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Path Analysis of Familial Resemblance in Blood Pressure in Middle Dalmatia, Croatia

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A B S T R A C T

The familial resemblance in blood pressure in Middle Dalmatia, Croatia, has been analyzed using the Path-analytic approach. The sample consisted of 1,126 examinees (526 males and 600 females, aged 17 to 87), inhabitants of the Middle Dalmatia's islands of Brač, Hvar, Korčula and the Pelješac peninsula. The Path analysis was performed with the assumption that each family member (father, mother, offspring 1 and 2) has a latent variable (C) that influences both the blood pressure values (P) and the morphological dimensions significantly correlated with blood pressure (Q). According to the estimates revealed from the most parsimonious models, the diastolic blood pressure has a more pronounced genetic component (h^2 = 30–32%) than the systolic blood pressure (h^2 = 15%). In contrast to the low intergenerational influences, the members of the same generation showed pronounced effects of shared environment. Common (non-transmitted) offsprings' environment (B) explains 44% of variance of the individual offspring's environment (C) in systolic and 33–35% in diastolic blood pressure. The correlation of father's and mother's environment (u^2) was high in the case of diastolic blood pressure (33–44%) but for the systolic blood pressure it was not significantly different from zero. According to the presented results in insular/peninsular population of Middle Dalmatia, family resemblance of systolic and diastolic blood pressure differs. The resemblance is higher in diastolic blood pressure with stronger additive genetic component and stronger environmental and/or genetic component related with morphology. The sources of high heritability of diastolic blood pressure in Middle Dalmatia as well as the sources of high prevalence of hypertension in the same population are the phenomena that might be connected and thus deserve to be further explored in incoming analyses.

Key words: *Path analysis, blood pressure, morphology, family, heritability, Croatia*

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Introduction

Obesity, as well as hypertension, belongs to main risk factors for the development of coronary heart disease. It is also well-known that family members resemble each other not only in morphological characteristics, but there is a tendency for hypertension to aggregate in families[1–19]. Since we find it very important to explore to what degree the variation in blood pressure values can be attributed to genetic *vs.* environmental family factors, the path analysis of systolic and diastolic blood pressure has been performed.

The specific purpose of the present study was to test the congruence of the measured family correlations to those expected by the proposed path model, with an attempt to examine the contribution of genetic and various environmental family effects (direct and indirect, via morphology) as a source of aggregation of blood pressure values in first degree relatives.

Material and Methods

The data used in this study are a subset of the extensive material collected from the random sample of inhabitants of the Middle Dalmatia's islands of Brač, Hvar, Korčula and the Pelješac peninsula. The number of subjects included in this study (1,126 examinees, 526 males and 600 females, aged 17 to 87) was determined by the coincidence that two (or more) participants of the original random sample were members of the same family.

The applied Path model[4] encompasses two manifest (measured) variables (*P, Q*) and four latent (unmeasured) variables (*G, C, B* and *H*) while the relations among the variables are described by 8 parameters (h, c, i, k, u, b, f_M, f_F). The graphic presentation of Path model ($C \rightarrow P$, $C \rightarrow Q$) along with the description of manifest and latent variables is shown on Figure 1.

The Path analysis was performed with the assumption that each family member has a latent environmental variable *(C)* that influences both the blood pressure values (P = phenotype) and the morphological dimensions significantly correlating with blood pressure ($Q = P–M$, where M = blood pressure adjusted by means of multiple regression for significant effects of 32 anthropometric traits). The model also includes latent variables determining the effects of the individual, non-familial environment (for each family member) on both manifest variables (P and Q). Since they involve all variance not explained by model parameters, they are not presented.

In order to select the »best« variant among a group of competing variants that adequately fit the data (i.e. have a non-significant χ^2), the likelihood ratio test has been used. The selection of the most parsimonious model was performed in two steps. First, all possible null-hypotheses are tested (results not shown), whereas those showing the significant χ^2 values are rejected, meaning that parameters in question are substantial for explaining the variability of the trait.

The parameters from all non-rejected hypotheses are then used to build the most constrained variant. This variant together with other less-restricted variants and all non-rejected null-hypotheses are then compared by means of χ^2-statistics. If the difference in χ^2 values between the tested variant and the most constrained non-significant variant (referent) is significant for their difference in degrees of freedom, it implies that the tested variant is better than the referent one. Thus, the selection of the most parsimonious model is the selection of the variant, which with the smallest number of parameters achieves the lowest non-significant χ^2 value.

