RESEARCH | Article in Press

The impact of coronary heart disease-associated genetic variants on heart rate dynamics

Habib Al Ashkar · Nihad Kharrat Helu · Nora Kovacs · Gergo Turi · Szilvia Fiatal · Roza Adany · Peter Piko

Received: 6 February 2026 / Accepted: 19 August 2026

Abstract

Background Exercise-induced heart rate response (ΔHR) reflects autonomic regulation and cardiovascular fitness. While coronary heart disease (CHD)-associated genetic variants are known to influence vascular and metabolic pathways, their role in modulating heart rate dynamics remains underexplored. This study aimed to evaluate and functionally characterize CHD-related genetic variants associated with ΔHR using integrated statistical, network-based, and regulatory approaches.

Methods Sixteen CHD-linked single-nucleotide polymorphisms (SNPs) were analyzed in a Hungarian population-based cohort (n = 665) using adjusted linear regression models. YMCA 3 min step test was carried out, with HR measured at rest, immediately post-exercise, and during recovery at 5 and 10 min. An optimized genetic risk score (oGRS) was constructed through stepwise inclusion based on model performance. Functional clustering was performed using STRING network analysis, and regulatory potential was assessed via RegulomeDB.

Results Four SNPs—rs6725887 (*WDR12*), rs964184 (*ZPR1*), rs9349379 (*PHACTR1*), and rs1746048 (*CXCL12*)—showed individually significant positive associations with ΔHR ($p < 0.05$). An additional four variants—rs646776 (*CELSR2*), rs46522 (*UBE2Z*), rs10455872 (*LPA*), and rs12190287 (*TCF21*)—were retained in the final oGRS based on incremental model improvement, yielding a cumulative p-value of 6.97×10^{-9}. The oGRS was significantly associated with multiple heart rate parameters, including HR_{exerc}, ΔHR_{5min}, and ΔHR_{10min} (Bonferroni-corrected $p < 0.00625$). STRING analysis identified a functional cluster comprising five genes (*CELSR2*, *PHACTR1*, *UBE2Z*, *WDR12*, and *ZPR1*), while *CXCL12*, *LPA*, and *TCF21* remained unclustered, suggesting functional heterogeneity. All oGRS variants exhibited high regulatory potential (RegulomeDB ranks 1b–1f), with rs9349379 (*PHACTR1*) showing the highest transcriptional relevance (score 0.99).

Conclusions These findings demonstrate that CHD-associated genetic variants significantly influence exercise-induced heart rate dynamics. The oGRS framework provides a reproducible approach for dissecting polygenic contributions to autonomic cardiovascular traits in a general population, with implications for functional genomics and personalized cardiovascular risk stratification.

Keywords Heart rate dynamics · Optimized genetic risk score · STRING network analysis · YMCA step test · Coronary heart disease

https://doi.org/10.1186/s40246-026-01035-5

Published online: 02 September 2026

Introduction

Cardiovascular diseases (CVDs) remain the leading cause of death worldwide: in 2022 they were responsible for an estimated 19.8 million deaths, corresponding to roughly one-third of all global deaths [1]. Coronary heart disease (CHD) continues to be one of the most prevalent and clinically impactful CVD subtypes and remains the leading single cause of CVD mortality in global burden of disease analyses [2].

In Hungary, the CVD burden remains severe: circulatory diseases caused ~ 64,000 deaths in 2022 (46.8% of total deaths), rising from 57,964 in 2021, with the Dél-Alföld region exceeding 50% share—far above the EU average of 32.4%. [3]. In 2024, circulatory diseases accounted for 60,305 deaths out of ~127,500 in total (~47.3%). Age-standardized hypertension prevalence among adults (≥18 years) is 55.9% in men and 40.9% in women. These figures (~47% CVD-related deaths) position Hungary as a high-risk population for genetic epidemiological studies of cardiovascular traits and their modifiable risk factors [3].

Heart rate dynamics, especially the acute response to physical exertion, serve as robust indicators of autonomic regulation and cardiovascular fitness [4–7]. Attenuated heart rate recovery has been associated with increased risk of CHD incidents, arrhythmias, and all-cause mortality [5, 8–11]. Twin studies and genome-wide association analyses have demonstrated that both resting heart rate and heart rate variability exhibit substantial heritability, with estimates ranging from 30 to 50% depending on the trait and population studied [12–15].

