



The genetics of self-reported trait impulsivity: Contribution of catecholaminergic gene variants in European ancestry individuals

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ABSTRACT

Increased trait impulsivity is a core element in several mental disorders. Given the durable and consistent nature of trait impulsivity, studies have explored its relation to stable biological measures. Variation in catecholaminergic neurotransmission by genetic variants could be one of these biological substrates.

Here, 905 participants of European-ancestry completed the Barratt Impulsiveness Scale-11 and were genotyped in three single nucleotide polymorphisms related to catecholaminergic neurotransmission: the DRD2/ANKK Taq1A, the C957T DRD2 and the Val158Met of the COMT gene.

We found significant main effects of Val158Met and C957T on BIS-11 score. Also, interactions with gender were significant in both SNPs with a tendency to slightly different genotype and allele associations with the BIS-total score between male and female participants. Whereas in females, higher impulsivity scores were obtained by participants with the Val158Met heterozygous genotype (Met/Val), data indicate a trend towards a higher impulsivity score in male Val-allele carriers. In the case of C957T, only a tentative association between male T-allele carriers and higher impulsivity scores in comparison to CC genotype carriers could be established. No significant associations were found between BIS-11 and Taq1A.

We provide further evidence for a gender-specific implication of Val158Met and C957T in trait impulsivity.

1. Introduction

Impulsivity is both a normal dimensional behavior as well as a core feature in several mental disorders. It refers to the predisposition to act rapidly without foresight, leading to premature actions without enough consideration of potential undesirable consequences (Moeller et al., 2001). Lately, research has pointed out the distinction between state and trait impulsivity. *State impulsivity* refers to a transient, momentary

response to an intrinsic or extrinsic stimulus derived from the dysregulation of inhibitory processes, including impulsive decision-making, behavioral disinhibition and impulsive response initiation (Pan et al., 2021). On the other hand, *trait impulsivity* refers to more stable and consistent personality characteristics that influence an individual's day-to-day activities and actions (Nguyen et al., 2018). In this sense, normal variations in trait impulsivity are one of several features that compose personality, but extreme high impulsivity is related to the manifestation

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of socially inappropriate and maladaptive behaviors and is a core element in several mental disorders, including eating disorders (Malloquí-Bagué et al., 2020), obsessive-compulsive disorder (Xu et al., 2021), bipolar disorder (Lombardo et al., 2012) and especially substance use disorder (Verdejo-García & Albein-Urios, 2021). Given the durable and consistent nature of trait impulsivity, an important number of studies have explored its relation to stable biological measures. In this sense, multiple neurotransmitter systems have been shown to modulate impulsivity, and especially the dopaminergic system has been frequently linked to variations in trait impulsivity.

Positron emission tomography (PET) has been able to reveal several dopaminergic components associated with impulsivity scores like the D2/D3 receptors in the substantia nigra/ventral tegmental area (Buckholz et al., 2010) and the dopamine active transporter (DAT) in the ventral striatum (Smith et al., 2018). These studies show that reduced availability of these components leads to increased trait impulsivity presumably due to a consequent increase in dopamine release in these areas.

One reason behind changes in the availability and binding potential of these neurotransmitter components is likely to be of genetic nature. Twin studies have shown that trait impulsivity is moderately heritable, accounting for genetic factors for about 45 % of the variance (Congdon & Canli, 2008). Variants in genes belonging to the dopaminergic system are suitable to be associated with trait impulsivity, and therefore variants of the dopamine receptor D2 (*DRD2*) or the catechol-O-methyltransferase (*COMT*) gene are first-choice candidate genes for trait impulsivity (Varga et al., 2012). The *DRD2* C957T (rs6277) variant is a synonymous single nucleotide polymorphism (SNP) in exon 7 of the *DRD2* gene and has been shown to affect *DRD2* mRNA stability and receptor synthesis, as well as its binding potential in the human striatum (Hirvonen et al., 2004). The C957T SNP is also in high linkage disequilibrium with the *DRD2/ANKK1* Taq1A (rs1800497) variant, which is thought to alter *DRD2* expression and dopamine synthesis (Hirvonen et al., 2009). The *COMT* enzyme is responsible for degrading catecholamine among other neurotransmitters and plays a key role in clearing dopamine in the prefrontal cortex (Käenmäki et al., 2010). Data indicate that around 60 % of the dopamine catabolism in the prefrontal cortex is carried out by the *COMT* enzyme (Hosák, 2007; Karoum et al., 2002) but it also influences dopamine release in other brain regions such as the striatum (Simpson et al., 2014). Within the *COMT* gene variants, the most interesting and frequently studied one is the Val158Met SNP (rs4680). This polymorphism is functional and affects the thermostability of the enzyme, leading to modifications in its enzymatic activity. Therefore, the Met (A) allele variant presents a four times lower catabolic rate than the Val (G) allele, leading to a lower synaptic dopamine level (Chen et al., 2004).

