

## Introduction

As a social species, humans tend to have strong needs for social connection. The negative emotions one experiences when their needs for social connection are not met (sadness, frustration, sorrow, shame, desperation) are referred to as loneliness. Besides leading to these negative emotions and a darker worldview, loneliness can have detrimental consequences for one's health, especially when it is persistent. Lonely individuals are at an increased risk for psychiatric disorders, substance abuse, cardiovascular health problems, impaired immune functioning, and early mortality in general.

Under circumstances that decrease fitness, negative emotions were useful while positive emotions were harmful. How one experiences these emotions may (partly) be regulated by personality. Neuroticism partly reflects the (over)sensitivity to negative emotions, while extraversion may (partly) reflect the sensitivity to positive emotions. Hence, a genetic disposition for neuroticism and/or extraversion may result in a genetic disposition for loneliness.

## (SNP) Heritability & Genetic Correlations

Loneliness and the big five personality dimensions were measured with the shortened R-UCLA Loneliness questionnaire (three items) and NEO (twelve items per dimension) respectively in 4,246 genotyped Dutch individuals ( $N_{\text{twin\_families}} = 2,374$ , Affy6, ~500k SNPs after QC). We used a method by Zaitlen et al (2013; doi: 10.1371/journal.pgen.1003520) that allows for the simultaneous estimation of the narrow sense heritability ( $h^2$ ) and the heritability explained by genotyped SNPs ( $h_g^2$ ), by including both closely and distantly related pairs of individuals. We estimated the heritability components and the genetic correlation for each component between loneliness and the five personality dimensions. We corrected for ancestry-informative PCs, CQC, genotyping batch, age, sex, and year of birth.

**Table 1 (below):** 14% of individual differences in Loneliness are explained by genotyped SNPs (narrow sense heritability = 26%). There are two personality dimensions with a significant  $h_g^2$ : Openness to Experience (30%) and Neuroticism (22%). The only significant genetic correlation captured by genotyped SNPs is between Loneliness and Neuroticism: .71,  $p = .007$ .

	SNP heritability			Residual/ "Missing" heritability			Narrow sense heritability			Genetic correlation with loneliness		
	$h_g^2$ (SE) [p]	$h_{\text{res}}^2$ (SE) [p]	$h^2$ (SE) [p]	rG (SE) [p] - $h_g^2$	rG (SE) [p] - $h_{\text{res}}^2$	rG (SE) [p] - $h^2$	$h_g^2$ (SE) [p]	$h_{\text{res}}^2$ (SE) [p]	$h^2$ (SE) [p]	rG (SE) [p] - $h_g^2$	rG (SE) [p] - $h_{\text{res}}^2$	rG (SE) [p] - $h^2$
Loneliness	.14 (.08) [.04]	.13 (.09) [.07]	.26 (.03) [ $8 \times 10^{-16}$ ]									
Openness to Experience	.30 (.09) [.0004]	.28 (.09) [.001]	.58 (.02) [0]	.37 (.30) [.10]	-.08 (.36) [.41]	.18 (.06) [.002]						
Conscientiousness	.002 (.09) [.49]	.44 (.09) [ $2 \times 10^{-16}$ ]	.44 (.03) [0]	-1 (5.35) [.31]	-.57 (.27) [ $4 \times 10^{-5}$ ]	-.50 (.07) [ $3 \times 10^{-11}$ ]						
Extraversion	.06 (.09) [.23]	.34 (.09) [.0001]	.40 (.03) [0]	-.64 (.54) [.17]	-.77 (.28) [.001]	-.68 (.06) [0]						
Agreeableness	.10 (.09) [.14]	.24 (.09) [.007]	.33 (.03) [0]	.17 (.60) [.38]	-.80 (.37) [.02]	-.39 (.08) [ $2 \times 10^{-6}$ ]						
Neuroticism	.22 (.09) [.005]	.20 (.09) [.02]	.43 (.03) [0]	.71 (.20) [.007]	.98 (.25) [.02]	.83 (.04) [0]						

$$\Sigma = K \otimes \sigma_{\text{SNP}}^2 + K_{\text{aac} > 0.05} \otimes \sigma_{\text{res}}^2 + I \otimes \sigma_E^2$$

