Original Article

Heritability of ambulatory and office blood pressure in the Swiss population

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Background: Blood pressure (BP) is known to aggregate in families. Yet, heritability estimates are population-specific and no Swiss data have been published so far. We estimated the heritability of ambulatory and office BP in a Swiss population-based sample.

Methods: The Swiss Kidney Project on Genes in Hypertension is a population-based family study focusing on BP genetics. Office and ambulatory BP were measured in 1009 individuals from 271 nuclear families. Heritability was estimated for SBP, DBP, and pulse pressure using a maximum likelihood method implanted in the Statistical Analysis in Genetic Epidemiology software.

Results: The 518 women and 491 men included in this analysis had a mean (±SD) age of 48.3 (±17.4) and 47.3 (±17.7) years, and a mean BMI of 23.8 (±4.2) and 25.9 (±4.1) kg/m^2, respectively. Narrow-sense heritability estimates (±standard error) for ambulatory SBP, DBP, and pulse pressure were 0.37 ± 0.07, 0.26 ± 0.07, and 0.29 ± 0.07 for 24-h BP; 0.39 ± 0.07, 0.28 ± 0.07, and 0.27 ± 0.07 for day BP; and 0.25 ± 0.07, 0.20 ± 0.07, and 0.30 ± 0.07 for night BP, respectively (all $P < 0.001$). Heritability estimates for office SBP, DBP, and pulse pressure were 0.21 ± 0.08, 0.25 ± 0.08, and 0.18 ± 0.07 (all $P < 0.01$).

Conclusions: We found significant heritability estimates for both ambulatory and office BP in this Swiss population-based study. Our findings justify the ongoing search for the genetic determinants of BP.

Keywords: ambulatory blood pressure, cross-sectional, heritability, population

Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, Blood pressure; EPOGH, European Project on Genes in Hypertension; h2, heritability; PP, pulse pressure; S.A.G.E., Statistical Analysis in Genetic Epidemiology; SKIPOGH, Swiss Kidney Project on Genes in Hypertension

INTRODUCTION

Hypertension – a major risk factor for cardiovascular disease [1] – affects one in three adults worldwide and accounts for 13% of global deaths annually [2]. Hypertension results from a complex interplay between genetic and environmental factors, and previous studies have demonstrated that up to 50% of blood pressure (BP) variance can be explained by genetic factors [3]. Estimating the heritability of a trait is of interest as it represents one of the first steps in the gene-mapping process [4].

Heritability estimates are population-specific as they depend on the ratio of the additive genetic variance to the total phenotypic variance, which in turn is influenced by environmental conditions. To date, the vast majority of studies that have estimated BP heritability have been twin studies that rely principally on single-visit office BP. However, as ambulatory BP has been shown to be a better predictor of cardiovascular risk as compared to office BP [5,6], knowing the heritability of ambulatory BP monitoring (ABPM) is of specific interest [7]. Only one study to our knowledge has estimated BP heritability using ABPM on a population-based level [8]. The British GRAPHIC (Genetic Regulation of Arterial Pressure of Humans in the Community) study ($n = 2020$) found a higher heritability estimate for 24-h DBP (41%) in comparison to office DBP (32%) [8]. The five other family studies that have estimated the heritability of ambulatory BP used inclusion criteria to select their study population [7,9–12]. Three of these studies used hypertensive probands [10–12], one primarily ascertained probands who had a family history of

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hypertension [7], and one study was conducted among highly consanguineous families [9]. These studies also found that 24-h ambulatory BP tended to have higher heritability estimates as compared to office BP.

In this study, we estimated the heritability of ambulatory and office SBP, DBP, and pulse pressure (PP) in a population-based sample of persons aged 18 years and older, not selected on the basis of their BP level or family history of hypertension, in three Swiss cantons.

METHODS

The Swiss Kidney Project on Genes in Hypertension (SKIPOGH) is a population-based cross-sectional family study that examines the genetic determinants of BP. SKIPOGH is nested within the larger international European Project on Genes in Hypertension (EPOGH) study and shares the same validated methods [13].