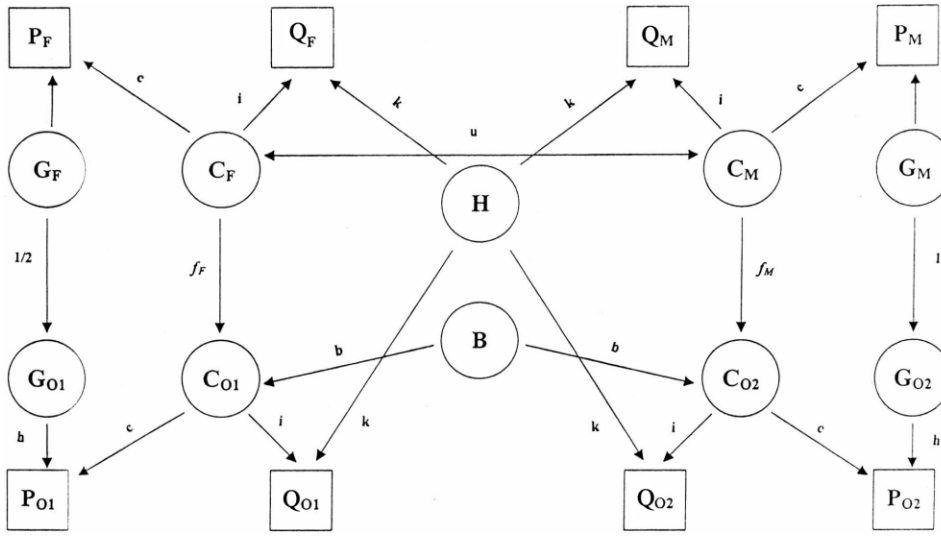

Fig. 1. Graphic presentation of the Path model: C→P, C→Q[4].

LEGEND
Measured variables: P = blood pressure (systolic or diastolic); *Q* = morphological dimensions significantly correlated with blood pressure.
Latent (unmeasured) variables: G = genotype (for P); *C* = individual family environment influencing P and Q; *B* = common (non-transmitted) offsprings' environment; *H* = residual family environment influencing Q of each family member equally.
Subscriptions: M = mothers, F = fathers, O1, O2 = offspring 1 and 2

Results

The descriptive statistics and inter-correlations of age, systolic and diastolic blood pressure in males and females are presented on Tables 1 and 2, respectively. Tables 3 and 4 give the family correlations and cross-correlations for both manifest variables (*P* and *Q*). Those correlations – calculated on sex- and age-adjusted data – serve as the observed, input data for the Path analysis.

The goodness-of-fit statistics of all competing variants are presented in Table 5 for systolic and in Table 6 for diastolic blood pressure. For the systolic blood pressure, the referent variant: $k = u = 0$, $f_M = f_F$ (χ^2=33.623, df=23, p=0.071) is also the most parsimonious one, since from the group of competing variants none provided a significant improvement in the χ^2-statistics. For diastolic blood pressure, two variants showed to be significantly better than the referent one ($k = b = f_M = 0$). The first MP variant is: $k = f_M = 0$ (χ^2 = 18.423, df = 22, p = 0.681) and the second is: $k = 0$, $f_M = f_F$ (χ^2 = 18.320, df = 22, p = 0.687).

The final results of the Path analyses for systolic and diastolic blood pressure are presented in Table 7 and could be summarized as follows:

According to the estimates revealed from the most parsimonious Path models, the diastolic blood pressure has a more pronounced genetic component (h^2 = 30–32%) than the systolic blood pressure (h^2 = 15%). For both blood pressures only

TABLE 1
AVERAGE VALUES, STANDARD DEVIATIONS AND RANGES OF AGE, SYSTOLIC (SBP) AND DIASTOLIC (DBP) BLOOD PRESSURE VALUES IN MALES AND FEMALES

Variable	Males (N = 526)		Females (N = 600)	
	X (SD)	Range	X (SD)	Range
Age	46.40 (14.58)	17–87	48.95 (14.40)	18–81
SBP	141.14 (17.39)	100–195	142.90 (22.60)	100–210
DBP	88.39 (11.48)	60–120	88.02 (11.78)	60–120