Full GRM (K):

1			
0.502	1		
-0.01	0.005	1	
0.002	0.024	0.001	1

"Family" GRM ( $K_{\text{aac} > 0.05}$ ):

1			
0.502	1		
0	0	1	
0	0	0	1

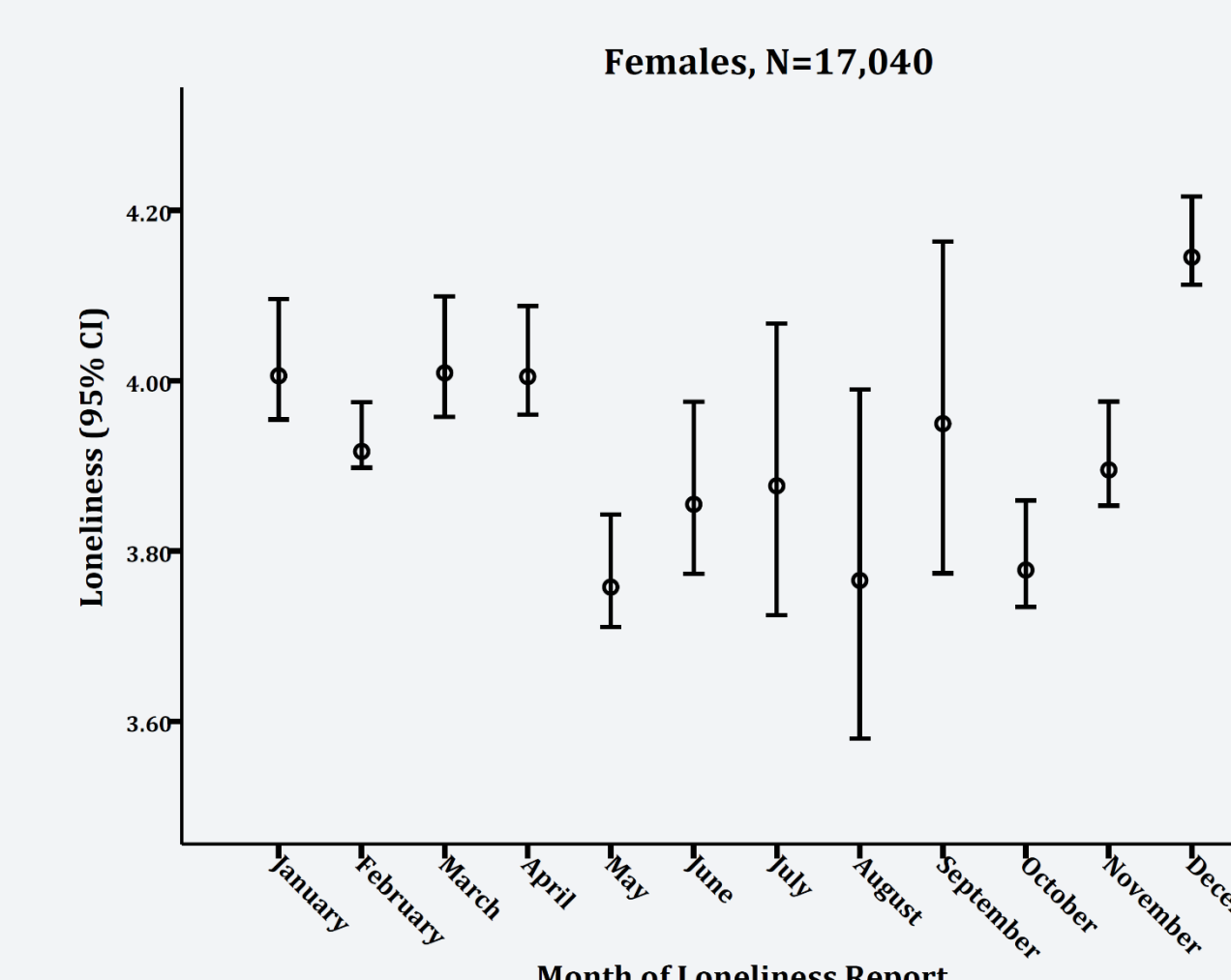
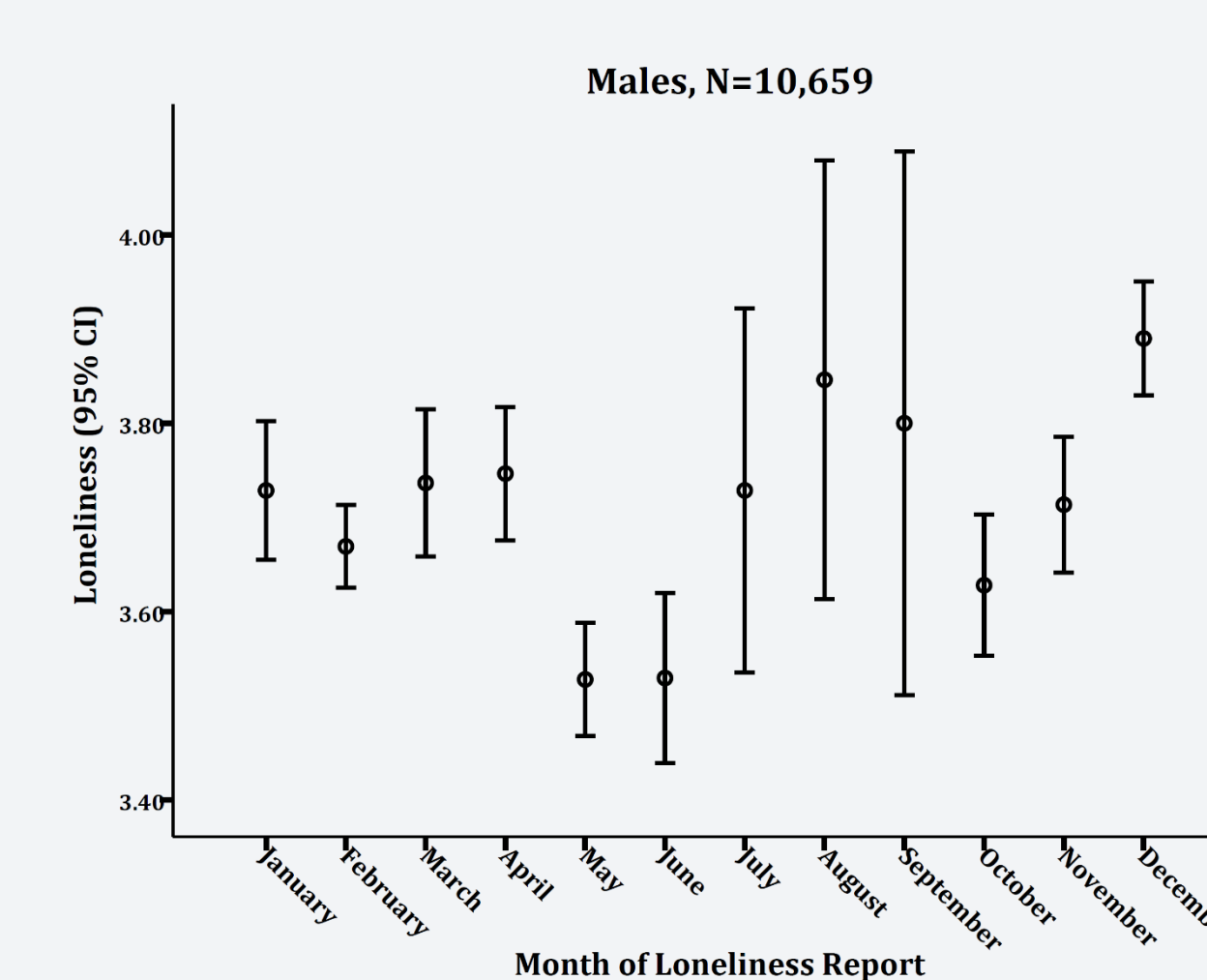
Pair of siblings