CHD and heart rate traits share overlapping genetic determinants [13, 15]. For example, the rs9349379 variant in the *PHACTR1* locus has been implicated in both vascular remodeling and autonomic regulation [16–18]. Similarly, rs964184 near *ZPR1* influences lipid metabolism and heart rate response [19, 20]. These findings suggest a convergent genetic architecture that may underlie both structural and functional cardiovascular phenotypes. Moreover, regulatory polymorphisms within neurohormonal systems, such as the renin–angiotensin–aldosterone axis and adrenergic receptor pathways, have been shown to modulate cardiac remodeling and progression of heart failure [21–23]. Understanding these genetic contributions could provide insights into the pleiotropic effects of CHD-related genetic variants and may inform personalized cardiovascular risk assessment and intervention strategies.

This study examines the effect of CHD-associated single-nucleotide polymorphisms (SNPs) on the exercise-induced heart rate response in a Hungarian population cohort. By integrating statistical association testing, polygenic score optimization, functional network clustering, and regulatory annotation, the analysis aims to elucidate the genetic contributions to autonomic cardiovascular traits in a high-risk European setting.

Materials and methods

Study population and design

This cross-sectional study utilized data from a previously published complex health survey conducted in northeastern Hungary (Hajdú-Bihar and Szabolcs-Szatmár-Bereg counties) in 2018. For complete details, please refer to Ádány et al. [24]. Adults aged 20–64 from two population groups, the general Hungarian population and the Roma minority, were included. The Roma sample was recruited from 25 randomly selected segregated colonies, each with more than 100 residents. Within each colony, 20 households were randomly selected, and one adult from each household was invited to participate. Face-to-face interviews were conducted by trained Roma university students under professional supervision to ensure cultural sensitivity.

The sample of the Hungarian general population was drawn from 20 randomly selected general medical practices that participate in the General Practitioners' Morbidity Sentinel Stations Program (GPMSSP). This is a national registry that was established to monitor the prevalence of chronic diseases [25]. From each practice, 25

individuals were randomly selected. In total, 832 individuals were enrolled: 417 from the general population and 415 from the Roma population.

After applying rigorous quality control procedures, which included the exclusion of incomplete or technically invalid heart-rate recordings, failure to complete the standardized 3-minute exercise protocol, missing questionnaire data required for covariate adjustment, genotyping quality-control failures (call rate <95% or unreliable genotype), and acute conditions or arrhythmias affecting heart-rate response, a final analytic sample of 665 participants was retained for statistical analysis. This final sample included individuals with complete genotype data for all SNPs, valid heart-rate measurements, and full covariate information necessary for multivariable modeling.

Data collection protocol

The study employed a standardized, three-pillar methodology comprising questionnaire-based interviews, physical examinations, and laboratory testing. This methodology has been used previously to investigate cardiometabolic risk profiles, including the prevalence of metabolic syndrome [26, 27] and insulin resistance [24] in these populations. Including both majority and minority groups within the same geographic region allows for a robust assessment of ethnicity-related health disparities while controlling for regional environmental influences.

The resulting dataset comprises over 1.5 million data points. It provides a unique opportunity to explore the interactions between genes and the environment, as well as the physiological responses to lifestyle factors such as physical activity, diet, and socioeconomic status. Furthermore, it allows for robust comparisons to be made between the Hungarian general population and the Roma minority.

The protocol is based on internationally harmonized standards, including the European Health Interview Survey (EHIS wave 2—[28]) and the European Health Examination Survey (EHES—[29]). These standards ensure methodological consistency and cross-study comparability. The laboratory panel was selected to capture key cardiometabolic and inflammatory biomarkers. Including DNA extraction enables downstream genotyping and polygenic risk modeling.

I. Questionnaire-based interviews: Participants completed the European Health Interview Survey (EHIS) Wave 2, which was supplemented with additional validated question sets on lifestyle, socioeconomic status, and health determinants. These included the 12-Item General Health Questionnaire (GHQ-12), a tool that has been used in previous national and international surveys.
II. Physical examinations: Standardized measurements, including height, weight, waist circumference, and blood pressure, were taken following the EHES protocol. Body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared (kg/m^2).
III. Laboratory tests: After an overnight fast, venous blood samples were collected for biochemical analysis and DNA extraction. Serum and plasma were separated by centrifugation and stored at −80 °C until analysis. Different laboratory parameters were measured, of which the followings were used in the present study: fasting glucose, insulin, lipid profile (total cholesterol, HDL-C, LDL-C, and triglycerides), liver enzymes (ALT, AST, and GGT), and the inflammatory marker C-reactive protein (CRP).

