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Shared heritability of blood pressure and pulse wave velocity:

Insights from the STANISLAS cohort

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Abstract

Background: Pulse wave velocity (PWV) is a marker of arterial stiffness, which is intrinsically highly correlated with blood pressure (BP). However, the interplay of PWV and BP heritability has not been extensively studied. This study aimed to estimate the heritability of PWV and BP, and determine the genetic correlation between PWV and BP.

Methods: The heritability of PWV and BP was estimated in 1080 subjects from the STANISLAS cohort with at least one relative using a linear mixed model within one frequentist and one Bayesian framework implemented respectively in the Gaston and MCMCglmm R packages. Then their genetic correlations were also estimated.

Results: The heritability estimations for PWV were within the same range of the heritability of systolic (SBP) and diastolic BP (DBP) (23%, 19% and 27%, respectively). Daytime heritability of BP was higher than nighttime BP. In addition, phenotypic correlations between PWV and SBP/DBP were respectively 0.34 and 0.23, whereas non-significant genetic correlations were 0.08 and 0.22 respectively, indicating that PWV and DBP shared more polygenic co-determinants than PWV and SBP.

Conclusion: Our results suggest that the heritability of PWV is more than 20%, and within the same range as BP heritability. It also suggests that the link between PWV and BP goes beyond phenotypic association: PWV and BP (in particular diastolic BP) share common genetic determinants. This genetic interdependence of PWV and BP appears largely polygenic.

Key words: heritability, genetic correlation, pulse wave velocity, blood pressure, arterial stiffness

List of abbreviations or acronyms

ABPM : ambulatory blood pressure monitoring

BMI : body mass index

BP : blood pressure

CVD : cardiovascular diseases

DBP: diastolic blood pressure

eGFR: estimated glomerular filtration rate

GRM: genetic relatedness matrix

MBP: mean BP

MCMC: Markov Chain Monte Carlo (MCMC)

PWV: pulse wave velocity

SBP: systolic blood pressure

STANISLAS : Suivi Temporaire Annuel Non-Invasif de la Santé des Lorrains Assurés Sociaux

Introduction

Arterial stiffness and hypertension resulting from elevated blood pressure (BP) are major risk factors for cardiovascular morbidity and mortality [1, 2]. Arterial stiffness is assessed by pulse wave velocity (PWV), which has long been acknowledged as the 'gold standard' measurement [3].

From an epidemiological standpoint, determining the genetic part of these traits and their potential genetic correlation could further inform researchers of their inherited nature. The total variance of many continuous phenotypic traits can be partitioned into different components (genetic, environmental, etc.). Genetic variance can also be divided into additive and non-additive (dominance, epistasis, etc.) effects. Most studies focused on heritability estimation only retained additive genetic effects, which is designed as "narrow-sense" heritability [4]. The heritability estimate is a ratio between genetic variance and total variance and is comprised between 0 and 1. If the influence of genetic factors is high, the estimate of heritability will be close to 1.

The estimation of heritability in family study has been traditionally performed using pedigree analysis, however, the accuracy of estimation can be improved by the recent use of genetic relatedness matrix (GRM) calculated from GWAS data.

PWV measurements and blood pressure have previously been shown to exhibit a wide range of heritability estimates, based on twin or familial studies. When focusing on carotid-to-femoral PWV, estimations of heritability ranged from 26% to 67% [5-8], while estimation for systolic and diastolic BP ranged from 17% to 59% and 19% to 59% respectively [6, 9-13], with differences according to ethnicities of the studied populations [11].

Although elevated BP and higher PWV are associated with increased risk factors of cardiovascular diseases (CVD) and are often clinically related and phenotypically correlated,

only sparse studies have investigated the potential genetic correlation between these risk factors [8, 14].

The Suivi Temporaire Annuel Non-Invasif de la Santé des Lorrains Assurés Sociaux (STANISLAS) cohort is a longitudinal transgenerational study from the Nancy region of France characterized by a familial structure and long follow-up (up to 23 years). In this cohort, individuals underwent an extensive cardiovascular evaluation, including PWV assessment and ambulatory BP monitoring (ABPM).

The aims of the present study were 1) to estimate the heritability of PWV and of systolic and diastolic BP (with different measurements obtained from 24-hour, nighttime and daytime APBM) using both self-reported pedigree and GRM, and 2) to assess the genetic correlation between PWV and BP.