Two GRMs simultaneously fitted in GCTA

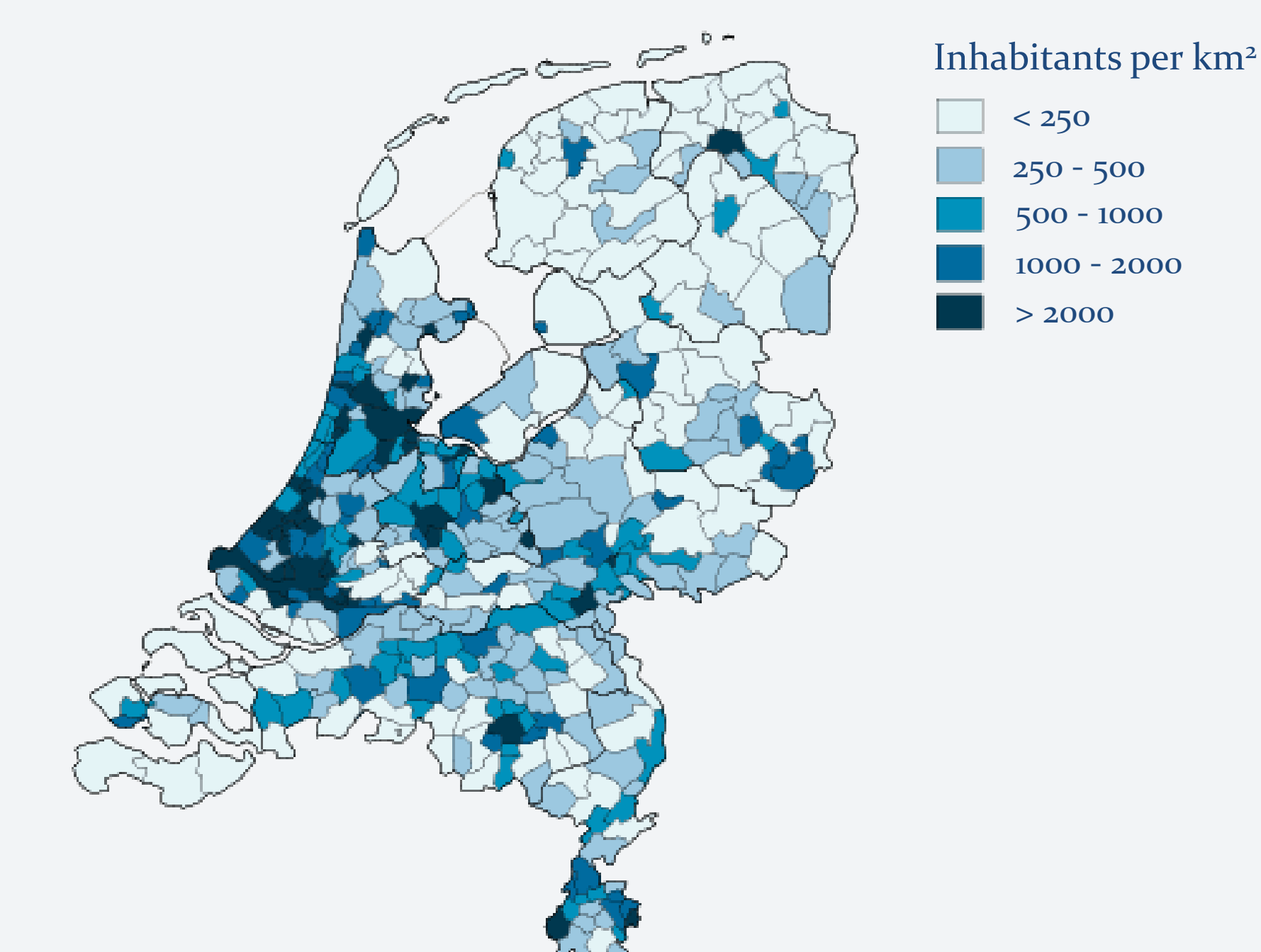
## SNP signals increase after accounting for environmental factors

