

## THE PRESENCE OF MINOR PHYSICAL ANOMALIES OF A HAND IN PATIENTS WITH MENTAL DISORDERS

Paula Marinovic<sup>1</sup>, Laura Pavicic<sup>2</sup>, Nikola Prpic<sup>3</sup>, Marina Sagud<sup>1,3</sup>, Maja Bajcs Janovic<sup>1</sup>,  
Sasa Jevtovic<sup>1</sup> & Alma Mihaljevic-Peles<sup>1,3</sup>

<sup>1</sup>Department of Psychiatry and Psychological Medicine, University Hospital Center Zagreb, Zagreb, Croatia

<sup>2</sup>Department of Emergency Medicine of Krapina, Krapina, Croatia

<sup>3</sup>School of Medicine, University of Zagreb, Zagreb, Croatia

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### SUMMARY

**Introduction:** Minor physical anomalies (MPA) are subtle morphological deviations with little to none clinical significance that are developed prenatally and therefore could be an indicator of structural changes in the brain developing at the same time. Aim of this study was to determine whether the MPA of the hand can distinguish psychotic patients from patients with non-psychotic diagnoses as well as from the healthy individuals.

**Subjects and methods:** 100 consecutive patients from the University Hospital Center Zagreb, Department of psychiatry, were included in this case-control study along with 100 healthy control subjects. Investigators examined the dorsal and palmar side of the hand and were blind to the patient's diagnoses previous to the examination. Examined MPA included thenar crease, proximal transverse crease, proximal interphalangeal joint, eponychium of the middle digit, fingernail size and digital flexibility.

**Results:** Results showed significant differences in the quantity of MPA between the patients and the control group, as well as differences between patients with psychosis and the healthy subjects.

**Conclusions:** Despite the fact that previous studies demonstrated characteristic distribution of specific MPA in schizophrenia, this study did not prove such results. Moreover, this study showed that all the MPA are equally common in both schizophrenia and other psychoses.

**Key words:** schizophrenia – bipolar – psychosis - biological markers - dermatoglyphics

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### INTRODUCTION

For the most part, the process of creating a correct psychiatric diagnosis is still based on symptom recognition and patient evaluation during a psychiatric interview. Patient's unwillingness to cooperate or inability to communicate combined with the incomplete history taken from their families mostly result in an inadequate first diagnosis which additionally draws out the process of prescribing adequate medication.

Since longer periods of untreated psychosis are associated with poorer prognosis (Penttilä et al. 2014), diagnostic methods that are more objective would enable earlier intervention and improve patient outcomes which would consequently reduce patient morbidity as well as health care costs.

Neurodevelopmental theory of schizophrenia suggests the combined influence of both epigenetic and genetic factors on development of schizophrenia. According to neurodevelopmental theory, symptoms of schizophrenia develop as a result of errors in neuronal proliferation and migration in-utero (Ismail et al. 2000, Jaaro-Peled et al. 2020). During puberty, reorganization of synaptic networks is finalized with numerous synapses being formed and shortly after many of them dissolving. These newly formed synaptic networks interact with abnormalities formed during early development which finally results in development of psychotic

symptoms (Limosin et al. 2014). Structural and functional changes in the brain occurring during the prenatal phase of development along with the influencing factors from childhood and early adolescence equally contribute to the higher risk of developing schizophrenia (Ismail et al. 2000). Brain imaging studies, done in patients suffering from various illnesses of the neurodevelopmental spectrum, such as autism, dyslexia, ADHD, schizophrenia, bipolar disorder and OCD, (Ryan 1999, Myers et al. 2017), confirm the need to investigate more biological markers.

The MPA concept evolved from the research of behavioral disturbances such as hyperactivity and impulsivity among children (Waldrop et al. 1968). Over time, MPA became a point of interest in the research of neurodevelopmental disorders, including schizophrenia. A 2007 meta-analysis on MPAs among schizophrenic individuals yielded results of disproportionately high number of craniofacial anomalies, as well as high prevalence of anomalies of the mouth region (Weinberg et al. 2007). Commonly assessed physical anomalies include features such as reduced head circumference, palatal abnormalities, fine electric hair, epicanthus, low-set ears, curved 5<sup>th</sup> finger, single transverse palmar crease, partial syndactyly of 2<sup>nd</sup> and 3<sup>rd</sup> toe. Waldrop associated these abnormalities with injury during the first trimester, (Waldrop et al. 1968) presumably because this period of development is the most critical for the

development of the ectodermal derivatives (Green et al. 1989). Waldrop's scale is the first ever measuring tool designed to evaluate MPAs.