TABLE 2
CORRELATION COEFFICIENTS BETWEEN AGE, SYSTOLIC (SBP) AND DIASTOLIC (DBP) BLOOD PRESSURES IN MALES AND FEMALES

		Males		
		SBP	DBP	Age
Females	SBP	1.000	0.619*** (N = 736)	0.301*** (N = 720)
	DBP	0.708*** (N=941)	1.000	0.135*** (N = 740)
	Age	0.472*** (N = 944)	0.353*** (N = 947)	1.000

* $p \leq 0{,}05$; ** $p \leq 0.01$; *** $p \leq 0.001$

TABLE 3
OBSERVED FAMILY CORRELATIONS FOR P (= SYSTOLIC BLOOD PRESSURE) AND Q (= MORPHOLOGICAL TRAITS SIGNIFICANTLY CORRELATED WITH SBP). M = MOTHERS, F = FATHERS, O1, O2 = OFFSPRING 1 AND 2

	Q_M	Q_F	Q_{O1}	Q_{O2}	P_M	P_F	P_{O1}	P_{O2}
Q_M	1.000							
Q_F	0.116	1.000						
Q_{O1}	0.109	0.094	1.000					
Q_{O2}	0.109	0.094	0.158	1.000				
P_M	0.271	0.070	0.052	0.052	1.000			
P_F	0.036	0.224	0.099	0.099	0.033	1.000		
P_{O1}	–0.023	0.046	0.362	–0.008	0.145	0.091	1.000	
P_{O2}	–0.023	0.046	0.035	0.246	0.145	0.091	0.112	1.000

17% of the variation, in both generations, can be attributed to effects of family environment (c^2).

The most parsimonious models for systolic and MP2 for diastolic blood pressure do not assume a difference between paternal and maternal transmission of their environment on the environment of offspring, and that parental environmental influence (f_M^2, f_F^2) showed to be very low (4% and 7%) for systolic and diastolic blood pressure, respectively.

TABLE 4
OBSERVED FAMILY CORRELATIONS FOR P (= DIASTOLIC BLOOD PRESSURE) AND Q (= MORPHOLOGICAL TRAITS SIGNIFICANTLY CORRELATED WITH DBP). M = MOTHERS, F = FATHERS, O1, O2 = OFFSPRING 1 AND 2

	Q_M	Q_F	Q_{O1}	Q_{O2}	P_M	P_F	P_{O1}	P_{O2}
Q_M	1.000							
Q_F	0.307	1.000						
Q_{O1}	0.193	0.258	1.000					
Q_{O2}	0.193	0.258	0.268	1.000				
P_M	0.259	0.182	0.151	0.151	1.000			
P_F	0.168	0.311	0.148	0.148	0.109	1.000		
P_{O1}	0.029	0.145	0.327	0.109	0.297	0.167	1.000	
P_{O2}	0.029	0.145	0.178	0.193	0.297	0.167	0.198	1.000

TABLE 5
COMPARISON OF COMPETING VARIANTS OF THE APPLIED PATH MODEL ($C \rightarrow P$, $C \rightarrow Q$) FOR SYSTOLIC BLOOD PRESSURE BY MEANS OF χ^2-STATISTICS AND SELECTION OF THE MOST PARSIMONIOUS VARIANT

Model	df	χ^2	p
$h = k = u = f_M = f_F = 0$	25	45.139	0.008
$h = k = u = f_M = 0$	24	39.628	0.023
$k = f_F = f_M = 0$	23	36.649	0.035
$k = u = f_M = 0$	23	35.344	0.048
$k = u = 0, f_F = f_M$	**23**	**33.623**	**0.071**
$f_F = f_M = 0$ ns	22	33.737	0.052
$k = u = 0$ ns	22	33.508	0.055
$k = f_M = 0$ ns	22	31.874	0.080
$k = 0, f_F = f_M$ 10%	22	30.922	0.098
$f_F = 0$ ns	21	32.541	0.052
$h = 0$ ns	21	32.434	0.053
$u = 0$ ns	21	32.095	0.057
$f_M = 0$ ns	21	31.344	0.068
$k = 0$ ns	21	30.812	0.077
$f_F = f_M$ ns	21	30.753	0.078
General model ns	20	30.626	0.060

In contrast to this low intergenerational influence, the members of the same generation showed a pronounced shared environment component: common (non-transmitted) offsprings' environment explains 44% of variance of the offspring's environment (b^2) for systolic and 33–35% for diastolic blood pressure. The correlation of the father's and mother's environment (u^2) was high in the case of diastolic blood pressure (33–44%) but for the systolic blood pressure it was not different from zero.