Phenotypic measurements

The cardiovascular response to exertion was assessed using the YMCA 3-min step test, which is a validated submaximal exercise protocol commonly used to estimate cardiorespiratory fitness [4, 30]. Participants stepped onto a 30-cm-high bench at a cadence of 96 beats per minute for three consecutive minutes, guided by a metronome or audio cue.

Heart rate was manually measured via radial pulse palpation for 60 s at four standardized time points: HR_{rest} (one minute before exercise), HR_{exerc} (immediately after exercise), HR_{5min} (five minutes after exercise), and HR_{10min} (ten minutes after exercise) and expressed in beats per minute (bpm).

The difference between HR_{rest} and HR_{exerc} was defined as delta HR (ΔHR), which reflects the acute heart rate response to physical activity. Additionally, heart rate changes were calculated as the difference between resting heart rate and heart rate 5 min (ΔHR_{5min}) and 10 min (ΔHR_{10min}) after physical activity. These serve as proxies for cardiovascular workload and fitness level.

$$\Delta \mathrm{HR} = HR_{exerc} - HR_{rest}$$

$$\Delta \mathrm{HR}_{5min} = HR_{5min} - HR_{rest}$$

$$\Delta \mathrm{HR}_{10min} = HR_{10min} - HR_{rest}$$

The predicted maximum heart rate [31] and percent of predicted maximum heart rate ($HR_{max\%}$) were calculated as follows:

$$HR_{max} = 208 - (0.7 \times age)$$

$$HR_{max\%} = \frac{HR_{exerc}}{HR_{max}} \times 100$$

Participants were divided into three age-adjusted ΔHR categories according to YMCA guidelines [4]. This approach enabled a standardized comparison of ΔHR across demographically relevant fitness levels. Sex-specific thresholds derived from YMCA normative data were applied to account for physiological differences in cardiovascular response. The resulting ΔHR categories were then used to examine associations with genetic, behavioral, and laboratory parameters, ensuring that any observed patterns were not distorted by disparities in baseline fitness. This grouping also facilitated subgroup analyses and improved the interpretability of the results in relation to public health benchmarks.

Participants were categorized into seven YMCA fitness levels (very poor, poor, below average, average, above average, good, excellent) based on age- and sex-specific post-exercise heart rate cut-offs. For analytical purposes, these categories were grouped into three strata: very poor/poor (n = 192), below average/average/above average (n = 298), and good/excellent (n = 175). The detailed normative criteria used for this classification are provided in Supplementary Table S1.

SNP selection and genotyping

The selection of the 16 CHD-associated SNPs examined in this study is based on the results of previous genome-wide association studies (GWAS) [32–35] and the results of research conducted on the Hungarian and Roma populations [36].

Genomic DNA was extracted from EDTA-anticoagulated whole blood samples using the MagNA Pure LC system (Roche Diagnostics) according to the manufacturer's protocol. Genotyping was performed using iPLEX Gold chemistry on the MassARRAY platform (Sequenom, Inc.) at the Mutation Analysis Facility of the Karolinska Institute to ensure high call rates and reproducibility across samples.

Hardy–Weinberg equilibrium (HWE) was assessed for each SNP using PLINK v1.9, and all variants conformed to HWE expectations ($p > 0.05$). Pairwise linkage disequilibrium (LD) was also evaluated to ensure independence of genetic signals, with R^2 values guiding the construction of a composite polygenic score in subsequent analyses.

Minor allele frequencies were calculated separately for the Hungarian general population and the Roma minority, and compared with external reference values from the NCBI ALFA European and Asian datasets [37].

Calculation of optimized genetic risk score

In order to investigate the genetic contribution to heart rate dynamics, an optimized genetic risk score (oGRS) was constructed based on selected CHD-linked SNPs. The primary outcome variable was ΔHR, which is defined as the difference between HR_{exerc} and HR_{rest}. This metric was chosen because, among other things, it reflects baseline autonomic tone and the acute cardiovascular response to exertion, serving as an indicator of autonomic flexibility and cardiac resilience.

SNPs were evaluated under the three most common inheritance models: dominant, recessive, and codominant. The heritability model for all SNPs that were most strongly associated with ΔHR (based on R^2 and p-value) was selected for inclusion. In this study, the term 'effect allele' refers to the allele associated with acute heart-rate response (ΔHR) in our cohort, rather than the CHD-risk allele reported in genome-wide association studies.