The SKIPOGH is a multicentre study, with participants being recruited in the cantons of Bern and Geneva, and the city of Lausanne. Detailed methods have been previously described [14,15]. Briefly, recruitment began in December 2009 and ended in April 2013. The study population included 1128 participants from 271 nuclear families. Index cases were randomly selected from the population-based CoLaus study in Lausanne [16], and from the population-based Bus Santé study in Geneva [17]. In Bern, index participants were randomly selected using the cantonal phone directory. Inclusion criteria were as follows: minimum age of 18 years; of European descent (defined as having both parents and grandparents born in a restricted list of countries); at least one, and ideally three, first-degree family members also willing to participate in the study. The SKIPOGH study was approved by the institutional ethical committees of the three participating institutions.

Participants filled in a detailed health questionnaire at home and attended the respective study centres in the morning where blood samples were collected after an overnight fast. Body weight and height were measured using precision electronic scales (Seca, Hamburg, Germany).

Blood pressure

Office BP was measured with a non-mercury auscultatory sphygmomanometer (A&D UM-101, A&D Company, Limited, Tokyo, Japan). This device has passed the International Protocol for validation of BP-measuring devices of the European Society of Hypertension [18] and has been internally validated by our research group [19]. BP was measured after 10 min of rest in the sitting position using both arms. Subsequently, five consecutive BP measurements were taken on the side with the higher BP. For the present analyses, the average of the last four office BP readings was used in order to reduce the white-coat effect. Twenty-four-hour ABPM was performed using a validated Diasys Integra device (Novacor; Rueil-Malmaison, France) that has fulfilled the validation criteria set forth by the British Hypertension Society and Association for the Advancement of Medical Instrumentation (AAMI) protocols [20]. Measurements were taken every 15 min during the day and every 30 min during the night (from 2200 to 0700 h). Invalid BP values were defined as SBP greater than 280 mmHg or less than 60 mmHg, DBP greater than 200 mmHg or less than 40 mmHg, heart rate (HR) more than 200 beats/min or less than 40 beats/min, or DBP greater than or equal to SBP [21]. On average, there were 66 BP readings per participant, of which three were considered as outliers. We used the awake and asleep periods as reported by participants to define day and night. Mean BP readings were then calculated using the valid 24-h, daytime, and night-time measurements. PP was computed for office and ambulatory BP as the difference between SBP and DBP (SBP − DBP).

Statistical analysis

Differences between men and women in baseline characteristics and BP traits were tested using the chi-square test for categorical variables and a likelihood-ratio test for continuous variables using Stata 12.0 (Stata, College Station; Texas, USA).

Heritability

Heritability is a measure of familial resemblance. Narrow-sense heritability (h^2) is defined as the ratio of the additive genetic variance to the total phenotypic variance [4]. We used the ASSOC software in the Statistical Analysis in Genetic Epidemiology (S.A.G.E.) package, version 6.3 (Case Western Reserve University; Ohio, USA) [22] to compute the heritability estimates. ASSOC uses a linear regression model in which the total residual variance is partitioned, after regressing on covariates, into the sum of an additive polygenic component, a random sibship component, and an individual-specific random component [23]. Heritability was estimated as the polygenic component divided by the total residual variance. The models included a sibship component of variance, which allows dominance variance and common sibling environmental variance. All heritability estimates reported take into account a sibship variance component, except for office PP, where the program was unable to find a maximum likelihood estimate when a sibship component of variance was included in the model. We included study centre, sex, age, and BMI as covariates in the models. We used a two-tailed *t* test to explore the differences in heritability estimates between ambulatory and office BP, and between daytime and night-time BP. Significance was set to *P* value less than 0.05.

We conducted sensitivity analyses to see whether excluding certain sub-sets of the study population modified the heritability estimates. We first explored whether the completeness of ambulatory BP measurements had an effect on heritability estimates. We calculated the percentage of programmed BP measurements by dividing the actual number of BP readings available by the maximum number of readings that could be recorded during the time interval in which the participant wore the device. We then compared BP heritability estimates among participants with more than 75, 80, and 90% of programmed measurements separately. We also explored the effect of antihypertensive medication on heritability estimates. We first estimated heritability while excluding participants on antihypertensive medication. We then estimated BP heritability among all participants, but accounted for antihypertensive

