (Ioannidis, 2005). Since there might be a publication bias in SBP estimates, large sample studies with standard methods (such as recruitment of twins, phenotypes measurement, data cleaning and analytical models) needs to be conducted.

The pooled heritability of SBP (54%) was a little more than DBP estimates (49%) in twin studies, whereas their 95% CIs overlapped, showing the 5% differences were not significant. The genetic basis contributing to heritability was found in genome-wide association studies (GWAS). A recent study found 29 independent genetic variants influence blood pressure, and collectively explained 2.2% of the phenotype variance for SBP and DBP (Ehret et al., 2011). In another meta-analysis ( $N > 29,000$ ) of multiple population cohorts, the most significant loci (*ATP2B1*) explained 0.11% SBP variance but 0.09% DBP variance (Munroe et al., 2013; Wang & Snieder, 2010). Six loci for SBP and nine for DBP were discovered, of which two overlapped, yielding 13 independent genome-wide significant signals (Levy et al., 2009; Newton-Cheh et al., 2009). Besides, GWAS meta-analysis in East Asians found four loci and a newly discovered variant near *TBX3* was related to blood pressure (Kato et al., 2011). The genetic etiology behind the heritability of HR (61%) and PP (50%) was identified by GWAS: 14 new loci and 7 previously established loci had confirmed association with HR (den Hoed et al., 2013). Four new PP loci were found in related publications (Eijgelsheim et al., 2010; Wain et al., 2011). By comparing twin studies and GWAS, it was suggested that the identified loci generally accounted for a small fraction of the genetic variance estimated from twin

studies. The large gap between those heritability estimates might be bridged by progress in increasing the coverage of the genome, increasing study sample size through meta-analyses and advancing statistical methods. Further analysis of gene-environment interaction could be expected to account for the missing heritability of blood pressure (Kaprio, 2012).

Association between zygosity determination and SBP heritability was no longer significant after excluding the Kennedy et al. (2005) study. This result of the sensitivity analysis showed that the zygosity determination effect might not be a real effect, because it was explained by a small study that used different software to estimate heritability. Although another scholar thought questionnaire-based zygosity determination might underestimate heritability, because such questionnaire were upon subjective assessment, any non-differential misclassification error would inflate the E component and reduce the additive genetic component (Elks et al., 2012). Our study might not support the view of zygosity determination affecting blood pressure heritability variance.

We found that SOLAR, AE or ACE models were related to the SBP and DBP heritability. SOLAR is a flexible and extensive software package for genetic variance components analysis, including linkage analysis, quantitative genetic analysis, and covariate screening (Fava et al., 2008; Hassan et al., 2009; Sung et al., 2009). A workshop simulated a set of data to compare twin heritability by SOLAR or AE\ACE models. It was suggested that AE\ACE models would be less biased compared to SOLAR without known common environment contribution (C) or under the assumption  $C > 0$  in twin studies. But when given  $C = 0$ , SOLAR would be less biased than AE\ACE models (Almasy & Blangero, 1998; Boker et al., 2011). Not surprisingly, heritability (variance attributed to the A component) was higher in studies reporting the AE model than the ACE

model, presumably because the variance that would have been attributed to C is reallocated to components A rather than E in these analyses.

Sensitivity analysis showed that sample size might be negatively associated with heritability variance in DBP but not SBP. A probable explanation was that the large Wu et al. (2011) study (with a sample size of 2,076), which reported a fairly low DBP heritability of 0.27, could detect a significant effect of C given their large sample size, and therefore used an ACE rather than an AE model. As such, although it appears that the sample size had a negative effect on the DBP heritability, this may have been simply a function of model choice (AE vs. ACE model), as we have also found.

It was important to emphasize that there were several strengths and limitations in this study. The first and foremost strength was that we completed the whole comprehensive process of the systematic review and meta-regression in twin studies with wide range of the literature search, methodological evaluation and bias analysis to get more reliable results (Borenstein et al., 2011). Second, we first systematically analyzed the factors that might be associated with SBP and/or DBP heritability in twins, which could be confirmed or interpreted by further genetic studies. However, there was a limitation to our study based on the published literature, that is, other unreported factors might have an impact of heritability estimates. For example, a recent meta-analysis of twins found that BMI heritability was sensitive to the study population's average BMI, gross domestic product (GDP) and GDP growth (Min et al., 2013). Another limitation was we could only include one predictor at a time in the meta-regression due to the power consideration (Higgins et al., 2002; Schmid et al., 2004).