Genotypes were coded according to the selected model with respect to the allele associated with heart-rate response in our dataset: in the codominant model, homozygotes carrying two HR-associated alleles were coded as 2, heterozygotes as 1, and homozygotes with no HR-associated allele as 0. In the dominant model, genotypes carrying one or two HR-associated alleles were coded as 2, and those with no HR-associated allele as 0. In the recessive model, only homozygotes carrying two HR-associated alleles were coded as 2, while heterozygotes and homozygotes without the HR-associated allele were coded as 0.

The oGRS was created using a stepwise multivariable linear regression approach. First, the SNP with the strongest association with ΔHR (lowest p-value) was selected. Then, additional SNPs were added in ascending order of p-value. Inclusion depended on improving the performance of the model (i.e. reducing the p-value and increasing the R-square). Variants that increased the p-value or reduced the R-square were excluded from the final oGRS.

LD was formally assessed for all SNPs included in the oGRS using SNPStats and LDlink (LDmatrix); all pairwise LD measures (D, r, and r^2) indicated no meaningful LD, confirming that the variants represent independent signals.

Participants were divided into three groups according to their optimized genetic risk score (oGRS), calculated as the sum of HR-associated alleles across the selected SNPs; observed scores ranged from 2 to 16. Thresholds for stratification were chosen based on natural separation points in the oGRS distribution to produce balanced group sizes and were set as oGRS ≤ 6 (n = 193), oGRS 7–9 (n = 348), and oGRS ≥ 10 (n = 124).

Effect-size–weighted GRS models were not applied because the β coefficients available from large CHD genome-wide association studies quantify risk for clinically manifest CHD and are not valid predictors of the phenotype examined in this study (heart-rate response to exercise). Unweighted GRS models are recommended when allele-burden differences between populations are compared or when external effect sizes are not directly transferable across cohorts. Therefore, the unweighted, additive GRS provided the most appropriate and robust approach for quantifying the cumulative burden of CHD-associated alleles in our population.

String analysis was performed using the Markov Cluster Algorithm (MCL) with an inflation parameter of 3, and the eight genes included in the oGRS were evaluated for functional clustering.

Statistical analysis

Descriptive statistics were used to characterize the study population and key variables. Categorical variables were compared using the chi-squared test. Differences between two independent groups were assessed using the Mann–Whitney U test, as several continuous variables were not normally distributed. Pairwise comparisons between the three AHRR groups (A vs B, A vs C, B vs C) were performed using Bonferroni-adjusted post-hoc tests to correct for multiple testing.

The Kolmogorov–Smirnov test was used to assess the normality of the quantitative variables. Where the normality assumption was violated, the data were normalized using Templeton's two-step transformation method prior to parametric analysis [38].

To examine trends across oGRS categories—reflecting increasing levels of genetic risk—the Jonckheere–Terpstra trend test [39] was employed for heart rate–related outcomes.

Associations between genetic risk and heart rate-related outcomes were examined using adjusted linear regression models. All models included relevant covariates to control for potential confounding factors, including ethnicity (the Hungarian general population was used as the reference group), sex (male was used as the reference group), age, BMI, waist circumference, systolic and diastolic blood pressure, the four main domains of physical activity (work, transport, domestic and gardening activities, and leisure time), education, self-reported financial status, current smoking status, alcohol consumption, vehicle use and an optimized polygenic exercise score [40].

Multicollinearity was assessed using variance inflation factors (VIFs). The VIF values for systolic and diastolic blood pressure were 2.11 and 1.99, respectively, and the mean VIF of the full model was 1.75. All values were well below commonly accepted thresholds (VIF < 5 [41] or < 10 [42]), indicating that the inclusion of both blood-pressure measures did not compromise model stability.

Ethical approval

The study was conducted in full accordance with the principles outlined in the Declaration of Helsinki. The Hungarian Scientific Council on Health granted ethical approval under protocol number 61327-3/2017/EKU. Written informed consent was obtained from all study participants prior to their enrolment.

Results

Participants' characteristics across heart rate recovery categories

The demographic, anthropometric, behavioral, and genetic characteristics of the participants were stratified according to acute heart rate response categories: excellent/good (group A, n = 192), average (group B, n = 298), and very poor/poor (group C, n = 175).

Participants in the excellent/good group were older on average and exhibited more favorable anthropometric profiles, including significantly lower waist circumference (p for trend < 0.001). Diastolic blood pressure increased progressively across categories ($p = 0.008$), while systolic blood pressure showed inconsistent pairwise differences. Although BMI tended to be lower in the excellent/good group, the trend did not reach statistical significance ($p = 0.089$).