Structural changes of the brain found in schizophrenia occurring early in life have been linked to the findings of subtle morphological physical anomalies in some psychiatric patients (Petronis 2004, Jaaro-Peled et al. 2020). These findings are consistent with the embryological evidence connecting the ectodermal origin of the brain to the same origin of the distal upper limb, both developing at the beginning of the second trimester. Conclusion can be drawn that various environmental factors affecting the fetus in the second trimester directly affect the neuronal migration as well as the development of a hand (Bracha et al. 1991, Compton et al. 2009). Minor physical anomalies refer to subtle morphological deviations with little to none clinical significance that form as a part of prenatal development and could be beneficial to prognosis and diagnostics of different disorders (Pinsky 1985). Research on MPA so far is mostly inconclusive partially due to different research methodology (Csábi et al. 2008) and partially due to a rather small patient sample. In comparison to studies made up to this point, in which MPA have mostly been associated with schizophrenia (Compton et al. 2009), the novelty of our study is inclusion of all psychoses. The MPAs have been analyzed on different parts of the body such as ears, eyes, face, head, mouth, hands and feet (Gourion et al. 2004, Zvi Shamir et al. 2015). The most variable results came from hand analysis which was mainly studied in relation to schizophrenia without real evidence regarding other psychoses. The MPA studied involve: thenar crease, proximal transverse crease, proximal interphalangeal joint, eponychium of the middle digit, fingernail size and digital flexibility. These particular anomalies were chosen in this research mainly for the purpose of simpler comparison to the previous research (Domany et al. 2017) with the similar hypothesis as well as their availability to examination and the remote likelihood of subjective interpretation. The simplicity of the method of inspection used for these particular anomalies is precisely why, if proven to be associated to all or any of the psychoses, it would be an outstandingly useful tool in the psychiatric diagnostic process. Previous research shows that the combination of anomalies when compared to the appearance of a single anomaly is a better indicator of schizophrenia (Zvi Shamir et al. 2013, Tikka et al. 2019). The combinations include proximal interphalangeal joint with proximal transverse crease and eponychium of the middle digit. Since there are other psychiatric conditions with psychotic features the question remains, are MPA only present in schizophrenia or could they be associated with psychosis in general and become a useful diagnostic tool in psychiatry, helping speed up the process of making an adequate first diagnosis.

The aim of this study was to determine whether schizophrenia and other psychiatric conditions with

psychotic symptomatology are associated with MPA of a hand in comparison to other psychiatric conditions without psychotic symptoms and healthy individuals. The second aim of this study was to determine if there is a specific anomaly that is significantly more frequented in patients diagnosed with schizophrenia.

Our hypothesis was that MPA are more common in patients diagnosed with psychosis in comparison to patients diagnosed with other non-psychotic disorders and healthy individuals.

## SUBJECTS AND METHODS

### Patients

117 consecutive patients with diverse psychiatric diagnoses admitted for treatment between December 2017 and April 2018 to the University Hospital Center (UHC) Zagreb, Department of psychiatry were originally included in the study. The patients' diagnoses fall into groups of psychotic disorders, mood and anxiety disorders and eating disorders. Inclusion criteria were psychiatric diagnosis made at least 5 years before this study based on ICD-10 criteria, adult patients aged from 18 to 65, consecutive patients admitted for inpatient or outpatient treatment. Exclusion criteria included major structural deformity of a hand occurring as a result of rheumatoid arthritis, osteoarthritis, various congenital anomalies, morbid obesity and nail extensions, patients currently in a state of acute psychotic decompensation, unable to understand or sign the informed consent. 17 patients were excluded on this basis so final analyses were performed on 100 patients. 63 patients were diagnosed with psychosis of which 25 was schizophrenia. Other 37 patients were mostly diagnosed with different mood disorders. The patients' demographics are shown in Table 1. Control group included 100 healthy individuals, School of Medicine University of Zagreb students and UHC Zagreb employees. The age and sex range in control group was the same as in the patient group. Out of 200 participants, both groups, the healthy

**Table 1.** Demographic characteristics of the patients

	Male (N=%)	Female (N=%)
<b>Residence</b>		
< 5000 inhabitants	9	3
< 25000 inhabitants	2	8
> 25000 inhabitants	11	5
> 100000 inhabitants	34	28
<b>Level of education</b>		
Primary	7	6
Secondary	34	26
Higher	15	12
<b>Employment</b>		
Unemployed	18	11
Employed	23	19
Retired	15	14
Mean age (years)	42.40±10.601	44.32±12.674

individuals and the patients, were equally distributed so that each group consisted of 100 participants, distributed as following: 56 male and 44 female participants in each group. In total there were 112 male participants and 88 female participants. All patients gave written informed consent approved by the ethics committee.

Ethical approval received from the Ethics Committee of University Hospital Center Zagreb in April 2017, number 02/21 AG, and Ethics Committee of the School of Medicine, University of Zagreb in May 2017, number 23/072/2-17.