TABLE 1. Characteristics of study participants by sex

	Men ($n=491$)	Women ($n=518$)	*P*
Age (years)	47.3 (17.7)	48.3 (17.4)	0.354
Antihypertensive treatment (%)	89 (18.1)	66 (12.7)	0.018
BMI (kg/m^2)	25.9 (4.1)	23.8 (4.2)	<0.001
SBP (mmHg)			
Office	120.7 (15.6)	114.7 (17.6)	<0.001
24-h	123.3 (11.4)	116.5 (13.6)	<0.001
Daytime	127.3 (12.0)	120.4 (14.2)	<0.001
Night-time	110.1 (13.0)	104.4 (14.3)	<0.001
DBP (mmHg)			
Office	78.1 (9.2)	73.4 (9.5)	<0.001
24-h	79.1 (7.8)	75.4 (7.5)	<0.001
Daytime	81.9 (8.6)	78.4 (8.3)	<0.001
Night-time	70.2 (7.5)	66.3 (7.9)	<0.001
Pulse pressure (mmHg)			
Office	42.6 (12.3)	41.3 (12.5)	0.102
24-h	44.2 (8.5)	41.1 (9.4)	<0.001
Daytime	45.4 (8.7)	42.1 (9.5)	<0.001
Night-time	39.9 (10.5)	38.1 (10.8)	0.005

Data are mean (SD) or *n* (%).

medication by adding a constant. As has been done in previous studies [8,24], we added a constant of 15 mmHg for office SBP and 10 mmHg for office DBP. We used the same constants when adjusting daytime BP for the effect of antihypertensive therapy. For night-time BP, we used two-thirds of the daytime BP constant, therefore adding 10 mmHg for night-time SBP and 7.5 mmHg for night-time DBP. Finally, to adjust 24-h ambulatory BP, we used a weighted average of the day and night constants based on average day and night durations (13.1 mmHg for SBP and 9.1 mmHg for DBP).

RESULTS

From the 1128 individuals who participated in the study, we excluded 117 participants who had missing ambulatory BP data and 2 who had missing office BP data, leaving 1009 participants from 271 families [4 with one generation, 199 with two generations, and 68 with three generations, with a mean (SD) size of 5.1 (2.3)] for the present analysis. Characteristics of the study participants by sex are presented in Table 1. Mean age (±SD) was 48.3 ± 17.4 years among women and 47.3 ± 17.7 years among men. Men had a significantly higher BMI then women (25.9 versus 23.8 kg/m^2; $P < 0.001$), as well as significantly higher ambulatory and office BP (both $P < 0.05$).

Table 2 displays heritability estimates for BP. Mean 24-h ambulatory BP had higher heritability estimates as compared to office BP, although this difference did not reach statistical significance ($P = 0.137$ for 24-h SBP as compared to office SBP; $P = 0.903$ for 24-h DBP as compared to office DBP). The heritability estimates [±standard error (SE)] for 24-h SBP, DBP, and PP were 0.37 ± 0.07, 0.26 ± 0.07, and 0.29 ± 0.07, respectively (all $P < 0.001$). Heritability estimates (±SE) for office SBP, DBP, and PP were 0.21 ± 0.08, 0.25 ± 0.08, and 0.18 ± 0.07 (all $P < 0.01$). Heritability estimates for daytime BP were not significantly different from those for night-time BP ($P = 0.201$ for daytime versus night-time SBP, and $P = 0.441$ for daytime versus night-time DBP).

TABLE 2. Heritability of SBP, DBP, and pulse pressure

	h^2 (SE)	*P*	λ_1
SBP			
Office	0.21 (0.08)	0.005	0.35
24-h	0.37 (0.07)	<0.001	0.65
Daytime	0.39 (0.07)	<0.001	0.70
Night-time	0.25 (0.07)	<0.001	0.61
DBP			
Office	0.25 (0.08)	<0.001	0.83
24-h	0.26 (0.07)	<0.001	0.81
Daytime	0.28 (0.07)	<0.001	0.76
Night-time	0.20 (0.08)	0.006	0.71
PP			
Office	0.18 (0.07)	0.004	0.32
24-h	0.29 (0.07)	<0.001	0.61
Daytime	0.27 (0.07)	<0.001	0.62
Night-time	0.30 (0.07)	<0.001	0.66

All estimates are adjusted for study centre, sex, age, and BMI. λ_1 is the power transformation estimated to normalize the residuals. h^2, heritability; PP, pulse pressure; SE, standard error.