Nevertheless, genetic association studies exploring the above-mentioned candidate genes influencing trait impulsivity, rather than state impulsivity, are few and have obtained mixed and inconclusive results. In this sense, some studies have shown a significant association between the *COMT* Val158Met variant and trait impulsivity, but others do not. Regarding the *DRD2/ANKK1* Taq1A, since the year 2010, to the best of our knowledge, only two studies have explored its association with trait impulsivity finding mainly no significant associations with impulsivity (Gullo et al., 2014; Varga et al., 2012). Finally, for the *DRD2* C957T, only one study has explored so far its association with the BIS-11 total impulsivity score obtaining a significant association (Markett et al., 2014). Those differences in results of previous studies are likely attributable to several factors, such as sample size, gender, or ethnicity. In this present study, we aim to shed some light on the contribution of three catecholaminergic gene variants on trait impulsivity measured by the BIS-11 questionnaire, addressing some of the possible confounding factors by using a large sample of 905 healthy European-only young adults and considering gender as a possible determining factor for specific allele-associations.

2. Material & methods

2.1. Participants

Nine hundred and seventy-nine ($N = 979$) voluntary young adult undergraduate students were recruited from the Complutense University of Madrid and the Autonomous University of Madrid. To reduce population stratification, only participants who reported European ancestry were included in the analysis. In addition, data from five participants (one male and four female) who obtained a BIS-11 score 3 standard deviations higher than the total mean (>90.56) were excluded from the analysis. Finally, 905 participants (80.2 % women) were enrolled in the final analysis. The mean age was 19.83 (± 2.26) within the age range of 17–35 years.

2.2. Instruments

Trait impulsivity was measured by the Spanish version of the *Barratt Impulsiveness Scale-11A* (Oquendo et al., 2001). This instrument has been chosen because it is one of the most widely used scales to assess impulsivity. Table 1 in the Supplementary material offers an overview of the most used trait impulsivity assessment scales. The BIS-11 assessed trait impulsivity according to three subscales: *Attentional impulsiveness* (inability to focus attention or concentrate), *Motor impulsiveness* (acting without thinking), and *Non-planning impulsiveness* (lack of forethought).

Since the Spanish version of Oquendo et al. (2001) was elaborated from an initial version of BIS-11 (BIS-11A) (Barratt, 1993), which has some variations in comparison to the final version (Patton et al., 1995), only 24 items common to both versions have been considered (International Society for Research on Impulsivity, 2013). However, both the total score and subscale scores were transformed to BIS-11 scores by dividing them by the number of common items and multiplying by the corresponding number of items in the final version. In this way, they could be compared to those of studies using the more common final version. In this study, Cronbach's alpha coefficient for the questionnaire was 0.76.

2.3. Procedure

Each participant signed two informed consent sheets, one related to impulsivity data and the other related to genetics data, after which they filled out the BIS-11 questionnaire and donated a saliva sample. All procedures were approved by The Research Ethics Committee of the Complutense University of Madrid (Faculty of Psychology).

2.4. DNA genotyping

Following single nucleotide polymorphisms (SNP) have been selected for genotyping: *DRD2/ANKK1* Taq1A (rs1800497), *DRD2* C957T (rs6277), and *COMT* Val158Met (rs4680). These SNPs have been chosen because of their functional implication in dopaminergic neurotransmission and the lack of clarity regarding their implication in trait impulsivity. Table 2 of the supplementary material shows a relation of gene variants that have been explored in previous gene association studies for their association with trait impulsivity. This table also illustrates the conflicting findings regarding the three SNPs used in the present study.