A post hoc power analysis was performed using GPower (version 3.1.9.4) [Faul, F., Erdfelder, E., Lang, A.-G., & Buchner, A. (2007). G\*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*, 39, 175-191]. An effect size of 0.6778 was determined based on Wilks's lambda of 0.596 and type I error probability was set at 0.05. The analysis yielded statistical power of 1.00 and a non-centrality parameter of 135.5705 (critical F = 2.144).

## Procedure

At the beginning of this study three researchers constructed a short demographic questionnaire containing a few basic questions about the patient's socioeconomic status (SES) which was, previous to every examination, answered by the subjects. Immediately after answering the questionnaire two previously educated investigators, final year medical students, began the examination of patient's hands, each investigator individually followed by a mutual conclusion about grading a certain MPA,

excluding their subjective impression, after which they consulted the third investigator, professor of psychiatry at the University of Zagreb, School of medicine. Investigators examined the dorsal and palmar side of the hand and marked each of the six MPA with 0 for an absent anomaly and 1 for a present one. Investigators were blind to the patient's diagnoses previous to the examination. The results were then submitted to statistical analyses (Figure 1).

## Instruments

Instruments used in this study were published photos from the previous study (Domany et al. 2017), as well as the photos taken for the purpose of this study. Investigators graded the presence of each of the six previously mentioned anomalies based on photogrammetry of photos used in previous studies. Methods used in this study were only similar, not identical to the methods used in previous studies because of different conditions in our investigation. Domany et al. investigated and graded MPA through the sets of photos taken during examination, while we measured the hands directly during the examination and graded the MPA with 0 for an absent anomaly and 1 for a present one, each investigator separately. Ill-defined proximal interphalangeal joint suggests a flattened exterior joint surface as shown in the photos from the previous research. Persons general body construction was taken into account here which is explained more in detail through our exclusion criteria. The criterion for the extended eponychium to score 1 (present anomaly) is that it is well over the base of the nail which automatically shapes smaller nails.