Physical activity levels, assessed across four domains (work, transport, domestic, and leisure-time MET-min/week), declined markedly with worsening ΔHR. The most pronounced differences were observed in leisure-time activity, which was significantly higher in the excellent/good group compared to both the average and poor groups ($p < 0.001$). Transport-related activity also showed a significant decreasing trend ($p = 0.002$), with pairwise differences between excellent and poor groups ($p = 0.006$).

Genetic predisposition, captured by the optimized polygenic score for exercise (oPGS), was strongly associated with categories. Participants in the poor group had significantly lower oPGS values compared to both other groups ($p < 0.001$).

Sex distribution varied significantly across categories, with women overrepresented in the excellent/good group (79.2%) and underrepresented in the average group (56.0%, p for trend = 0.010). Roma ethnicity showed a bimodal distribution, being more prevalent in both the excellent/good and poor groups compared to the average group ($p < 0.001$ for A vs. B and B vs. C).

Self-reported financial status and alcohol consumption did not differ significantly across categories, although a higher proportion of frequent alcohol consumers was noted in the average group ($p = 0.037$). Educational attainment showed mixed associations: participants with vocational or high school education were more common in

the average group, while those with lower education were more prevalent in the excellent/good and poor groups (Table 1).

Comparison of allele frequences and estimated effect of CHD-associated genetic variants on ΔHR

Minor allele frequencies differed between the Hungarian general population and the Roma minority for several CHD-associated SNPs (Supplementary Table S1). Nominally significant differences ($p < 0.05$) were observed for rs964184 (Hungarian 13.83%, Roma 17.86%; $p = 0.044$), rs1122608 (24.32% vs. 29.17%; $p = 0.046$), rs4977574 (51.67% vs. 42.41%; $p = 0.030$), rs2895811 (41.49% vs. 33.33%; $p = 0.002$) and rs17465637 (27.81% vs. 34.67%;

Table 1 Basic characteristics of the three groups based on acute heart rate response (AHRR—assessed as the difference between post-exercise and resting heart rate—delta heart rate—ΔHR)

		A—Excellent or good AHRR (n = 192)	B—Average AHRR (n = 298)	C—Very poor or poor AHRR (n = 175)	*p* for trend	A versus B	A versus C	B versus C
		Average (95%CI)				*p*-value		
Age (years)		44.99 (43.29–46.70)	43.01 (41.57–44.46)	41.53 (39.70–43.36)	0.006*	0.224	0.019*	0.624
Waist circumference (cm)		91.21 (89.07–93.36)	96.53 (94.74–98.32)	96.45 (94.10–98.80)	< 0.001*	< 0.001*	0.003*	1.000
Body mass index (kg/m^2)		26.53 (25.69–27.37)	27.53 (26.87–28.19)	27.60 (26.63–28.57)	0.089	0.196	0.308	1.000
Average systolic blood pressure (mmHg)		123.11 (120.94–125.28)	127.42 (125.63–129.21)	124.23 (121.64–126.82)	0.730	0.025*	1.000	0.059
Average diastolic blood pressure (mmHg)		77.03 (75.76–78.29)	80.26 (79.22–81.30)	80.06 (78.60–81.52)	0.008*	0.001*	0.036*	1.000
Work (MET-min/week)		5105 (4280–5930)	5361 (4648–6074)	4030 (3168–4893)	0.087	1.000	0.233	0.045*
Transport (MET-min/week)		1885 (1558–2211)	1474 (1248–1700)	1111 (915–1306)	0.002*	0.053	0.006*	0.809
Domestic work and gardening (MET-min/week)		3287 (2888–3693)	3042 (2712–3371)	1471 (2046–2896)	< 0.001*	< 0.001*	0.626	0.007*
Leisure-time (MET-min/week)		1557 (1160–1755)	1266 (1070–1462)	760 (538–981)	< 0.001*	1.000	< 0.001*	0.001*
Polygenic risk score optimized for ΔHR		7.63 (7.32–7.94)	7.60 (7.35–7.86)	6.55 (6.17–6.94)	< 0.001*	1.000	< 0.001*	< 0.001*
		Prevalence in % (95%CI)			*p* for trend	*p*-value		
Women		79.17 (73.01–84.45)	56.04 (50.37–61.59)	67.43 (60.24– 74.04)	0.010*	< 0.001*	0.033*	0.044*
Use of transportation		45.31 (38.39–52.38)	55.70 (50.03–61.27)	44.57 (37.35–51.97)	0.981	0.074	1.000	0.058
Self-reported financial status	Bad	19.27 (14.17–25.29)	20.13 (15.88–24.96)	21.71 (16.10–28.25)	0.920	1.000	1.000	1.000
	Average	57.81 (50.75–64.64)	56.38 (50.71–61.92)	53.71 (46.32–60.99)		1.000	1.000	1.000
	Good	22.92 (17.41–29.24)	23.49 (18.95–28.54)	24.57 (18.65–31.33)		1.000	1.000	1.000
Education	Less than primary or primary	58.85 (51.80–65.64)	45.64 (40.05–51.31)	61.14 (53.79–68.13)	0.776	0.013*	1.000	0.003*
	Vocational or high school	35.42 (28.91–42.36)	43.62 (38.08–49.29)	27.43 (21.23–34.37)		0.212	0.301	0.001*
	College or university	5.73 (3.08–9.70)	10.74 (7.60–14.63)	11.43 (7.35–16.77)		0.167	0.150	1.000
Current smoking status		51.56 (44.51–58.56)	44.30 (38.73–49.97)	52.57 (45.18–59.88)	0.914	0.347	1.000	0.245
Self-reported alcohol consumption	Never	52.60 (45.55–59.58)	45.64 (40.05–51.31)	56.00 (48.60–63.21)	0.784	0.396	1.000	0.089
	Once per month	36.46 (29.89–43.43)	34.90 (29.65–40.44)	25.71 (19.67–32.55)		1.000	0.080	0.114
	More than 2 times per month	10.94 (7.11–15.93)	19.46 (15.28–24.24)	18.29 (13.10–24.51)		0.037*	0.136	1.000
Roma ethnicity		58.33 (51.28–65.14)	39.93 (34.49–45.57)	60.00 (52.63–67.05)	0.914	< 0.001*	1.000	< 0.001*