TABLE 6
COMPARISON OF COMPETING VARIANTS OF THE APPLIED PATH MODEL ($C \rightarrow P$, $C \rightarrow Q$) FOR DIASTOLIC BLOOD PRESSURE BY MEANS OF χ^2-STATISTICS AND SELECTION OF THE MOST PARSIMONIOUS VARIANT

Model	df	χ^2	p
$h = k = b = f_M = f_F = 0$	25	108.054	0.000
$k = b = f_M = f_F = 0$	24	72.627	0.000
$k = f_M = f_F = 0$	23	44.699	0.004
$k = b = 0$, $f_F = f_M$	23	31.063	0.121
$k = b = f_M = 0$	**23**	**27.501**	**0.235**
$f_F = f_M = 0$ ns	22	32.761	0.065
$b = k = 0$ *	22	22.685	0.420
$k = f_M = 0$****	22	18.423	0.681
$k = 0$, $f_F = f_M$ ****	22	18.320	0.687
$h = 0$ ns	21	26.174	0.200
$f_F = 0$ ns	21	22.226	0.387
$f_F = f_M$**	21	18.871	0.593
$f_M = 0$ **	21	18.422	0.622
$k = 0$ ***	21	17.949	0.653
General model **	20	17.450	0.624

**** $p < 0.005$; *** $0.005 < p < 0.01$; ** $0.01 < p < 0.025$; * $0.025 < p < 0.05$

TABLE 7
FINAL RESULTS OF THE PATH ANALYSIS: PARAMETER ESTIMATES ACCORDING TO THE GENERAL AND MOST PARSIMONIOUS MODEL FOR SYSTOLIC AND DIASTOLIC BLOOD PRESSURE

Parameter	Systolic blood pressure		Diastolic blood pressure		
	General model	MP model: $k = u = 0$, $f_F = f_M$	General model	MP1 model: $k = f_M = 0$	MP2 model: $k = 0$, $f_F = f_M$
h^2	14%	15%	30%	32%	30%
c^2	20%	17%	18%	17%	17%
i^2	32%	37%	54%	48%	56%
k^2	3%	–	1%	–	–
b^2	45%	44%	34%	33%	35%
u^2	6%	–	32%	44%	33%
f_M^2	2%	4%	2%	–	7%
f_F^2	4%	4%	14%	27%	7%

h^2 = % P variance explained by additive genetic effects;
c^2 = % P variance explained by family environment effects;
i^2 = % Q variance explained by family environment effects;
k^2 = % Q variance explained by residual effects of the common family environment;
f_M^2, f_F^2 = % variance of the offspring's family environment explained by mother's (M) and father's (F) family environment;
b^2 = % variance of the offspring's family environment explained by the common offsprings' environment (not shared with parents);
u^2 = correlation of family environment of father and mother

Discussion

The Path analysis of blood pressure family data has been performed with the assumption of the environmental variable (usually denoted as index (I)) – that with clearer interpretation in view – was filled only with one potential environmental factor. This environmental factor *Q* indicates morphological dimensions showing significant correlation with blood pressure and it was constructed as BP – BP adjusted for significant effects of 32 anthropometric traits.

Applied Path model ($C \rightarrow P$, $C \rightarrow Q$) assumes that latent variable *C* influences both the blood pressure and the morphology that is significantly correlated with diastolic (systolic) blood pressure. Having in mind the increasing evidence of genetic correlation (shared genetic effects i.e. pleiotropy) between blood pressure and obesity-related phenotypes[12,13,15], it is to be expected that latent (non-measured) »environmental« variable *C* could partially have its genetic component. In the cases where the correlation between phenotype and supposed environment could have genetic background, heritability estimates will be underestimated and the estimates for environmental component (c^2) overestimated[20,21]. The estimates of c^2 also depend on how the environmental component *C* is constructed. When index is composed by multiple factors (e.g. morphology, smoking, nutrition, education, economic factors etc.) estimated c^2 will be higher than in case when index is composed of only one factor[22]. Having above considerations in mind the estimated heritability (h^2) is most probably underestimated in the present study (or more precisely it is the heritability of blood pressure without the part that is connected with morphology), while family environment effects on *P* (c^2) could be either over- or under-estimated in the present study.