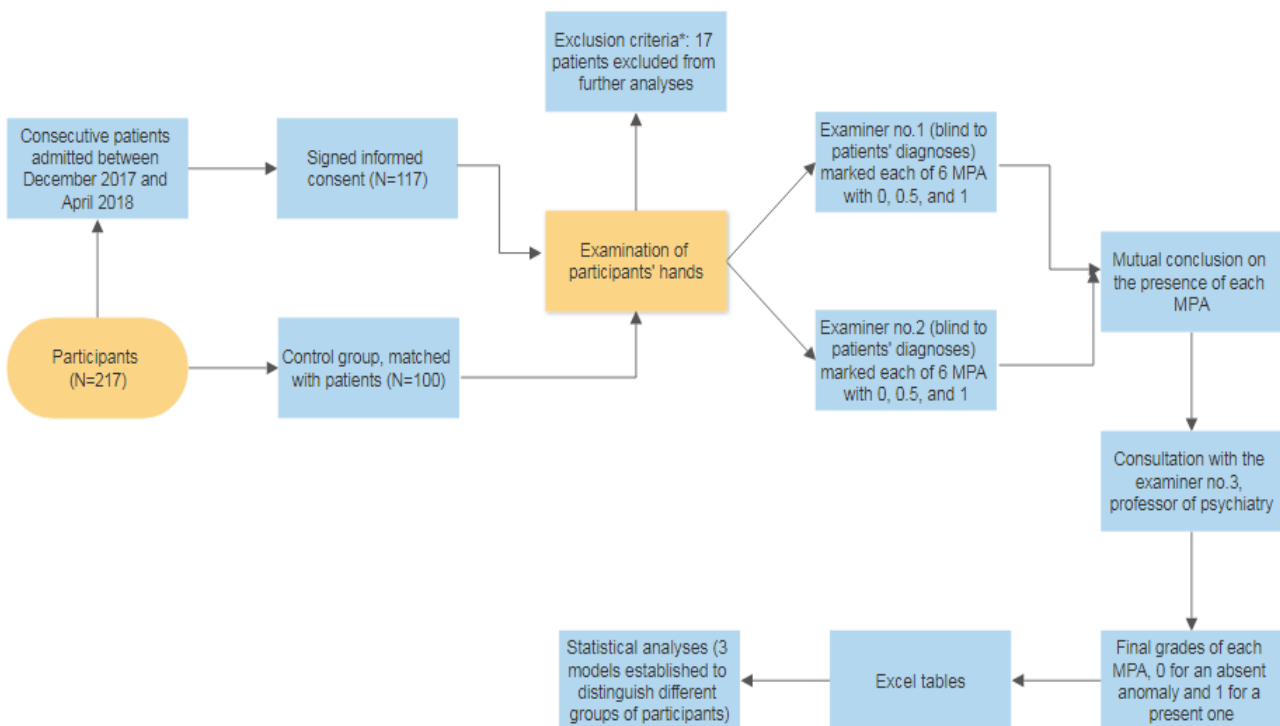
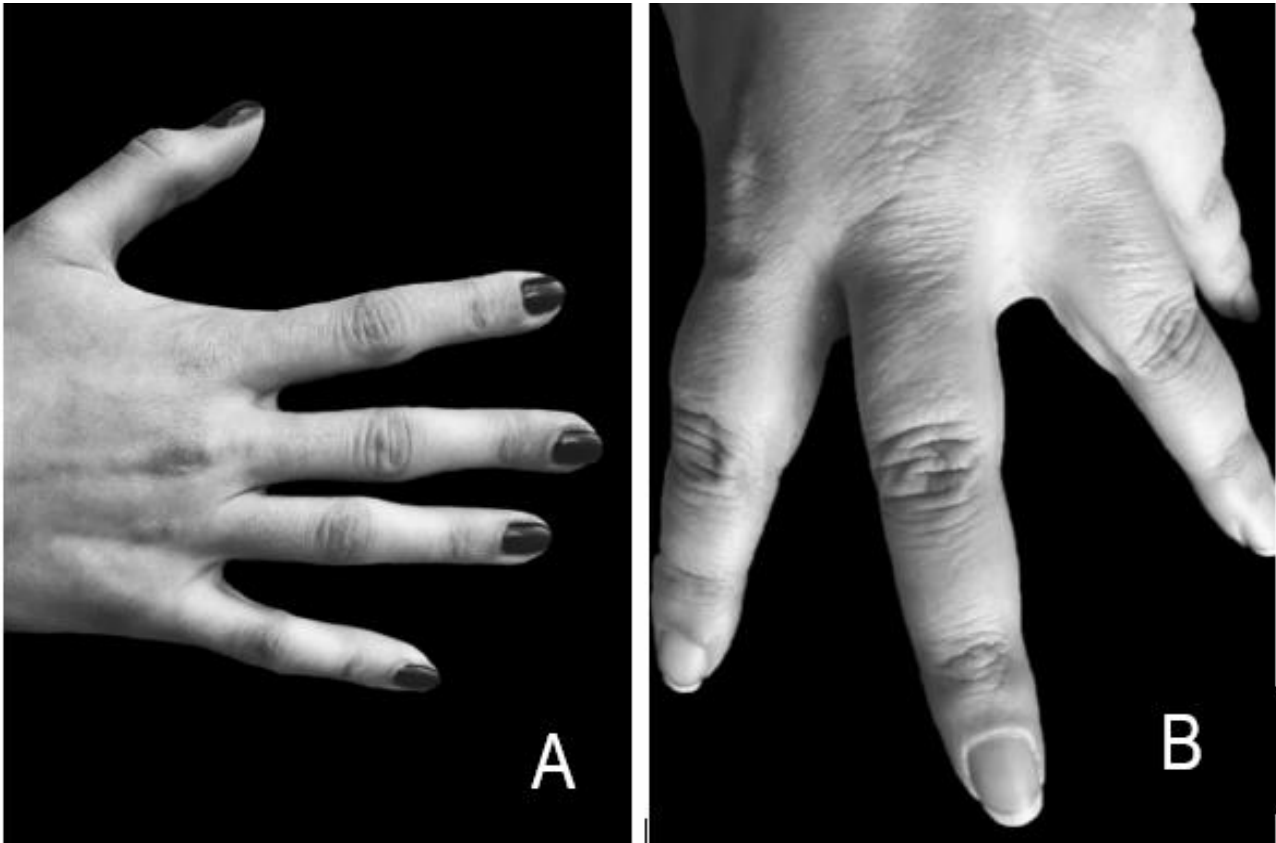
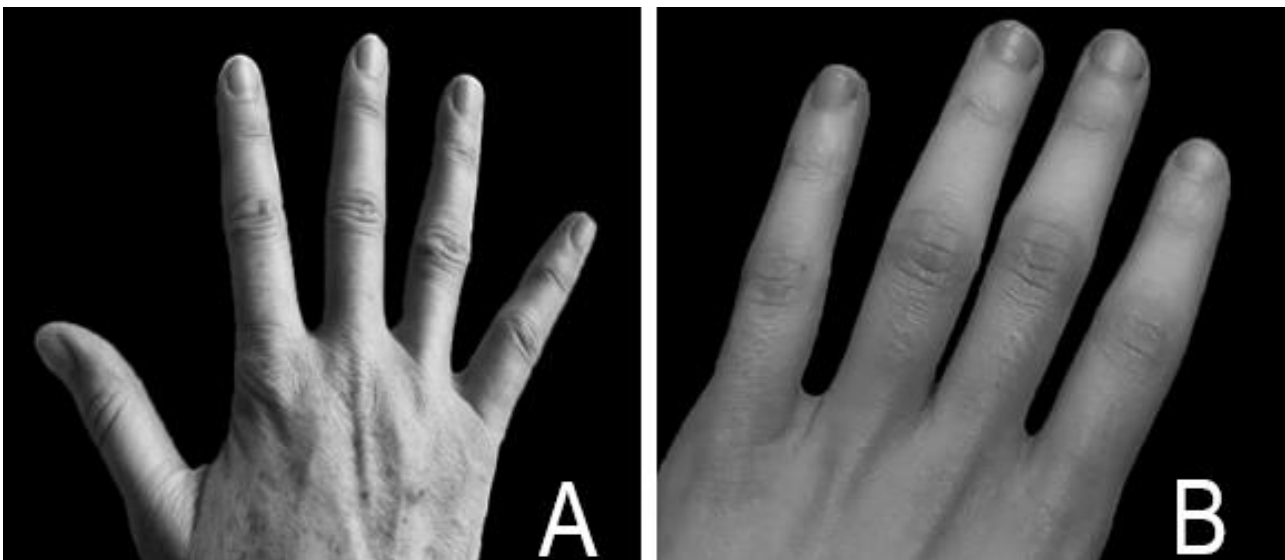