95 CI 95 confidence intervals; *: $p < 0.05$

p = 0.007). After Bonferroni correction (p < 0.00625), rs10455872 (5.32% vs. 1.79%; p < 0.001), rs12190287 (33.59% vs. 45.09%; p < 0.001), rs3184504 (50.30% vs. 37.65%; p < 0.001), rs2895811 (41.49% vs. 33.33%; p = 0.002) and rs17465637 (27.81% vs. 34.67%; p = 0.007) remained statistically significant. For more details see Supplementary Table 2.

Each SNP was analyzed using the most appropriate genetic inheritance model (dominant, codominant, or recessive) based on model fitting. Of the 16 variants tested, four showed statistically significant positive associations with ΔHR. More specifically, rs6725887 (*WDR12*, dominant model), rs964184 (*ZPR1*, codominant model), rs9349379 (*PHACTR1*, codominant model), and rs1746048 (*CXCL12*, dominant model) were found to be associated with an increase in ΔHR of between approximately +2.2 and +4.8 bpm.

The association of the remaining SNPs (including those in *CELSR2*, *UBE2Z*, *LPA*, *TCF21*, *ZC3HC1*, *SH2B3*, ABO, *SMARCA4*, *CDKN2B-AS1*, *HHIPL1* and *MIA3*) with ΔHR was not statistically significant. Their estimated effects were generally small, accompanied by wide confidence intervals, indicating limited or no contribution to ΔHR in this cohort (Table 2).

The GRS optimization procedure resulted in eight SNPs being included: rs6725887 (*WDR12*), rs964184 (*ZPR1*), rs9349379 (*PHACTR1*), rs1746048 (*CXCL12*), rs646776 (*CELSR2*), rs46522 (*UBE2Z*), rs10455872 (*LPA*) and rs12190287 (*TCF21*). These variants collectively enhanced the predictive capacity of the oGRS for ΔHR. The remaining SNPs, despite nominal associations, were excluded due to redundancy or lack of incremental explanatory value (Table 3).

The oGRS was found to be significantly associated with multiple heart rate parameters that reflect the cardiovascular response to exercise. Following Bonferroni correction (threshold p < 0.00625), six associations remained statistically significant: HR_{exerc}, HR_{5min}, HR_{10min}, and the corresponding delta values (ΔHR, ΔHR_{5min}, ΔHR_{10min}). These results indicate that individuals with higher oGRS values tend to exhibit greater heart rate elevations during and after physical exertion, consistent with enhanced autonomic responsiveness.