In conclusion, in our meta-analyses that aggregated the results of a number of previous twin studies, we provided more robust estimates of the genetic influences on SBP\DBP\HR\PP. Because our analyses averaged estimates over samples of different sizes and demographic make-up, our findings were likely to be more generalizable than the individual study. The results indicated that heritability estimates based on twin studies of both SBP and DBP are around 50%. Our study confirmed that the blood pressure heritability calculation should pay attention to statistical methods which estimate genetic contribution. Reporting the AE rather than the ACE model, the variance due to C ended up in A (but not in E). So indeed, the AE model might overestimate heritability if a small contribution of C existed.

## Acknowledgments

This study was supported by China Medical Board (01-746), National Natural Science Foundation of China (81202264) and the Specific Research Project of Health Public Service, Ministry of Health, China (201002007).

## References

- Almasy, L., & Blangero, J. (1998). Multipoint quantitative-trait linkage analysis in general pedigrees. *The American Journal of Human Genetics*, *62*, 1198–1211.
- Altman, D. G., & Bland, J. M. (2011). How to obtain the P value from a confidence interval. *British Medical Journal*, *343*, d2304–d2304.
- Baird, J., Osmond, C., MacGregor, A., Snieder, H., Hales, C. N., & Phillips, D. I. (2001). Testing the fetal origins hypothesis in twins: The Birmingham twin study. *Diabetologia*, *44*, 33–39.
- Blokland, G. A. M., de Zubicaray, G. I., McMahon, K. L., & Wright, M. J. (2012). Genetic and environmental influences on neuroimaging phenotypes: A meta-analytical perspective on twin imaging studies. *Twin Research and Human Genetics*, *15*, 351–371.
- Boker, S., Neale, M., Maes, H., Wilde, M., Spiegel, M., Brick, T., . . . Bates, T. (2011). OpenMx: An open source extended structural equation modeling framework. *Psychometrika*, *76*, 306–317.
- Borenstein, M., Hedges, L. V., Higgins, J. P. T., & Rothstein, H. R. (2011). *Introduction to meta-analysis*. Chichester, UK: John Wiley & Sons.
- Conley, D., Rauscher, E., Dawes, C., Magnusson, P. K. E., & Siegal, M. L. (2013). Heritability and the equal environments assumption: Evidence from multiple samples of misclassified twins. *Behavior Genetics*, *43*, 415–426.
- Cooney, M. T., Vartiainen, E., Laakitainen, T., Juolevi, A., Dudina, A., & Graham, I. M. (2010). Elevated resting heart rate is an independent risk factor for cardiovascular disease in healthy men and women. *American Heart Journal*, *159*, 612–619.
- Dalageorgou, C., Ge, D., Jamshidi, Y., Nolte, I. M., Riese, H., Savelieva, I., . . . Snieder, H. (2008). Heritability of QT interval: How much is explained by genes for resting heart rate? *Journal of Cardiovascular Electrophysiology*, *19*, 386–391.
- De Geus, E. J. C., Kupper, N., Boomsma, D. I., & Snieder, H. (2007). Bivariate genetic modeling of cardiovascular stress reactivity: Does stress uncover genetic variance? *Psychosomatic Medicine*, *69*, 356–364.
- Den Hoed, M., Eijgelsheim, M., Esko, T., Brundel, B. J. M., Peal, D. S., Evans, D. M., . . . Handsaker, R. E. (2013). Identification of heart rate-associated loci and their effects on cardiac conduction and rhythm disorders. *Nature Genetics*, *45*, 621–631.
- Ehret, G. B., Munroe, P. B., Rice, K. M., Bochud, M., Johnson, A. D., Chasman, D. I., . . . Johnson, T. (2011). Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. *Nature*, *478*, 103–109.
- Eijgelsheim, M., Newton-Cheh, C., Sotoodehnia, N., de Bakker, P. I. W., Müller, M., Morrison, A. C., . . . O'Donnell, C. J. (2010). Genome-wide association analysis identifies multiple loci related to resting heart rate. *Human Molecular Genetics*, *19*, 3885–3894.
- Elks, C. E., den Hoed, M., Zhao, J. H., Sharp, S. J., Wareham, N. J., Loos, R. J. F., . . . Ong, K. K. (2012). Variability in the