Figure 1. Procedure flowchart



**Figure 2.** Proximal interphalangeal joint (A) well defined proximal interphalangeal joint (B) ill-defined proximal interphalangeal joint

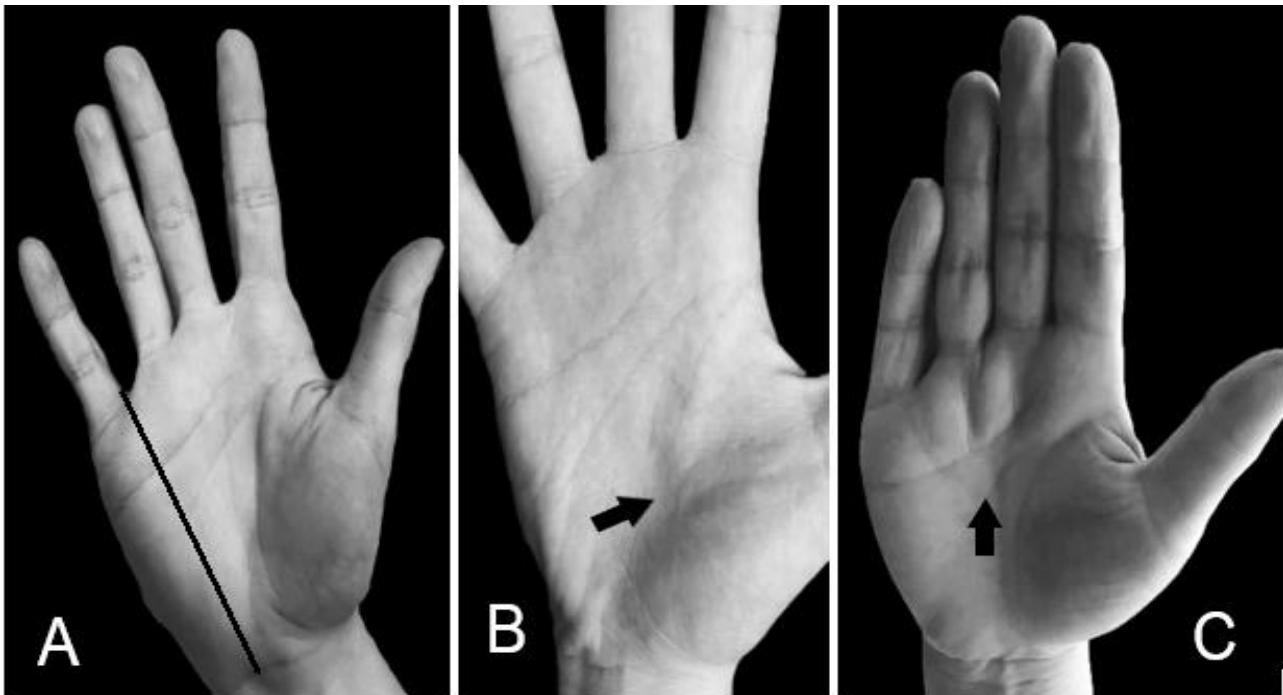


**Figure 3.** Eponychium of the middle digit and nail size - (A) Distal edge of the nails extends almost the whole width of the distal phalanges (normal nails). Eponychium (proximal nail fold) of the middle digit is not extended, distinct cuticle; (B) Nails diminished in size, eponychium of the middle digit is extended, hidden cuticle

Normal dermatoglyphics include a proximal transverse crease that extends beyond the midline of the ring digit with a visible thenar crease as shown in Figure 4. Following photos were taken by the investigators with a digital camera after examination. Photos were chosen based on which ones represented a certain MPA best as well as their quality. Chosen photos are shown in figures 2-4.