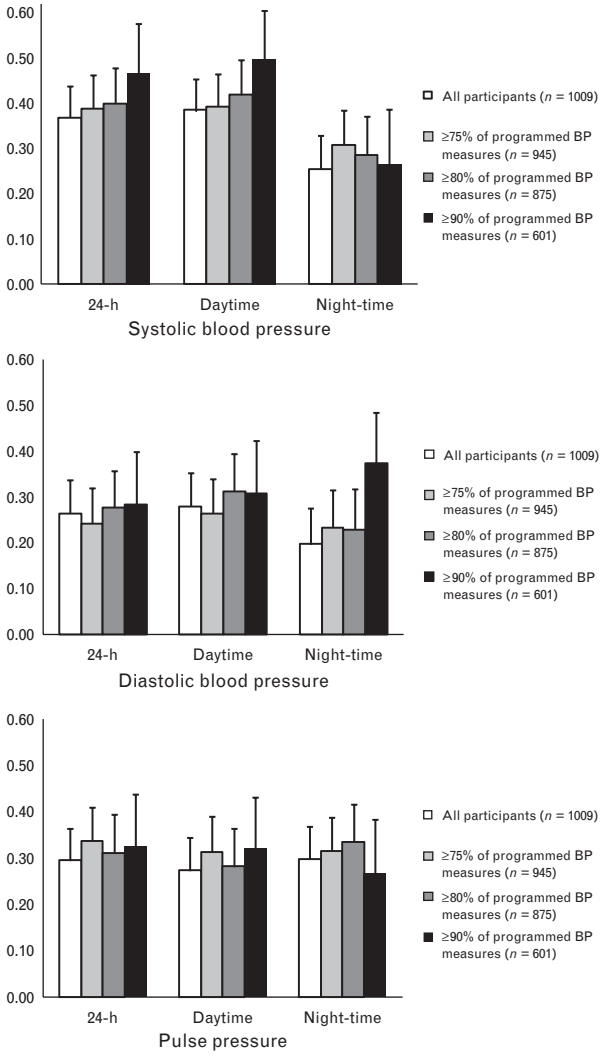

FIGURE 1 Heritability of 24-h SBP, DBP, and pulse pressure by completeness of programmed blood pressure (BP) measurements.

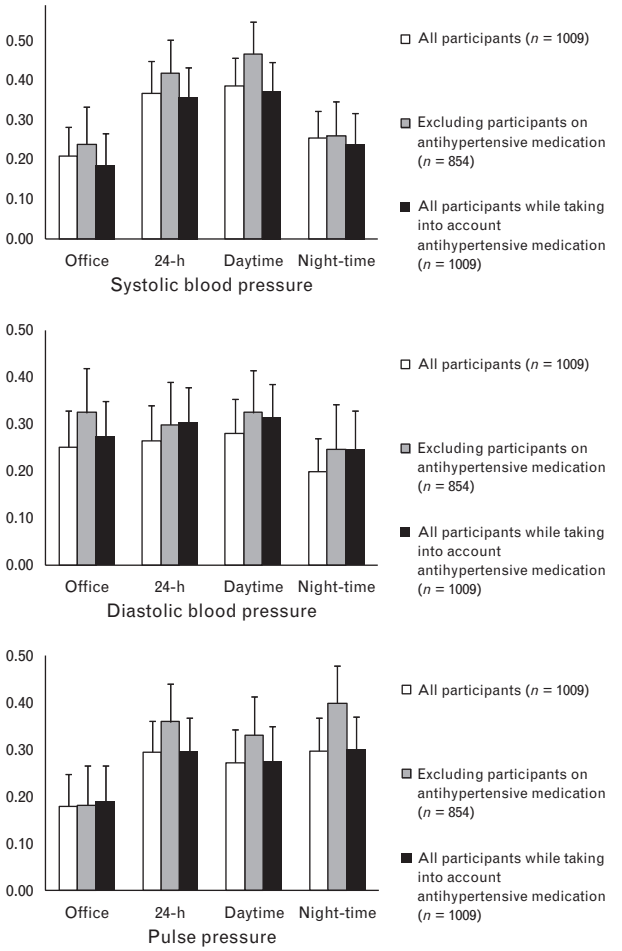

FIGURE 2 Heritability of 24-h SBP, DBP, and pulse pressure when excluding participants on antihypertensive medication and when accounting for the effect of antihypertensive medication (i.e. adding a constant of 15/10 mmHg for office and daytime SBP/DBP, 10/7.5 mmHg for night-time SBP/DBP, and 13.1/9.1 mmHg for mean 24-h SBP/DBP).