DNA from saliva was genotyped as previously described (Bühler et al., 2014). Briefly, DNA was collected using Oragene DNA Self-Collection kit (DNA Genotek, Ontario, Canada) and purified from 250- μ l aliquots using the ethanol precipitation protocol as described by the manufacturer. TaqMan genotyping was performed using pre-designed and validated TaqMan SNP genotyping assays (Assay IDs: rs6277, rs1800497, and rs4680) for humans from Applied Biosystems (Foster City, CA94404, USA). These genotyping assays were performed with a LightCycler 480II-machine (Roche Diagnostics, Barcelona, Spain) with

an endpoint genotyping method. Color fluorescence measures after amplification were analyzed with LightCycler 480 endpoint genotyping software version 1.5 (Roche Diagnostics, Barcelona, Spain).

2.5. Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences of International Business Machines (IBM SPSS Statistics 27 for Windows, SPSS Inc., Chicago, IL). First, a repeated-measures ANOVA was performed, with the three BIS-11 subscales as within-subjects factor and the genotypes in Val158Met, C957T, and TaqIA, as well as gender, as inter-subject factors. Next, a univariate ANOVA was independently performed for both genders, with the total score in BIS11 as the dependent variable and the three SNPs as fixed factors. To assess pairwise differences between genotypes within each SNP, estimated marginal means for SNPs with significant main effects were compared with Bonferroni-corrected nominal *p*-values ($p < 0.05$). Age has been included as a covariate in all analyses.

3. Results

3.1. Genotyping

Genotype distribution data of the three SNPs are shown in [Table 1](#). The genotype distribution of the three SNPs did not deviate from Hardy-Weinberg equilibrium (*DRD2* C957T $\chi^2 = 0.001$, $p = 0.974$; *DRD2/ANKK1* Taq1A $\chi^2 = 0.34$, $p = 0.559$; *COMT* Val158Met $\chi^2 = 0.022$, $p = 0.87$). Allele frequency distributions of C957T, Taq1A y Val158Met were consistent with the NIH NCBI dbSNP database for European ancestry, where the minor allele frequency were stated as C957T T(54 %), Taq1A T(19 %), and Val158Met (50,8 %). Since the sample only included 36 TT genotype carriers, TT genotype and CT genotype carriers were combined into one single T-allele carrier group to increase statistical power in the further analysis regarding this gene variant.

3.2. BIS-11 score

The mean total BIS-11 score was 62.99 (± 9.206). Descriptive values for the subscales were the following: Attentional Impulsiveness mean 20.44 (± 4.123), Motor impulsiveness mean 19.88 (± 3.737) and Non-planning impulsiveness mean 22.602 (± 4.387). Significant differences between gender were observed in the BIS-11 total score ($F(1) = 7.273, p = 0.007$), Attentional Impulsiveness ($F(1) = 8.984, p = 0.003$) and Motor impulsiveness ($F(1) = 8.785, p = 0.003$). In all three cases, men reported higher impulsivity scores than women (Fig. 1).

3.3. BIS-11 score and genotype associations

In the repeated measures ANOVA, the main effects of Val158Met and C957T genotype on the BIS-11 total score were significant (Val158Met $F(2,870) = 9.196$; $p < 0.001$; partial $\eta^2 = 0.021$; C957T $F(2,870) = 4.061$; $p = 0.018$; partial $\eta^2 = 0.009$). Interactions with gender were significant in both SNPs (Val158Met \times gender $F(2,870) = 4.441$; $p = 0.012$; partial $\eta^2 = 0.010$; C957T \times gender $F(2,870) = 3.271$; $p = 0.038$; partial $\eta^2 = 0.007$). In the case of the Taq1A factor, neither the main effect nor the interaction with gender was statistically significant. Neither were any of the interactions between genotypes significant nor their interaction with the subscales factor.

After splitting the analysis by gender, the data for female participants indicate a significant main effect of Val158Met genotype on BIS-11 total score ($F(2,708) = 4.452; p = 0.012$; partial $\eta^2 = 0.012$). Female carriers of the Val/Val (GG) genotype had a significantly lower BIS-11 total score than the carriers of the Met/Val (AG) genotype ($MD = 2.510$; $SE = 1.030$; $p = 0.045$) (Fig. 2). The main effect of the C957T genotypes was not statistically significant.

In the case of males, the main effect of the Val158Met genotype was

Table 1
C957T, Taq1A and Val158Met genotype distribution.