We explored whether time and location influence loneliness reports. Both genders report higher levels of loneliness from December to April (see Figure below). We tested whether variables related to weather could capture this effect. Of the weather circumstances tested, temperature, airpressure, and humidity were significantly associated with loneliness after accounting for multiple testing. The level of urbanization was also significantly associated with loneliness (based on the postal code of the current living address). We repeated the heritability and genetic correlation analyses including the significant weather variables and level of urbanization as additional covariates. This caused the SNP heritability and the genetic correlation to increase for Loneliness and Neuroticism (Table 2).

**Seasonal effects:** Subjects tend to report higher levels of loneliness in the winter.



**Demographic effects:** People in more urbanized areas report higher levels of loneliness (males:  $\beta = .037$ ,  $p = 7 \times 10^{-3}$ ; females:  $\beta = .04$ ,  $p = 7 \times 10^{-7}$ )



**Table 2 (below):** After accounting for weather and urbanization variables, the SNP heritability of loneliness increases from 14% ( $p = .04$ ) to 20% ( $p = .009$ ), and for neuroticism from 22% ( $p = .005$ ) to 31% ( $p = .0006$ ). The genetic correlation between loneliness and neuroticism that is captured by SNPs also increases from .71 ( $p = .007$ ) to .75 ( $p = 1 \times 10^{-8}$ ).

	SNP heritability			Residual/ "Missing" heritability			Narrow sense heritability			Genetic correlation with loneliness		
	$h_g^2$ (SE) [p]	$h_{\text{res}}^2$ (SE) [p]	$h^2$ (SE) [p]	rG (SE) [p] - $h_g^2$	rG (SE) [p] - $h_{\text{res}}^2$	rG (SE) [p] - $h^2$	$h_g^2$ (SE) [p]	$h_{\text{res}}^2$ (SE) [p]	$h^2$ (SE) [p]	rG (SE) [p] - $h_g^2$	rG (SE) [p] - $h_{\text{res}}^2$	rG (SE) [p] - $h^2$
Loneliness	.20 (.09) [.009]	.07 (.09) [.22]	.27 (.03) [ $6 \times 10^{-16}$ ]									
Openness to Experience	.33 (.10) [.0004]	.20 (.10) [.02]	.53 (.03) [0]	.34 (.26) [.09]	-.27 (.64) [.32]	.17 (.07) [.005]						
Conscientiousness	.02 (.10) [.42]	.40 (.10) [ $6 \times 10^{-5}$ ]	.42 (.03) [0]	-1 (1.65) [.18]	-.54 (.43) [.0008]	-.53 (.07) [ $1 \times 10^{-11}$ ]						
Extraversion	.05 (.09) [.27]	.34 (.10) [.0003]	.40 (.03) [0]	-.95 (.75) [.07]	-.78 (.45) [.004]	-.68 (.06) [ $6 \times 10^{-17}$ ]						
Agreeableness	.10 (.10) [.17]	.25 (.10) [.01]	.34 (.03) [0]	-.16 (.46) [.37]	-.81 (.58) [.06]	-.42 (.08) [ $7 \times 10^{-7}$ ]						
Neuroticism	.31 (.10) [.0006]	.11 (.10) [.14]	.42 (.03) [0]	.75 (.16) [ $1 \times 10^{-8}$ ]	1 (.54) [.5]	.85 (.04) [0]						

## Conclusions

Genotyped common SNPs explain a considerable part of variation in Loneliness, Openness, & Neuroticism. They also capture a significant genetic correlation of  $> .7$  between Loneliness & Neuroticism. SNP signals increase for Loneliness and Neuroticism when correcting for environmental factors associated with loneliness (seasonal effects & urbanization), while accounting for these factors barely changes their total heritability or total variance. This may be due to a decrease in heterogeneity, which may partly explain inflated narrow sense heritability estimates based on familial relationships.