The strongest association was observed for ΔHR (B = 2.528, 95% CI 1.683–3.374, $p = 6.97 \times 10^{-9}$), followed by HR_{exerc} (B = 2.285, $p = 4.23 \times 10^{-8}$), and ΔHR_{5min} (B = 1.016, $p = 2.15 \times 10^{-4}$). These associations remained

Table 2 Effects of SNPs on acute heart rate response (ΔHR) based on adjusted linear regression analysis

SNP (allele associated with ΔHR)	Gene	Genetic model	B-value (95% CI)	*p*-value
rs6725887 (C)	*WDR12*	Dominant	3.584 (1.194—5.975)	0.003*
rs964184 (G)	*ZPR1*	Codominant	4.827 (1.277—8.377)	0.008*
rs9349379 (C)	*PHACTR1*	Codominant	2.359 (0.398—4.321)	0.018*
rs1746048 (T)	*CXCL12*	Dominant	2.223 (0.330—4.116)	0.021*
rs646776 (A)	*CELSR2*	Dominant	3.469 (−0.974—7.912)	0.126
rs46522 (T)	*UBE2Z*	Codominant	1.643 (−0.871—4.156)	0.200
rs10455872 (A)	*LPA*	Recessive	2.181 (−1.430—5.792)	0.236
rs12190287 (G)	*TCF21*	Codominant	1.610 (−1.068—4.288)	0.238
rs11556924 (C)	*ZC3HC1*	Codominant	1.079 (−1.666—3.824)	0.440
rs3184504 (C)	*SH2B3*	Dominant	0.790 (−1.568—3.148)	0.511
rs579459 (C)	*ABO*	Dominant	0.486 (−1.354—2.326)	0.604
rs1122608 (G)	*SMARCA4*	Codominant	0.572 (−2.281—3.425)	0.694
rs3798220 (T)	*LPA*	Codominant	1.166 (−11.028—13.359)	0.851
rs4977574 (A)	*CDKN2B-AS1*	Recessive	0.161 (−2.033—2.355)	0.885
rs2895811 (T)	*HHIPL1*	Codominant	0.147 (−2.445—2.740)	0.911
rs17465637 (A)	*MIA3*	Dominant	0.004 (−1.834—1.843)	0.996

MET-min/week metabolic equivalent task minutes per week, *95% CI* 95% confidence intervals, *Chr.* chromosome, *WDR12* WD Repeat Domain 12, *ZPR1ZPR1* zinc finger, *PHACTR1* phosphatase and actin regulator 1, *CXCL12* C-X-C motif chemokine ligand 12, *CELSR2* cadherin EGF LAG seven-pass G-type receptor 2, *UBE2Z* ubiquitin conjugating enzyme E2 Z, *LPA* lipoprotein(a), *TCF21* transcription factor 21, *ZC3HC1* zinc finger C3HC-type protein 1, *SH2B3* SH2B adaptor protein 3, *ABO* alpha 1-3-N-acetylgalactosaminyltransferase and alpha 1-3-galactosyltransferase, *SMARCA4* SWI/SNF related BAF chromatin remodeling complex subunit ATPase 4, *CDKN2B-AS1CDKN2B* and *CDKN2A* antisense cis and trans regulatory RNA 1, *HHIPL1* HHIP like 1, *MIA3* MIA SH3 domain ER export factor 3. *: $p < 0.05$

Table 3 Association of SNPs (coded according to the best-fitting genetic model) with acute heart rate response (ΔHR) in adjusted linear regression models

SNP (allele associated with ΔHR)	*p*-value	R-square	Include/exclude
rs6725887 (C)	4.08×10^{-3}	0.139	Included
rs964184 (G)	3.50×10^{-5}	0.151	Included
rs9349379 (C)	2.84×10^{-6}	0.158	Included
rs1746048 (T)	1.54×10^{-7}	0.165	Included
rs646776 (A)	4.34×10^{-8}	0.168	Included
rs46522 (T)	4.16×10^{-8}	0.168	Included
rs10455872 (A)	1.56×10^{-8}	0.171	Included
rs12190287 (G)	6.97×10^{-9}	0.173	Included
rs11556924 (C)	7.04×10^{-9}	0.173	Exclude
rs3184504 (C)	1.15×10^{-8}	0.172	Exclude
rs579459 (C)	4.17×10^{-8}	0.168	Exclude
rs1122608 (G)	1.40×10^{-8}	0.171	Exclude
rs3798220 (T)	7.22×10^{-9}	0.173	Exclude
rs4977574 (A)	6.15×10^{-8}	0.167	Exclude
rs2895811 (T)	2.77×10^{-8}	0.169	Exclude
rs17465637 (A)	1.15×10^{-7}	0.166	Exclude