According to the presented results family resemblance of systolic and diastolic blood pressure in insular/peninsular population of Middle Dalmatia differs. It seems that diastolic blood pressure has a more pronounced both genetic and environmental family component, when compared to systolic blood pressure and should be further discussed. The significant correlation of parental environment in the case of diastolic but not in the case of systolic blood pressure, indicates that the effect of cohabitation has a pronounced role in determination of (only) diastolic blood pressure values. Along with the finding of the substantial proportion of morphology connected with DBP *(Q)* determined by the environmental variable *C* (i^2 = 56%) is suggestive of a stronger environmental and/or genetic component related with morphology in diastolic blood pressure than in systolic blood pressure.

As it is well known, heritability estimates are equally characteristic for the trait in question and for the population to which the sample belongs (along with the environmental factors in specific time influencing both)[23]. Therefore, it is of interest to note that in the island/peninsular population of Middle Dalmatia, heritability of diastolic blood pressure is higher than that of systolic blood pressure and this finding is contrary to what is most frequently found in other populations[11,13,14,17–19]. As the results of high heritability estimates revealed from the applied Path model have been repeatedly obtained in the same population by differently designed analyses[6,7,9], we are entitled to believe that it is not an artifact revealed by the bias of the applied model, but that it is a real characteristic of this population. Middle Dalmatian island population is characterized by several characteristics that might influence the above finding: it is relatively isolated and inbred population[24,25], sharing rather homogenous environment[26] (climate, nutrition, life style,

etc.), and characterized by high prevalence of hypertension[27] in spite of »healthy«, low-fat diet. The source of high heritability of diastolic blood pressure in Middle Dalmatia and the source of high prevalence of hypertension in this population might be inter-connected phenomena and thus deserve to be further explored in incoming analyses.

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PATH ANALIZA KRVNOG TLAKA I MORFOLOŠKIH OSOBINA U UZORKU OBITELJI SREDNJODALMATINSKE OTOČKE POPULACIJE

S A Ž E T A K

Obiteljska sličnost u vrijednostima krvnog tlaka u Srednjoj Dalmaciji, Hrvatska, analizirani su Path-analitičkim pristupom. Uzorak je sačinjavalo 1126 ispitanika (526 muškaraca i 600 žena, dobi od 17 do 87) stanovnika srednjodalmatinskih otoka Brača, Hvara, Korčule te poluotoka Pelješca. Path analiza je provedena uz pretpostavku da svaki član obitelji (otac, majka, dijete 1 i 2) ima latentnu varijablu *(C)* koja ima utjecaja i na vrijednosti oba krvna tlaka *(P)* i na vrijednosti morfoloških dimenzija koje značajno koreliraju s krvnim tlakom *(Q)*. Prema procjenama proizašlim iz najparsimoničnijeg modela, dijastolički krvni tlak ima izraženiju genetsku komponentu (h^2 = 30–32%) od sistoličkog krvnog tlaka (h^2 = 15%). U suprotnosti s niskim međugeneracijskim utjecajima okolinske komponente, članovi iste generacije pokazali su naglašen utjecaj zajedničkog okoliša. Zajednički okoliš djece (B) (koji je neprijenosni s generacije na generaciju) objašnjava 44% varijance okoliša (latentne varijable C) kod sistoličkog odnosno 33–35% kod dijastoličkog krvnog tlaka. Korelacija pak okoliša oca i majke (u^2) visoka je u slučaju dijastoličkog krvnog tlaka (33–44%), no kod sistoličkog, ona se ne razlikuje od nule. Prema dobivenim rezultatima u otočkoj/poluotočkoj populaciji Srednje Dalmacije obiteljska sličnost sistoličkog i dijastoličkog krvnog tlaka je različita. Ona je veća kod dijastoličkog tlaka i to i uz snažniju aditivnu genetsku komponentu i uz snažniju okolinsku i/ili genetsku komponentu koja je povezana s morfologijom. Kako je veća genetska nasljednost dijastoličkog krvnog tlaka od one sistoličkog manje čest nalaz u drugih populacija, držimo da je riječ o specifičnosti ove populacije koja uz druge osobitosti karakterizira i visoka prevalencija hipertenzije te je moguće da su ta dva fenomena povezana.