C957T (rs6277)																			
								Alleles											
C								T											
CC				CT				TT				C				T			
	Male	Female	Total	Male	Female	Total	TOTAL	Male	Female	Total	Male	Female	Total	Male	Female	Total	TOTAL		
n	34	115	149	82	355	437	905	63	256	319	735	150	585	735	208	867	1075	1810	
%	3.8	12.7	16.5	9.1	39.2	48.3	100.0	7.0	28.3	35.2	40.6	8.3	32.3	40.6	11.5	47.9	59.4	100.0	
Taq1A (rs1800497)																			
								Alleles											
C								T											
CC				CT				TT				C				T			
	Male	Female	Total	Male	Female	Total	TOTAL	Male	Female	Total	Male	Female	Total	Male	Female	Total	TOTAL		
n	121	477	598	51	221	272	905	7	28	35	905	293	1175	1468	65	277	342	1810	
%	13.4	52.7	66.1	5.6	24.4	30.1	100.0	0.8	3.1	3.9	100.0	16.2	64.9	81.1	3.6	15.3	18.9	100.0	
Val158Met (rs4680)																			
								Alleles											
A								G											
AA				AG				GG				A				G			
	Male	Female	Total	Male	Female	Total	TOTAL	Male	Female	Total	Male	Female	Total	Male	Female	Total	TOTAL		
n	38	139	177	92	357	449	905	49	230	279	803	168	635	803	190	817	1007	1810	
%	4.2	15.4	19.6	10.2	39.4	49.6	100.00	5.4	25.4	30.8	44.4	9.3	35.1	44.4	10.5	45.1	55.6	100.0	

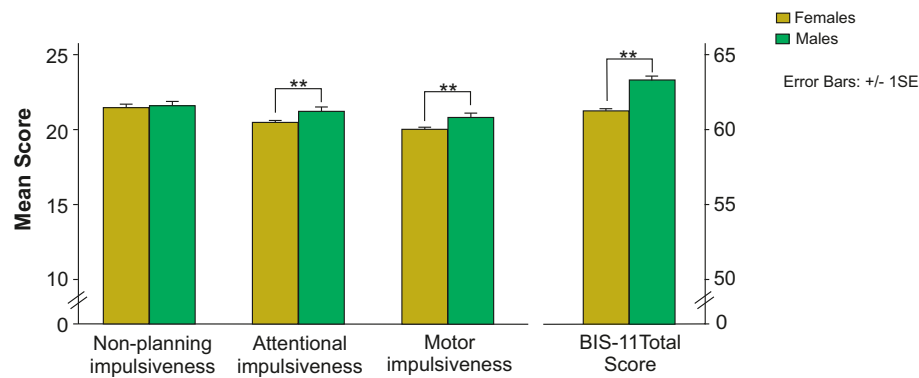


Fig. 1. Mean scores for females and males on the BIS-11 total scale and subscales. Significant differences between genders were found on the BIS-11 total score and on the attentional and motor impulsiveness subscales. In all cases, males scored higher in impulsivity than females.