Sensitivity analyses exploring whether the completeness of ambulatory BP measurements can influence heritability estimates are presented in Fig. 1. We observed progressively higher heritability estimates for 24-h and daytime SBP and night-time DBP among participants with 75, 80, and 90% of programmed readings, respectively. However, these differences in heritability estimates, when compared to the estimates among all study participants, did not reach statistical significance when formally tested.

Excluding participants on antihypertensive medication led to slightly higher BP heritability estimates, although the differences were not statistically significant (Fig. 2). Moreover, adjusting for antihypertensive treatment by adding a constant had little impact on the heritability estimates.

DISCUSSION

In this Swiss multicentric population-based sample, we found statistically significant heritability estimates for both ambulatory and office SBP, DBP, and PP. Moreover, mean 24-h ambulatory SBP had a higher heritability than office SBP, although this difference did not reach statistical significance. The British GRAPHIC population-based study reported higher heritability of 24-h ambulatory DBP than office DBP [8]. Although the heritability estimate for 24-h ambulatory SBP in the current study was quite similar to that found in the GRAPHIC study ($0.37 \pm .0.07$ versus 0.33 ± 0.05, respectively), heritability estimates for office SBP and DBP, and 24-h ambulatory DBP were higher in the British GRAPHIC Study as compared to the present study (0.21 ± 0.08, 0.25 ± 0.08, and 0.26 ± 0.07 for office SBP, office DBP, and 24-h ambulatory DBP for our study, respectively; 0.31 ± 0.04, 0.32 ± 0.04, and 0.41 ± 0.05 for the GRAPHIC study, respectively) [8]. Given that heritability estimates are population-specific, these differences may be attributed to differences in total phenotypic variance between the Swiss and the British populations. Note that the precision of heritability estimates was lower in our study as compared to the British study. As a consequence, we had low power to detect a significant difference between the heritabilities of office and ambulatory BP.

Other family studies that have estimated heritability of ambulatory BP were conducted in ethnically different

populations. Bochud *et al.* [10] ($n = 314$) found heritability estimates for SBP and DBP that are comparable to our results in a sample of families of African descent in the Seychelles. They reported higher heritability estimates when individuals treated for hypertension were excluded from the analyses. Likewise, we found higher heritability estimates when restricting the analyses to individuals free of hypertension, although the differences did not reach statistical significance. Kotchen *et al.* [11] also estimated heritability of ambulatory BP among hypertensive, hyperlipidaemic black sib pairs and similarly found that heritability estimates were higher when multiple BP readings were averaged over 24-h as compared to single measurements. In the Oman Family study, the heritability of SBP and DBP was 0.30 and 0.44 for 24-h ambulatory BP, as compared to 0.19 for both office SBP and DBP [9]. The two remaining family studies were conducted among Caucasian families. Fava *et al.* [7] reported a heritability of 0.30 and 0.29 for 24-h ambulatory SBP and DBP, respectively, among 260 Swedish siblings with a family history of hypertension, whereas office BP did not show significant heritability. Although ambulatory BP heritability estimates were similar in magnitude to ours, Fava *et al.* showed extremely low heritability estimates for office BP, which may result from a large environmental variance. In a study conducted among 247 British families ascertained through a hypertensive proband, Cunnington *et al.* [12] found night-time and not daytime BP to have higher heritability than office BP.

Another point to consider is not only the setting in which BP is measured (ambulatory versus office) but also the number of ambulatory BP readings available. For example, Bochud *et al.* [10] showed that BP heritability increased along with the number of BP measures. However, obtaining more than 10 ambulatory BP measures did not substantially increase the heritability estimate [10]. Interestingly, one family study demonstrated that BP heritability was higher when measured several times over 24 h in real-life conditions as opposed to hundreds of readings over a short period in laboratory conditions [9]. In this study, we found no clear advantage to restricting analyses to ambulatory recordings with nearly perfect completeness when studying the genetic determinants of BP.