Methods

Study population

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

The design of the STANISLAS cohort has previously been detailed elsewhere [15]. In brief, the STANISLAS cohort is a family-based longitudinal cohort, including 4598 healthy individuals of French origin from 1006 families living in the Lorraine region in northeastern France. Participants were examined every 5 to 10 years, over a period of 20 years. A total of 1705 participants returned for the fourth visit (V4), held between 2011 and 2016, consisting of a medical exam and an interview by trained nurses using a structured questionnaire, which included items pertaining to socio-demographic characteristics, medical and family history, smoking status, lifestyle, diet, and anthropometric data. Additionally, 24-hour

ambulatory blood pressure measurement (ABPM) was performed only in the fourth visit, and these participants were also genotyped using two chips: the Illumina Global Screening Array and the Illumina Exome Array [16].

The study protocols for all examinations were reviewed and approved by the local ethics committee of the CPP Est 3, France. All participants provided written informed consent to participate in the study.

Pulse wave velocity assessment

The measurement of PWV is reliable, non-invasive and performed with mechanical sensors applied on the sites of the arteries to assess pulse transit time. The travel distance is measured with a tape meter and PWV is calculated as the distance (multiplied by 0.8 to best fit the real aortic distance traveled by the pressure wave between the common carotid and the femoral arteries during the time which corresponds to the transit time between the two pressure curves recorded simultaneously on these 2 arterial segments) divided by transit time. Brachial-ankle or brachial PWV velocity can also be measured although this pathway includes both elastic and muscle arteries and the predictive value is generally poorer than carotid-femoral PWV, this latter is often referred to as “real PWV” [3, 17].

PWV measurements were performed with Complior® (Alam Medical, France) and/or Sphygmocor® CVMS (AtCor, Australia) devices. Peripheral blood pressure was measured after at least 10 min of rest in supine position, in a quiet room.

Carotid to femoral PWV was assessed with Complior® using the recommendations of the European Network for Noninvasive Investigation of Large Arteries [17]. Two sensors were placed simultaneously on the carotid artery and femoral artery. Two measurements were performed, with PWV calculated as the mean of the two acquisitions. If the two acquisitions differed by more than 0.5 m/s, a third measurement was performed and the PWV

established as the median value of the three measurements. The onboard foot-to-foot algorithm based on the second derivative waveforms was used for the determination of the transit time.

The carotid to femoral, carotid to sternal notch and sternal notch to carotid distances were measured with a tape measure. The distance used for PWV calculation was 0.8 times the direct carotid-femoral distance. Pulse wave velocity was then measured with the Sphygmocor® CVMS (AtCor, Australia) after installation of three chest electrodes for ECG synchronization. The Sphygmocor® probe was applied on the carotid and femoral artery in immediate succession at the same locations as the Complior® sensors. The same protocol with regard to the number of measurements was applied. The intersecting tangent algorithm was used to determine transit time. Measurements were performed by four trained operators.

Statistical analyses

The following parameters were quantified: 1) the heritability of PWV and blood pressure measurements from APBM (24-hour SBP, nighttime SBP, daytime SBP, 24-hour DBP, nighttime DBP, and daytime DBP), 2) the phenotypic correlation between PWV and the above BP measurements, and 3) the genetic correlation between these latter outcomes.

A linear mixed model was used for heritability estimation (i.e., the proportion of total phenotypic variance explained by heritable genetic determinants) of all outcomes.

Statistical analyses in R (version 4.1.2) were performed twice, firstly using the frequentist Gaston package (version 1.5.7) [18] and secondly using the MCMCglmm R package (version 2.32) [19] that fits models in a Bayesian framework using Markov Chain Monte Carlo (MCMC) methods. The detailed methodology of heritability estimation is described in detail elsewhere [20].

In brief, two random effects were added to the model. The first random effect corresponded to genetic relatedness implemented from one of the two matrices, the pedigree of the included subjects or the GRM calculated from polymorphic GWAS data within the subset of successfully genotyped subjects. Individuals with unknown parents were assumed to be unrelated. An additional random effect was defined to take into account the common household effect resulting from shared environment by nuclear families (i.e., parental couple and children aged less than 20 years old).