- heritability of body mass index: A systematic review and meta-regression. *Frontiers in Endocrinology*, 3, 29.
- Evans, A., Van Baal, G. C. M., McCarron, P., DeLange, M., Soerensen, T. I., De Geus, E. J. C., . . . Boomsma, D. I. (2003). The genetics of coronary heart disease: The contribution of twin studies. *Twin Research*, 6, 432–441.
- Fagard, R. H., Loos, R. J., Beunen, G., Derom, C., & Vlietinck, R. (2003). Influence of chorionicity on the heritability estimates of blood pressure: A study in twins. *Journal of Hypertension*, 21, 1313–1318.
- Fava, C., Ricci, M. S., Burri, P., Minuz, P., & Melander, O. (2008). Heritability of the ambulatory arterial stiffness index in Swedish families. *Journal of Human Hypertension*, 22, 298–300.
- Franklin, S. S., Khan, S. A., Wong, N. D., Larson, M. G., & Levy, D. (1999). Is pulse pressure useful in predicting risk for coronary heart disease?: The framingham heart study. *Circulation*, 100, 354–360.
- Hassan, M. O., Bayoumi, R. A., Lopez-Alvarenga, J. C., Snieder, H., Jaju, D., Al-Yahyaee, S., . . . Albarwani, S. (2009). Heritability of hemodynamic reactivity to laboratory stressors in a homogenous Arab population: Oman family study. *Twin Research and Human Genetics*, 12, 541–548.
- Higgins, J., Thompson, S., Deeks, J., & Altman, D. (2002). Statistical heterogeneity in systematic reviews of clinical trials: A critical appraisal of guidelines and practice. *Journal of Health Services Research & Policy*, 7, 51–61.
- Hottenga, J.-J., Whitfield, J. B., de Geus, E. J. C., Boomsma, D. I., & Martin, N. G. (2006). Heritability and stability of resting blood pressure in Australian twins. *Twin Research and Human Genetics*, 9, 205–209.
- Ioannidis, J. P. A. (2005). Why most published research findings are false. *PLoS Medicine*, 2, e124.
- Jermendy, G., Horváth, T., Littvay, L., Steinbach, R., Jermendy, A. L., Tárnoki, A. D., . . . Osztoivits, J. (2011). Effect of genetic and environmental influences on cardiometabolic risk factors: A twin study. *Cardiovascular Diabetology*, 10, 96.
- Jiang, W., Jiang, W., Zhang, D., Pang, Z., Li, S., Duan, H., . . . Tan, Q. (2012). Heritability and whole genome linkage of pulse pressure in Chinese twin pairs. *Twin Research and Human Genetics*, 15, 759–766.
- Kaprio, J. (2012). Twins and the mystery of missing heritability: The contribution of gene-environment interactions. *Journal of Internal Medicine*, 272, 440–448.
- Kato, N., Takeuchi, F., Tabara, Y., Kelly, T. N., Go, M. J., Sim, X., . . . He, J. (2011). Meta-analysis of genome-wide association studies identifies common variants associated with blood pressure variation in east Asians. *Nature Genetics*, 43, 531–538.
- Kennedy, B. P., Rao, F., Botiglieri, T., Sharma, S., Lillie, E. O., Ziegler, M. G., . . . O'Connor, D. T. (2005). Contributions of the sympathetic nervous system, glutathione, body mass and gender to blood pressure increase with normal aging: Influence of heredity. *Journal of Human Hypertension*, 19, 951–969.
- Levy, D., Ehret, G. B., Rice, K., Verwoert, G. C., Launer, L. J., Dehghan, A., . . . van Duijn, C. M. (2009). Genome-wide association study of blood pressure and hypertension. *Nature Genetics*, 41, 677–687.
- Li, M. D., Cheng, R., Ma, J. Z., & Swan, G. E. (2003). A meta-analysis of estimated genetic and environmental effects on smoking behavior in male and female adult twins. *Addiction*, 98, 23–31.
- Li, S., Duan, H., Pang, Z., Zhang, D., Duan, H., Hjelmberg, J. V. B., . . . Kyvik, K. O. (2013). Heritability of eleven metabolic phenotypes in Danish and Chinese twins: A cross-population comparison. *Obesity (Silver Spring, Md.)*, 21, 1908–1914.
- Martin, N. G., & Wilson, S. R. (1982). Bias in the estimation of heritability from truncated samples of twins. *Behavior Genetics*, 12, 467–472.
- Min, J., Chiu, D. T., & Wang, Y. (2013). Variation in the heritability of body mass index based on diverse twin studies: A systematic review. *Obesity Reviews*, 14, 871–882.
- Munroe, P. B., Barnes, M. R., & Caulfield, M. J. (2013). Advances in blood pressure genomics. *Circulation Research*, 112, 1365–1379.
- Mutikainen, S., Ortega-Alonso, A., Alén, M., Kaprio, J., Karjalainen, J., Rantanen, T., . . . Kujala, U. M. (2009). Genetic influences on resting electrocardiographic variables in older women: A twin study. *Annals of Noninvasive Electrocardiology*, 14, 57–64.
- Newton-Cheh, C., Johnson, T., Gateva, V., Martin, D., Grobbee, D. E., Onland-Moret, N. C., . . . Bots, M. L. (2009). Eight blood pressure loci identified by genome-wide association study of 34,433 people of European ancestry. *Nature Genetics*, 41, 666–676.
- Peeters, M. W., Thomis, M. A., Loos, R. J. F., Derom, C. A., Fagard, R., Vlietinck, R. F., . . . Beunen, G. P. (2008). Clustering of metabolic risk factors in young adults: Genes and environment. *Atherosclerosis*, 200, 168–176.
- Pickering, T. G., Hall, J. E., Appel, L. J., Falkner, B. E., Graves, J., Hill, M. N., . . . Roccella, E. J. (2005). Recommendations for blood pressure measurement in humans and experimental animals part 1: Blood pressure measurement in humans: A statement for professionals from the subcommittee of professional and public education of the American heart association council. *Hypertension*, 45, 142–161.
- Rice, T., Vogler, G. P., Perusse, L., Bouchard, C., & Rao, D. C. (1989). Cardiovascular risk factors in a French Canadian population: Resolution of genetic and familial environmental effects on blood pressure using twins, adoptees, and extensive information on environmental correlates. *Genetic Epidemiology*, 6, 571–588.
- Sanderson, S., Tatt, I. D., & Higgins, J. P. T. (2007). Tools for assessing quality and susceptibility to bias in observational studies in epidemiology: A systematic review and annotated bibliography. *International Journal of Epidemiology*, 36, 666–676.
- Schmid, C. H., Stark, P. C., Berlin, J. A., Landais, P., & Lau, J. (2004). Meta-regression detected associations between heterogeneous treatment effects and study-level, but not