### Statistical analyses

Statistical analyses were performed based on a discriminant analysis which divides participants into categories according to the characteristics observed in the study. Relatively large number of participants in each group (N=100) allows for the use of this technique and



**Figure 4.** Dermatoglyphics of a hand (proximal transverse crease and thenar crease) - (A) Normal dermatoglyphics (proximal transverse crease extends beyond the midline of the ring digit, thenar crease is well defined); (B) Ill-defined thenar crease; (C) Broken proximal transverse crease

**Table 2.** Comparison of minor physical anomalies of a hand distribution for patients and control group and the results of chi-squared test/ U-test (+ for a present anomaly, - for an absent one). Total number of MPA presents a quantitative description of any of the anomalies that appeared in patients and in the control group

MPA	Value	Patients (N)	Control group (N)	Chi-square/U-test	df	p-value																																																																										
PIP joint	(-)	35	83	47.623	1	0.000																																																																										
	(+)	65	17				Eponychium	(-)	61	82	10.821	1	0.001	(+)	39	18	Nail size	(-)	79	95	11.317	1	0.001	(+)	21	5	PTC	(-)	53	92	38.144	1	0.000	(+)	47	8	TC	(-)	59	88	21.589	1	0.000	(+)	41	12	Digital flexibility	(1)	17	19	4324.5		0.084	(2)	32	44	(3)	32	25	(4)	19	12	Total number of MPA of a hand	(1)	9	53	1558.5		0.000	(2)	23	36	(3)	32	9	(4)	22	2	(5)	8
Eponychium	(-)	61	82	10.821	1	0.001																																																																										
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	(+)	41	12				Digital flexibility	(1)	17	19	4324.5		0.084	(2)	32	44		(3)	32	25				(4)	19	12	Total number of MPA of a hand	(1)	9	53	1558.5		0.000	(2)	23	36		(3)	32	9				(4)	22	2		(5)	8	0				(6)	6	0																								
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	(4)	22	2																																																																													
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	(6)	6	0																																																																													

MPA - minor physical anomalies; PTC - proximal transversal crease; TC - thenar crease; PIP - proximal interphalangeal joint; df - degrees of freedom

therefore this method has been used without any modifications. Leave-one-out cross-validation was used to examine the robustness of the model. Three models were established in the study, each of them using 6 MPA (nail size, eponychium, PIP, PTC, TC, and digital flexibility) and the criterion “two or more” of any of the 6

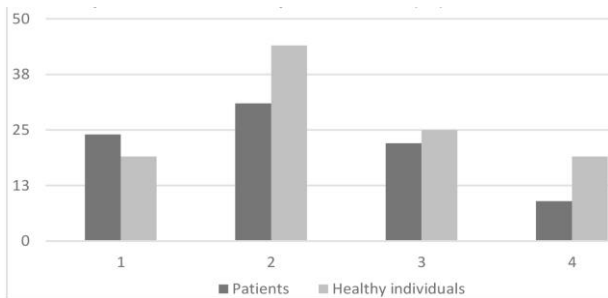
MPA present for every participant. First one was made to distinguish healthy individuals from the patients, second to distinguish psychotic from non-psychotic patients and the third one to distinguish schizophrenic patients from other psychotic patients as well as healthy individuals. Binary characteristics were analyzed using a chi-squared

test. Mann-Whitney U test was used for the analysis of the ordinal characteristics while Fischer's exact test was used for every case in which specific category has had the occurrence lesser than 5. In addition, the specific criterion determined for this study was the appearance of two or more anomalies, since it is more probable for one anomaly to be coincidentally present in patients.

## RESULTS

Age distribution slightly differed from the normal distribution (*Shapiro-Wilks's statistics* = 0.976, *df* = 200, *p* = 0.002, *Skew* = -0.104, *Kurtosis* = -0.904) with mean value of 43.24 (*Range* = 18-71, *95%CI* = 41.6-44.9, *standard deviation* = 11.75). Chi squared analysis of the age distribution based on the category of illness showed no significant difference between patients and healthy individuals ( $\chi^2 = 49.781$ , *df* = 44, *p* = 0.254).

Chi squared test and U test showed statistical significance in the occurrence of every characteristic except the digital flexibility (Figure 5).



**Figure 5.** Digital flexibility (graded 1 to 4), patients in comparison to healthy individuals (%)

In the first model analysis patients were compared to healthy individuals, 67% of patients and 11% of the control group matched the criterion of two or more anomalies. Percentage of each MPA is shown in Table 2. Discriminant analysis distinguished healthy individuals from the patients with *Wilks's lambda* of 0.595 ( $\chi^2 = 100.9$ , *df* = 7, *p* = 0.000). Digital flexibility was also included in the latter analysis, even though the results of the statistical analysis in Mann Withney U test yielded a *p* > 0.05. The standardized canonical discriminant coefficients for the six discriminant variables were: PIP = 0.343, eponychium = -0.201, nail size = -0.066, PTC = 0.259, TC = 0.016, digital flexibility = 0.037, number of anomalies = 0.757. The functions at group centroids were 0.82 for patients and - 0.82 for the healthy individuals. This analysis yielded 79.5% correct classifications, with a sensitivity (patients identified correctly) of 80% and specificity (healthy individuals identified correctly) of 79%. Leave-one-out cross-validation yielded 76.5% correct classification (Table 2).