For the fixed effects, in addition to common covariates (age and sex), body mass index (BMI), dyslipidemia, smoking status, hypertension medication and estimated glomerular filtration rate (eGFR) were tested for their association with PWV and BP using a multivariate linear model. All statistically significantly associated variables were added into the model.

To assess genetic correlation, the traits were first rescaled in order to have similar variance. The same fixed and random effects as in the single-trait models were used for these multi-trait models. The estimation of genetic correlation was only available using the MCMCglmm package.

The choice of prior distributions for random and fixed effects was made according to the example from the vignette of the MCMCglmm package [19], hence a distribution with a very long tail such as the Inverse-Gamma distribution ($V=1$, $\nu=0.002$) was chosen. MCMCglmm was run 3 times for each model, with 100,000 iterations, after a burn-in of 10,000 iterations. Values from every 10 iterations were saved. The model was run with an effective sample size of 9000, with convergence verified graphically.

The heritability of PWV and BP measurements and their correlation were also estimated with one other frequentist R packages (Sommer version 4.1.5 [21]

Results

Characteristics of included subjects

A total of 1080 individuals were included in the present analysis, the characteristics of whom are summarized in Table 1. Among the 1705 subjects from the fourth visit of the STANISLAS cohort, 147 subjects were excluded due to missing PWV or BP data. In order to maintain a degree of familial structure, only subjects with at least one other related parent present in the study population were included, (i.e., 478 singletons and couples without children were excluded from the present analysis). The participants belonged to 407 families, comprised of 2 to 7 members. A subset of 1003 individuals, successfully genotyped, were included in the analysis using the GRM.

The participants and non-participants at the end of follow-up had similar baseline characteristics (Table S1). Moreover, participants who attended the 4th visit but were not included in this analysis due to an insufficient number of family members with available data are described in Table S2.

Variance decomposition and heritability estimation

Among potentially associated variables, BMI and dyslipidemia were significantly associated with PWV (Table S3) and were included in the mixed model used for heritability estimations as fixed effects in addition to age and sex.

Variances of all the outcomes were decomposed into heritability (i.e., the variance explained by the additive effects of genetic determinants), environmental factors and residual variance, all of which are depicted in Figure 1 (and Table S4 and S5).

Similar results were obtained using both frequentist and Bayesian methodology, and using pedigree matrix or GRM. For the subset of genotyped subjects, we showed results with the

pedigree matrix to better compare the results, since the number of genotyped subjects is smaller.

The heritability of PWV was estimated at 20%, common environmental effects due to nuclear family accounted for 10 %, while 70% of the variance remained unexplained.

The heritability of 24-hour and daytime SBP was approximately 20%, i.e., in the same range as that for PWV, whereas the heritability of DBP was higher (27 and 28% for 24-hour and daytime DBP, respectively). In contrast, the effect of common environment was numerically higher for SBP (15-18%) than for DBP (13-14%). The heritability and impact of common environment of nighttime SBP and DBP were lower.

Phenotypic and genetic correlations

The genetic and phenotypic correlations between PWV and BP are represented in Figure 2.

PWV and systolic and diastolic BP were positively correlated, with a moderate but significant phenotypic correlation coefficient and with the same range of correlation for the different BP measurements (from 0.21 to 0.35; all with a P value <0.01) (Table S6).

Some differences in genetic correlations were observed between PWV and BP: the genetic correlation between PWV and DBP was numerically higher than the genetic correlation between PWV and SBP. Importantly, the genetic correlation between PWV and DBP was in the same range as the phenotypic correlation observed between PWV and DBP. However, these genetic correlations were not statistically significant since the 95% CI encompassed 0 (Table S6).

The estimations for heritability and genetic correlation with Sommer package showed quantitatively similar results (Tables S7 and S8).

Discussion

In our study including initially healthy subjects, the heritability of PWV, SBP and DBP were within the same range, i.e., approximately 20%. However, DBP had a moderately higher heritability than SBP (about 30% for DBP and less than 20% for SBP) whereas the heritability of both nighttime SBP and DBP was lower. In addition, PWV and SBP showed higher phenotypic correlation albeit with few genetic co-determinants whereas PWV and DBP showed more moderate phenotypic correlation but with higher genetic co-determinants. In short, the link between PWV and BP goes beyond a phenotypic association since PWV and BP (especially diastolic BP) both share correlated genetic determinants.