In addition to the method of BP measurement, BP heritability may also be influenced by the type of study design. Heritability estimates derived from twin studies tend to be higher than those obtained from family studies [3,25,26]. Heritability of 24-h ambulatory SBP and DBP can be as high as 0.71 for SBP and 0.69 for DBP [3]. This is partly because twins are more likely to share environmental factors than singletons, therefore overestimating heritability [27]. In this study, we dealt with the confounding effect of shared environment among siblings by adding a sibship component of variance, which was significant for office BP, and was close to significant for mean 24-h and night-time BP. This sibship component captures both a dominance genetic effect and a shared environmental component among sibs. Our results suggest that shared environment across siblings may explain part of the heritability estimates of BP. As the participants to this study were all adults, it may be that we were not able to capture an existing significant sibship effect because the shared environment is not as strong as for young siblings sharing the same household. Moreover, twin studies assume that twin pregnancies and births are representative of singleton pregnancies, which is frequently not true, especially given that twins have lower birth weights and are more likely to suffer from intrauterine growth retardation as compared to singletons [4,28]. This therefore questions the generalizability of twin studies as singletons make up the majority of the population [4].

Some previous studies have found night-time BP to be more heritable than daytime BP [7,11,12]. Although not statistically different in the present study, the heritability estimate for night-time SBP was higher than the heritability estimate for daytime SBP, whereas the heritability estimates for daytime and night-time DBP were very similar in magnitude. It has been suggested that studies investigating the genetics of hypertension using night-time BP may be more powerful than those using daytime BP, as night-time BP is less likely to be influenced by environmental factors [29]. However, studies that have found night-time BP to be more heritable have not examined whether the difference was statistically significant [29]. In one twin study, Wang *et al.* [29] found that there was no statistical difference between daytime and night-time heritability, which is in line with our results. Moreover, although Cunnington *et al.* [12] found higher heritability for night-time as compared to daytime BP, it is worthy to note that their heritability estimates for daytime BP were smaller in magnitude as compared to daytime BP heritability in this study (0.14 and 0.11 for daytime SBP and DBP versus 0.37 and 0.26 for daytime SBP and DBP, respectively). The heritability estimate for night-time SBP was similar to our study (0.24 in the study by Cunnington *et al.* versus 0.25 in the present study). Only night-time DBP had a higher heritably estimate as compared to the current study (0.35 versus 0.20, respectively) [12]. Bochud *et al.* [10] reported higher heritability estimates only for night-time as compared to daytime DBP, with night-time SBP and PP having similar heritability as daytime BP. In contrast, heritability of daytime BP was found to be higher than night-time BP in a sample of highly consanguineous Omani families [9]. Given these conflicting results, it is questionable whether night-time BP provides an advantage when looking for genetic determinants of BP, especially considering that sleep quality may be differentially affected across members of the same family, thereby adding noise.

Consistent with the previous findings [7,10,30], we found both ambulatory and office PP to be significantly heritable in this study. PP can be regarded as a measure of arterial stiffness, and has been shown to be associated with an increased risk for cardiovascular deaths, independently of mean BP level [31]. PP may therefore be a valuable phenotype when investigating the genetics of BP-related traits.

Strengths of our study include its population-based nature, the relatively large sample size, and the use of a standardized protocol across the three study centres. Among the limitations to consider for this study is that heritability is a population-specific measure and our results are thus mainly applicable to the Swiss population. However, the heritability estimates obtained from this study

were consistent with other non-Swiss studies, suggesting that the external validity of our results is reasonably good.

In conclusion, our study is the second family study to estimate heritability of ambulatory BP in which the results may be generalized to the population. We found significant heritability estimates for ambulatory and office BP and PP in this Swiss population-based study. Taking antihypertensive treatment into account had little influence on heritability estimates. Our findings justify the ongoing search for genetic determinants of BP.

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Conflicts of interest

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Reviewers' Summary Evaluations

Reviewer 1

Interesting findings from the population-based, well standardized family study SKIPOGH (Swiss Kidney Project on Genes in Hypertension) nested within a larger European study (European Project on Genes in Hypertension, EPOGH), reporting significant heritability estimates for both ambulatory and office blood pressure. Given the population-dependence of heritability estimates of blood pressure, more studies are needed in other ethnicities, settings, and countries, for both increasing generalizability and looking for clues on the influence of environmental and genetic factors.

Reviewer 2

Strengths: Given that heritability estimates are population-specific, this is the first heritability study in Swiss population. Both office and ambulatory BP measurements were carried out; day-time heritability estimates were therefore compared to night-time ones. The contribution of shared environment to BP heritability was estimated also as 'sibs-household effect'. Heritability estimates were compared to those obtained in similar studies and differences discussed.

Weaknesses: Low power to detect a significant difference between the heritabilities of office and ambulatory BP, probably due to poor precision of heritability estimates.