The second model was made to distinguish psychotic from non-psychotic patients and in that group presence of two or more anomalies was found in 73% of psychotic patients in comparison to 56.7% of non-psychotic

patients. Discriminant analysis of psychotic and non-psychotic patients reached a *Wilks's lambda* value of 0.89 ( $\chi^2 = 10.98$ , *df* = 7, *p* = 0.140), marking a non-significant canonical correlation matrix.

The third model was made to show differences between schizophrenic and psychotic patients, if there are any, as well as from healthy individuals. 72% of the schizophrenia group and 73.6% of other psychosis match the "two or more MPA" criterion, compared to 11% of the control group. Discriminant analysis of the patients with schizophrenia, other psychoses and the healthy individuals between the first and second function reached a *Wilks's lambda* value of 0.496 ( $\chi^2 = 123.225$ , *df* = 14, *p* > 0.001) and in the second function 0.948 ( $\chi^2 = 8.377$ , *df* = 6, *p* = 0.212), with the first function carrying 95.2% and the second one 4.8% of the variance. The standardized canonical discriminant coefficients of the first function were: PIP = 0.248, eponychium = -0.258, nail size = -0.230, PTC = 0.186, TC = -0.094, digital flexibility = 0.078, number of anomalies = 1.027. The standardized canonical discriminant coefficients of the second function were: PIP = 2.298, eponychium = 3.168, nail size = 1.748, PTC = 2.400, TC = 1.904, digital flexibility = 0.165, number of anomalies = -5.477. The functions at group centroids were 1.042, 0.492 for schizophrenic patients, 1.448, -0.265 for other psychosis and -0.811, -0.022 for healthy individuals. This analysis yielded a correct classification of 70.6% sensitivity. Leave-one-out cross-validation yielded 65.6% correct classification.

## DISCUSSION

The main finding of our study is the proof of equal occurrence of MPA in schizophrenia and other psychoses. Models made for our research successfully distinguished patients with psychoses from healthy individuals, based on different combinations of minor physical anomalies. Our hypothesis was partially affirmed, MPA are more common in patients diagnosed with psychosis in comparison to healthy individuals but are not proven to be more common in patients with psychosis in comparison to patients diagnosed with other non-psychotic disorders, possibly due to the relatively small sample of patients in each group. Unlike the latter result, the study conducted by Domany Y. et al. 2017. successfully distinguished patients suffering from schizophrenia from other psychiatric patients in 80% of the cases.

The results show age distribution in our sample is slightly different from normal distribution whereas statistical analysis shows no significant difference in age between healthy individuals and patients. The results demonstrate statistical significance in a comparison between the patients and the control group. 67% of all the patients show two or more anomalies, while only 11% of the healthy control group matches this criterion. The model in which each of six anomalies were analyzed based on their ability to distinguish certain groups of patients or patients and healthy individuals, was made, in order to differen-

tiate the two groups and to determine whether a specific anomaly or group of anomalies can be a biomarker of any of the psychiatric conditions. This model was able to distinguish patients from healthy individuals with the precision of 80%. Discriminant analysis distinguished healthy individuals from the patients with *Wilks's lambda* of 0.595 ( $\chi^2=100.9$ ,  $df=7$ ,  $p=0.000$ ). With this we have confirmation of the possibility to distinguish patients from the control group in our study by different combinations of two or more anomalies. It is one additional confirmation of all the previous studies which only adds even greater value to researching this area of biological markers in psychiatry. Second analysis was made to distinguish psychotic from non-psychotic patients. The appearance of two or more MPA is present in 73% of psychotic patients and in 56.7% of the group of non-psychotic patients. The difference in the presence of two or more anomalies between these two groups is not proven to be statistically significant as *Wilks's lambda* yielded 0.89 ( $\chi^2=10.98$ ,  $df=7$ ,  $p=0.140$ ). According to a study made by Zvi Shamir et al. 2013. the difference between the two groups exists which is contradictory to our results. These results could be interpreted in many ways, one of which includes the previously mentioned flaw of psychiatric diagnostics, the tendency to misdiagnose patients because of subjectivity of the diagnostic process, which means a number of patients with non-psychotic diagnosis may actually be psychotic. We believe this error would be avoided with a bigger sample of patients in a study. There is also a minority of non-psychotic patients that will eventually during their lifetime develop psychotic symptoms or some form of psychosis, which is still impossible to predict, but they could be having MPA before the onset of psychosis. This way MPA could provide useful information to a psychiatrist or even to a general practitioner (GP) about a person's predisposition to development of psychosis, and eventually they could be used in developing an objective screening test, if proven significant in a larger study. Additional research including more subjects is necessary to get more reliable results and establish whether these biomarkers can truly distinguish psychotic from non-psychotic patients. Moreover, if such studies were conducted, a model even more precise and sensitive in distinguishing these two groups, than the one created in our study, is possible to be made.