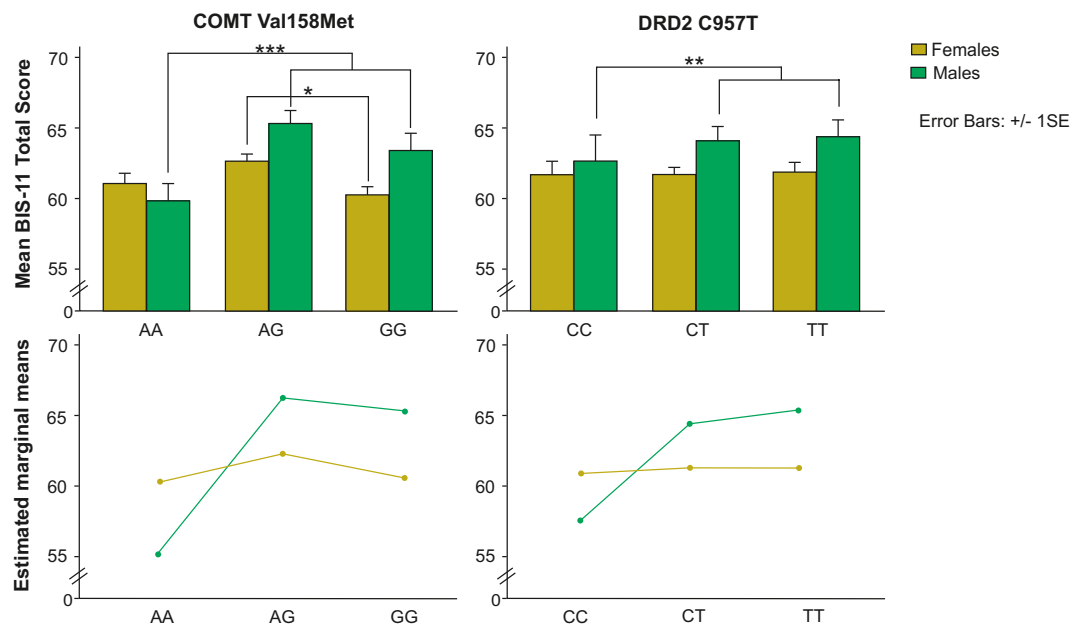


Fig. 2. Associations between COMT Val158Met and DRD2 C957T and BIS-11 total score. Bar charts represent the mean BIS-11 score for COMT Val158Met and DRD2 C957T genotypes (means, standard errors) separated by gender. Line graphs represent corresponding marginal means. Error bars for marginal means are not shown to improve clarity but are indicated in the main text (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$).

also statistically significant ($F(2,162) = 7.863$; $p = 0.001$; partial $\eta^2 = 0.088$). Male carriers of the Met/Met (AA) genotype had a significant lower BIS-11 total score than Met/Val (AG) and Val/Val (GG) genotype carriers (AG MD = 10.849; SE = 2.462; $p < 0.001$; GG MD = 9.984; SE = 2.607; $p = 0.001$). In males, the main effect of the C957T genotype was also significant ($F(2,162) = 5.311$; $p = 0.006$; partial $\eta^2 = 0.062$). Here, male carriers of the CC genotype had significant lower BIS-11 total scores than the CT and TT (CT MD = 6.689; SE = 2.270; $p = 0.011$ TT MD = 7.666; SE = 2.441; $p = 0.006$) (Fig. 2). Nevertheless, due to the differences in proportion between males and females in the sample, results regarding males should be interpreted cautiously.

4. Discussion

The present study shows a significant main effect of COMT Val158-Met and DRD2 C957T on the BIS-11 total score, displaying gender as a significant interaction effect with both SNPs. The data indicate that those female carriers of the COMT Val/Val genotype obtained significantly lower impulsivity scores than the Val/Met genotype. Even results regarding genotype-impulsivity associations in males should be

considered tentative due to differences in sample size in comparison to females, the data indicate that men Val-allele carriers scored significantly higher in impulsivity than the Met/Met genotype. Therefore it seems that female and male participants showed a tendency to have slightly opposite genotype and allele associations with the BIS-total score. In the case of DRD2 C957T, only men T-allele carriers (CT and TT genotype) obtained higher impulsivity scores than CC genotype carriers. These results are therefore in line with studies that associate dopamine-modulating genetic variants with trait impulsivity or impulsive-related disorders, such as addiction disorders and attention deficit hyperactivity disorders (ADHD), as well as attempted suicide (Moro et al., 2019; Smolnikova & Tereshchenko, 2020).

The COMT gene has been widely studied in the context of impulsivity and impulse-related disorders and several studies have found links between COMT genotype and trait impulsivity measured by the BIS-11 (SOEIRO-DE-SOUZA et al., 2013; Varga et al., 2012). Nevertheless, what remains elusive is how the different genotypes of the COMT variant influence specifically different aspects of impulsivity. Whereas some studies have found greater impulsivity scores for carriers of the Met allele, others have found the Val allele to increase impulsive behavior