Heritability of PWV and blood pressure

In the present study, approximately 20% of the total variance of the heritability of PWV was explained by genetic determinant. This estimation is lower than that reported in other familial and twin studies where between 26% to more than 40% were recorded [5-7]. The effect of common environment was low in our study, in keeping with the majority of studies on BP heritability [8].

With regard to PWV, our estimates of BP heritability were lower than those reported in the literature (analyses from twin studies or familial cohort) where heritability of SBP and DBP ranged between 30% to 60% [5, 9-12]. Nevertheless, a lower heritability of nighttime BP was also reported by Wang et al. [22] and Xu et al. [23] in which estimates declined by nearly 10% for nighttime compared to daytime estimations. Differences in daytime and nighttime BP heritability might be considered in the light of the implication of “clock genes” in genetic determinants of daytime and nighttime BP.

Overall, these discrepancies between studies may be attributable to differences in age, ethnicities and covariates used for the various studied populations. It should be

highlighted that heritability estimates are population-specific parameters and may change over time within a specific population [24]. Nevertheless, we did not find any correlation between mean age of the study population and heritability estimation. However, our cohort has the advantage of including families, which makes it particularly suitable for the assessment of heritability.

Comparison between estimations using pedigree matrix or GRM

We did not find any substantial differences between results from the pedigree matrix and GRM. However, the use of GRM provides three additional advantages: 1. it gives the opportunity to verify family declared relationship; 2. it provides a better estimation for sibling genetic relatedness; and 3. it takes into account the estimation of genetic relatedness between unrelated subjects [20].

Correlations between BP and PWV

In our study, PWV and SBP showed higher phenotypic correlation, albeit with few genetic co-determinants, whereas PWV and DBP showed more moderate phenotypic correlation (although remained <0.30) but with higher genetic co-determinants. There is evidence of a positive correlation between hypertension and arterial stiffness [14, 25] although the potential genetic link between BP and PWV has been sparsely investigated until recently. Cecelja et al. [8] identified more than 50% of shared genes between BP and PWV when assessing bivariate heritability, although accounted for only a small proportion of the total phenotypic correlation. Furthermore, using Mendelian randomization, the authors identified a bi-directional causal relationship between BP and arterial stiffness [8]. On the other hand, Rode et al. [14] showed that PWV shared a common genetic architecture with BP although the Mendelian randomization analyses conducted on this cohort suggested that arterial stiffness was a consequence rather than a cause of increased BP. As only two studies are

available, with some conflicting results, additional data using Mendelian randomization may be needed to better ascertain the existence and direction of causality linking BP and arterial stiffness.

We were unable to test for causal relationship between PWV and BP. However, we found that despite similar phenotypic correlations between PWV and SBP and DBP, this genetic correlation was only sizeable with DBP. Since DBP is less related to PWV, this would suggest that a genetic common background may have a common influence on these 2 markers (rather than the increase in PWV being a consequence of DBP modifications).

The relationship between blood pressure and arterial stiffness is complex. We can distinguish three levels of interactions between blood pressure levels and large artery stiffness. First, there are the acute effects of high mean BP (MBP): since the BP/ diameter relationship is not linear in presence of a higher distending pressure, distensibility (i.e., systolic-diastolic changes in diameter/(SBP-DBP)) will be decreased, and therefore an increased stiffness of the artery is observed even without any change in its intrinsic elastic properties (acute functional effect). Secondly, a chronic increase in MBP induces changes in the geometry, structure and function of the arterial wall leading to increased stiffness (chronic structural effect). Thirdly, an increase in arterial stiffness with age and other factors (for example, chronic hypertension, diabetes, etc.) increases SBP and decreases DBP, i.e., increases pulse pressure without significant change in MBP. This is the typical BP-profile change observed during the aging process. Therefore, a chronic increase in BP will be responsible for a more pronounced increase in arterial stiffness during the aging process which, in turn, will lead to a more pronounced increase in systolic and pulse pressures increasing the risk for target organ damage. For the above-mentioned reasons, in younger people, PWV is more closely related to DBP compared to SBP due to a more pronounced

impact of DBP on MBP determination. In the present study, aortic stiffness was assessed using the “real” PWV. Other approaches exist, in particular brachial-ankle or brachial PWV velocity, although these methods include both elastic and muscle arteries. Since aortic stiffness was targeted herein, carotid-femoral PWV was used in the present study [3].