- patient-level, factors. *Journal of Clinical Epidemiology*, *57*, 683–697.
- Slattery, M. L., Bishop, D. T., French, T. K., Hunt, S. C., Meikle, A. W., & Williams, R. R. (1988). Lifestyle and blood pressure levels in male twins in Utah. *Genetic Epidemiology*, *5*, 277–87.
- Snieder, H., Harshfield, G. A., & Treiber, F. A. (2003). Heritability of blood pressure and hemodynamics in African- and European-American youth. *Hypertension*, *41*, 1196–201.
- Sung, J., Lee, K., & Song, Y.-M. (2009). Heritabilities of the metabolic syndrome phenotypes and related factors in Korean twins. *The Journal of Clinical Endocrinology and Metabolism*, *94*, 4946–4952.
- Tarnoki, A. D., Tarnoki, D. L., Stazi, M. A., Medda, E., Cotichini, R., Nisticò, L., . . . Schillaci, G. (2012). Heritability of central blood pressure and arterial stiffness: A twin study. *Journal of Hypertension*, *30*, 1564–1571.
- Verweij, K. J. H., Zietsch, B. P., Lynskey, M. T., Medland, S. E., Neale, M. C., Martin, N. G., . . . Vink, J. M. (2010). Genetic and environmental influences on cannabis use initiation and problematic use: A meta-analysis of twin studies. *Addiction*, *105*, 417–30.
- Viechtbauer, W. (2010). Conducting meta-analyses in R with the metafor package. *Journal of Statistical Software*, *36*, 1–48.
- Vinck, W. J., Fagard, R. H., Loos, R., & Vlietinck, R. (2001). The impact of genetic and environmental influences on blood pressure variance across age-groups. *Journal of Hypertension*, *19*, 1007–1013.
- Wain, L. V., Verwoert, G. C., O'Reilly, P. F., Shi, G., Johnson, T., Johnson, A. D., . . . van Duijn, C. M. (2011). Genome-wide association study identifies six new loci influencing pulse pressure and mean arterial pressure. *Nature Genetics*, *43*, 1005–1011.
- Wang, X., & Snieder, H. (2010). Genome-wide association studies and beyond: What's next in blood pressure genetics? *Hypertension*, *56*, 1035–1037.
- Wang, Z. Q., Ouyang, Z., Wang, D. M., & Tang, X. L. (1990). Heritability of blood pressure in 7- to 12-year-old Chinese twins, with special reference to body size effects. *Genetic Epidemiology*, *7*, 447–452.
- World Health Organization (2013). *A global brief on Hypertension World Health Day 2013*. Geneva: Author.
- Wu, T., Snieder, H., Li, L., Cao, W., Zhan, S., Lv, J., . . . Hu, Y. (2011). Genetic and environmental influences on blood pressure and body mass index in Han Chinese: A twin study. *Hypertension Research*, *34*, 173–179.
- Zeegers, M. P., Rijdsdijk, F., Sham, P., Fagard, R., Gielen, M., De Leeuw, P. W., . . . Vlietinck, R. (2004). The contribution of risk factors to blood pressure heritability estimates in young adults: The east flanders prospective twin study. *Twin Research and Human Genetics*, *7*, 245–253.
- Zhang, S., Liu, X., Yu, Y., Hong, X., Christoffel, K. K., Wang, B., . . . Wang, X. (2009). Genetic and environmental contributions to phenotypic components of metabolic syndrome: A population-based twin study. *Obesity*, *17*, 1581–1587.