(Grant et al., 2015; SOEIRO-DE-SOUZA et al., 2013). As shown in different meta-analyses, COMT exerts an important pleiotropy and phenotypic specificity, suggesting that the Met and the Val allele have differential effects on cognition, emotion, and motivation (Mier et al., 2010; Taylor, 2018). In this way, the Met allele is related to a better performance in tasks that assess processes involving executive function, whereas the Val allele is related to tasks influenced by emotional processing. Moreover, the specific COMT Val158Met association also depends on other factors such as ethnicity and gender (Hoenicka et al., 2009; Wang et al., 2016), as we observe in our study. The Met and the Val allele show a tendency to exert opposite effects on males and females, leading the Val allele to lower impulsivity in females and to higher impulsivity in males. Furthermore, in males the influence of the Val allele was by far more pronounced. While we can only provide speculative explanations for these phenomena, it could be that males, because of the higher enzymatic activity of the Val-allele COMT enzyme in comparison to the Met/Met enzyme, carriers of the Val/Met and Val/Val genotypes would deal with lower extracellular dopamine levels in the PFC, which might affect efficient precortical functioning. Val-allele carriers show therefore reduced performance in executive and cognitive functioning, including reduced inhibitory control and greater impulsivity (Nolan et al., 2004). This would be in line with previous studies that show that male Met-allele carrier show greater neural activation during a response inhibition task in comparison to Val/Val carrier, presumably because Met-allele carriers have more optimal levels of dopamine (Congdon and Canli, 2008). Carriers of the Val/Val genotype would fall therefore to the left of the inverted U-shape response function of dopamine on executive functioning. Regarding females and the tendency to opposite results in the effect of the Val158Met COMT variant, as already stated by previous studies, this might be due to the mediating effects of estrogens on the transcriptional regulation of COMT expression, which downregulates COMT protein expression and therefore reduces COMT activity (Jiang et al., 2003). Estrogens have also been shown to modulate neurotransmission and neuronal excitability of the catecholaminergic system (Balthazart & Ball, 1998; Jacobs & D'Esposito, 2011) which might also contribute to the differential effects of COMT between genders.

Gender specificity is also observed in the association between C957T and trait impulsivity. As reported in this study, an association between C957T genotype and trait impulsivity could only be established in males. As this variant has been shown to reduce mRNA stability and synthesis with the consequent decrease in striatal D2 receptor availability, it has been proposed to be a plausible candidate gene variant related to changes in brain connectivity and activity (Hirvonen et al., 2005). While it should be noted that some previous studies point to the opposite association, many studies show the T allele to be specifically associated with impulsivity. These studies indicate that CC genotype or C allele carriers performed better in inhibition response tasks (Colzato et al., 2010, 2013) and obtained significantly lower BIS-11 total scores than the T allele carrier (Markett et al., 2014). This is in line with the results obtained in the present study since we observed that CC homozygous obtained significantly lower impulsivity scores than T allele carriers. An explanation could be that C957T not only reduces DRD2 receptor availability in the striatum but also increases D2 receptor availability in extrastriatal regions. In this line, Ray et al. (2012) observed a positive correlation between elevated D2/3 extrastriatal binding and impulsivity in Parkinson's patients with pathological gambling disorders. Moreover, an increased D2/3 receptor availability in extrastriatal regions, such as the cortex, has been associated with increased venturesomeness score, which is a key factor in trait impulsivity (Bernow et al., 2011). Finally, it is important to mention that most studies regarding the biological underpinnings of C957T have been carried out only with male participants, meaning that most findings related to changes in receptor availability have not been proved in females. Again, this would go in line with the gender specificity found in this present study.

One limitation of the present study is the specific nature of the

sample, being all participants university students of European ancestry. This signals the need for further replication in non-European ancestries and other age groups. Another sample-related limitation is the imbalance in the number of female and male participants, so that results regarding males should be considered with caution. However, our sample includes 179 men, a number at least equal to that found in other comparable genetic association studies (Nogueira et al., 2020; Panitz et al., 2018).

5. Conclusion

In conclusion, we provide further evidence for the implication of the catecholaminergic gene variants Val158Met and C957T in trait impulsivity in a sample of adults of European ancestry.

Even if our data do not allow us to establish a causal relationship between changes in dopaminergic transmission and trait impulsivity, it seems highly plausible that alterations specifically in areas such as the prefrontal cortex significantly mediate impulsivity traits, and moreover, in a possible gender-specific way.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.paid.2022.111906>.

CRediT authorship contribution statement

Kora-Mareen Bühler: Methodology, Investigation, Writing – original draft, Writing – review & editing. **Irene Rincón-Pérez:** Resources, Investigation, Writing – original draft, Writing – review & editing. **Javier Calleja-Conde:** Investigation, Writing – original draft. **Jacobo Albert:** Resources, Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Jose Antonio Hinojosa:** Resources, Conceptualization, Writing – original draft, Writing – review & editing. **Elena Giné:** Writing – review & editing. **Víctor Echeverry-Alzate:** Investigation. **Jose Antonio López-Moreno:** Resources, Conceptualization, Writing – review & editing. **Evelio Huertas:** Resources, Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing.

Data availability

The data that has been used is confidential.

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