With our last model we attempted to clarify the results of the two previous ones with comparing separately a group of schizophrenic patients, group of other psychotic patients and the control group. 72% of the schizophrenia group and 73.6% of other psychosis match the "two or more anomalies" criterion, compared to 11% of the control group. Discriminant analysis of the patients with schizophrenia, other psychosis and the healthy individuals between the first and the second function reached a *Wilks's lambda* value of 0.496 ( $\chi^2=123.225$ ,  $df=14$ ,  $p>0.001$ ) and in the second function 0.948 ( $\chi^2=8.377$ ,  $df=6$ ,  $p=0.212$ ). These results confirm findings from the previous two analyses. Schizophrenia group and other psychoses group could not be differentiated when each

anomaly was compared individually as well as none of the anomalies were specific to a single diagnosis. Previous research showed certain MPA being significantly more frequented in schizophrenic patients, while our study denies that finding (Compton et al. 2009, Gassab et al. 2013). The reason behind such different results of similar studies could be simply that the focus was always on finding the markers of schizophrenia, while other psychoses were neglected which is precisely why we wanted to explore if MPA are applicable to other psychoses as well, which we additionally confirmed. Nonetheless, additional research on a larger sample of patients is necessary to specify each MPA for each diagnosis, not only to a certain group of patients.

Comparing the results of all three analyses, one thing is certain; there is a significant difference between psychiatric patients and healthy controls in the frequency of MPA. Our research did not confirm previous findings about MPA being specific only to schizophrenia. It confirms MPA being equally represented in all psychoses. Furthermore, these findings are a valuable additional proof of neurodevelopmental theory of schizophrenia and other psychoses (Limosin 2014).

The sixth anomaly measured in this research was the finger flexibility. Digital flexibility is susceptible to many different factors, such as regular exercise, various physical conditions such as different connective tissue diseases (Ehlers-Danlos syndrome, Marfan syndrome etc.) as well as inflammatory diseases of the bones and joints. We find it very unlikely for flexibility to be a standalone biological marker of subtle functional brain changes developed prenatally ( $p=0.084$ ).

Despite these promising results, caution is necessary when analysing the influence of genetic and epigenetic factors on the development of psychosis, especially the timeline of their appearance during the prenatal development.

Moreover, our finding regarding appearance of minor physical anomalies equally in both schizophrenia and other psychoses is yet another proof supporting biological approach in the treatment of all psychotic disorders (Henry et al. 2004) with the same groups of pharmacological agents.

Limitations of this study include relatively small sample of patients in each group analysed (total of 100 patients, 25 of which diagnosed with schizophrenia, 38 diagnosed with other psychoses, and 37 with non-psychotic diagnoses) as well as the use of categorical variables in our measurements. Moreover, psychosis often accompanies congenital genetic syndromes, one of the exclusion criteria in our study, that are usually associated with dysmorphic features of various body parts. Our focus was on congenital anomalies of a hand such as claw hands or absence of one or more fingers because presence of those anomalies made impossible for the thorough hand examination to be performed. We can't claim with certainty that none of the patients we included in the study won't at some point in time discover an underlying congenital genetic syndrome since we haven't performed a genetic testing.

## CONCLUSIONS

To conclude, we were successful in building a model aiming to distinguish healthy individuals from patients. None of the MPA were specific to schizophrenia or any other diagnosis. These results are yet another confirmation of the neurodevelopmental hypothesis of schizophrenia, while the diagnostic potential of MPA needs more research with a bigger number of patients. The most valuable finding of this research was that MPA are not specific to schizophrenia, but they occur equally in other disorders with psychotic symptomatology.

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**Conflict of interest:** None to declare.

### Contribution of individual authors:

Paula Marinovic, Laura Pavicic & Alma Mihaljevic-Peles designed the study.

Paula Marinovic, Laura Pavicic, Marina Sagud, Maja Bajs Janovic, Sasa Jevtovic & Alma Mihaljevic-Peles acquired the data.

Nikola Prpic, NP statistically analyzed the data.

Paula Marinovic, Laura Pavicic, Nikola Prpic, Marina Sagud, Sasa Jevtovic & Alma Mihaljevic-Peles interpreted the data and critically revised the manuscript.

All authors took part in drafting of the manuscript, gave final approval, and agreed to be accountable for all aspects of the work.

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Correspondence:

Paula Marinovic, MD

Department of Psychiatry and Psychological Medicine, University Hospital Center Zagreb

Kispaticeva 12, 10 000 Zagreb, Croatia

E-mail: paula.marinovic77@gmail.com