Limitations

This study has certain limitations; the size of the STANISLAS cohort is relatively moderate when compared to other population studies; only 1705 subjects of the 4598 initially included subjects returned for the last visit. Indeed, recruitment and follow-up biases exist in epidemiological studies, however the characteristics of participants to the 4th visit have nonetheless been reported to be similar overall to subjects lost to follow-up or deceased [26] (Tables S1 and S2); consequently, these missing subjects are unlikely to substantially modify our results. Moreover, the whole cohort present a low mortality rate; in 2017, Ferreira et al [15] reported that only 111 participants of the total cohort (4295 participants) were deceased (all cause of mortality). In addition, the hypothesis of healthy worker effect, which indicate that data will be obtain only from healthy people, can be discarded in this cohort. Indeed, we can assess that the healthiest participants had perhaps the lowest probability to attend the 4th visit since they were unable to come because of work issues as there was no reimbursement for participating to this 4th visit those who were not in good health were pleased to undergo free exhaustive medical examination. Lastly, the loss of some participants during follow-up could potentially have modified the familial structure.

Another limitation is that our analysis was based on many statistical tests and is intrinsically subject to alpha inflation. These results should be replicated in other settings to maximize external validity.

An additional methodological limitation is that only a pedigree matrix was used instead of a genetic relatedness matrix based from genome-wide data. Genetic correlations were derived from pedigree matrix as the MCMCglmm package does not support the implementation of GRM. However, the heritability estimations for single trait were very similar using the pedigree matrix or the GRM which strongly suggest that the genetic correlations derived from pedigree analysis are trustworthy. Of note, the concept of heritability in quantitative genetics is primarily based on intra-family correlations and makes it possible to highlight genetic bases of a trait even in the absence of identified relevant genes.

Perspectives and clinical considerations

Hypertension shows a genetic basis, which varies from monogenic to polygenic forms, but with 95% of polygenic form [11]. In the last few years, PWV has been acknowledged as a useful prognostic marker when investigating aortic stiffness [27]. Nevertheless, the latter is typically perceived as a modification arising from SBP fluctuations rather than an autonomous manifestation. Our current analysis shows that there is a limited common genetic background of PWV and DBP, which suggests that the approach to PWV might not solely be focused on blood pressure management. In addition, from a conceptual point of view, given that there is an intrinsic genetic susceptibility to increased PWV, PWV may be worth investigating aside from BP. Nevertheless, while this concept is supported by our analysis, whether this additional assessment of PWV in a populational setting could have an impact on the management of individuals in preventing CV disease needs to be specifically tested.

Conclusion

Our results suggest that the heritability of PWV is approximately 20%, within the same range as BP heritability. Our findings also suggest that the link between PWV and BP goes beyond that of a phenotypic association: PWV and BP (in particular diastolic BP) share common genetic determinants. This genetic interdependence of PWV and BP appears largely polygenic.

What is new?

This study is the first to investigate the shared heritability of blood pressure and pulse wave velocity (i.e. the proportion of genetic correlations between these 2 traits) in a population setting (familial STANISLAS cohort).

What is relevant?

Pulse wave velocity, systolic and diastolic blood pressure had a heritability within the same range (about 20 %). Pulse wave velocity shared more phenotypic correlations with systolic blood pressure than diastolic blood pressure (respectively 0.34 and 0.23) whereas genetic correlation was higher with diastolic blood pressure than systolic blood pressure (respectively 0.22 and 0.08). This indicates that there is moderate shared heritability between pulse wave velocity and diastolic blood pressure.

Clinical / physiopathological implications

The moderate common genetic background of PWV and DBP suggests that our approach to PWV might not solely be focused on blood pressure. In addition, the level of heritability of blood pressure and PWV is rather low, suggesting that environmental factors are the most potent contributors to these variables.

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Disclosures

The authors have no conflict of interest to declare.

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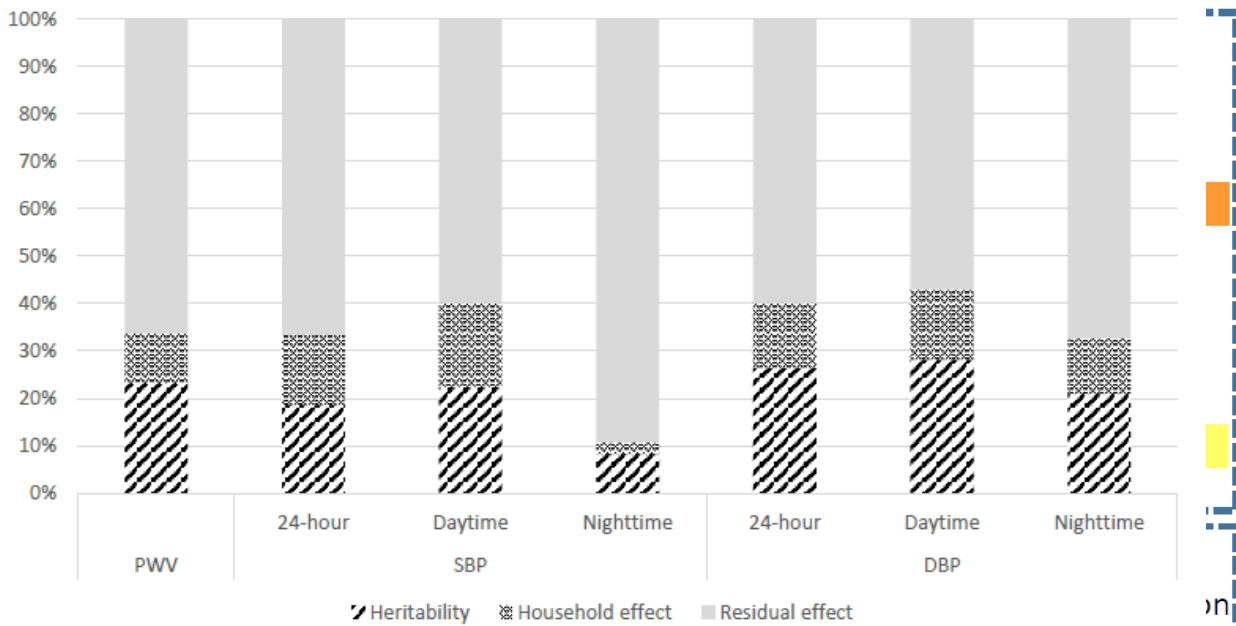
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Figure 1 : Variance decomposition for PWV and blood pressure, with age, sex, BMI

and dyslipidemia as covariates

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PWV, pulse wave velocity; SBP, systolic blood pressure; DBP, diastolic blood pressure

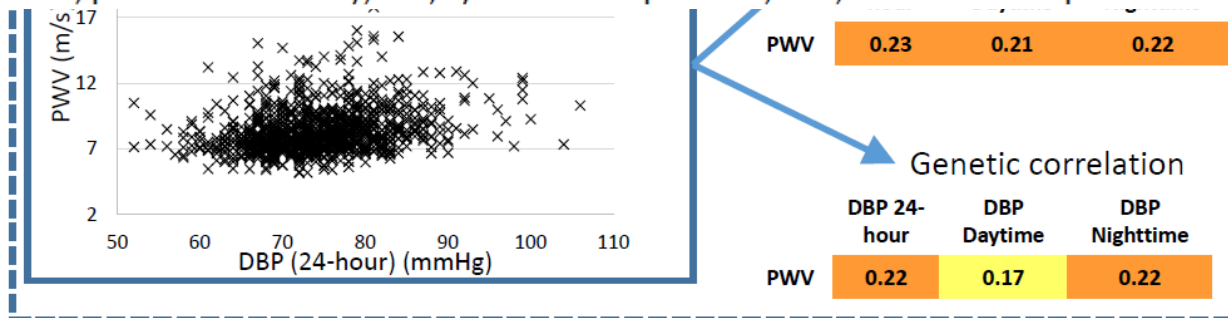


Figure 2 : Phenotypic and genetic correlation between PWV and SBP (A), and between PWV and DBP (B)

Shared heritability of blood pressure and pulse wave velocity: Insights from the STANISLAS cohort