SNPs are listed in order of increasing *p*-value

Table 4 Association of optimized genetic risk score (oGRS) with heart rate changes during exercise and recovery

	B-value (95% CI)	*p*-value
HR_{rest}	−0.471 (−0.809 to −0.133)	6.44×10^{-3}*
HR_{exerc}	2.285 (1.476–3.094)	4.23×10^{-8}**
HR_{5min}	0.988 (0.497–1.479)	8.62×10^{-5}**
HR_{10min}	0.769 (0.350–0.946)	2.25×10^{-5}**
ΔHR	2.528 (1.683–3.374)	6.97×10^{-9}**
ΔHR_{5min}	1.016 (0.480–1.551)	2.15×10^{-4}**
ΔHR_{10min}	0.637 (0.316–0.959)	1.10×10^{-4}**
$HR_{max\%}$	1.203 (0.716–1.690)	1.53×10^{-6}**

HR_{rest} resting heart rate, HR_{exerc} heart rate immediately after completing the physical exercise, HR_{5min} heart rate 5 min after the physical exercise, HR_{10min} heart rate 10 min after the physical exercise, ΔHR defined as HR_{exerc}—HR_{rest}, ΔHR_{5min} defined as HR_{5min}—HR_{rest}, ΔHR_{10min} defined as HR_{10min}—HR_{rest}, $HR_{max\%}$ Maximum heart rate expressed as a percentage of the predicted maximum heart rate, *95% CI* 95% confidence intervals; *: nominally significant *p*-value (<0.05); **: significant *p*-value (<0.00625) after Bonferroni correction

robust after correction for multiple testing, supporting the relevance of the oGRS in predicting acute cardiovascular fitness.

In contrast, the association between oGRS and HR_{rest} only reached nominal significance (B = −0.471, $p = 6.44 \times 10^{-3}$) and failed to meet the corrected threshold (see Table 4).

Heart rate parameters were compared across three groups defined by oGRS: ≤6 (n = 193), 7–9 (n = 348), and ≥10 (n = 124). No significant trend was observed for HR_{rest} ($p = 0.671$). In contrast, HR_{exerc} showed a significantly increasing trend across oGRS categories ($p = 0.001$), with mean values rising from 105.80 bpm to 120.07 bpm.

HR_{5min} and HR_{10min} increased with higher oGRS, reaching nominal significance ($p = 0.039$ and $p = 0.026$). There were significant positive trends in $HR_{max\%}$ and all delta heart rate measures (ΔHR, ΔHR_{5min}, and ΔHR_{10min}) ($p \leq 0.002$). ΔHR increased from 27.84 bpm to 43.23 bpm. Full estimates and confidence intervals can be found in Table 5.

Table 5 Trend analysis on heart rates obtained in different phases of the YMCA test, categorized by groups based on optimized polygenic score (oGRS) values

	oGRS (≤6) (n = 193)	oGRS (7 – 9) (n = 348)	oGRS (≥10) (n = 124)	*p* for trend
	Average beats per minute (bpm) (95% CI)			
HR_{rest}	77.95 (76.40–79.51)	77.58 (76.47–78.69)	76.84 (75.28–78.40)	0.671
HR_{exerc}	105.80 (102.82–108.78)	111.11 (108.36–113.86)	120.07 (114.32–125.82)	0.001**
HR_{5min}	92.01 (89.88–94.13)	92.41 (90.62–94.20)	98.13 (94.91–101.34)	0.039*
HR_{10min}	81.62 (79.93–83.31)	81.38 (80.16–82.60)	85.12 (82.84–87.40)	0.026*
ΔHR	27.84 (25.13–30.56)	33.53 (30.90–36.15)	43.23 (37.73–48.74)	< 0.001**
ΔHR_{5min}	14.05 (12.24–15.86)	14.83 (13.14–16.53)	21.29 (18.27–24.31)	0.002**
ΔHR_{10min}	3.67 (2.45–4.88)	3.80 (2.87–4.72)	8.28 (6.42–10.14)	< 0.001**
	Average percentage (95% CI)			
$HR_{max\%}$	59.80 (57.85–61.75)	62.74 (61.16–64.32)	67.21 (64.36–70.05)	< 0.001**

HR_{rest} resting heart rate, HR_{exerc} heart rate immediately after completing the physical exercise, HR_{5min} heart rate 5 min after the physical exercise, HR_{10min} heart rate 10 min after the physical exercise, ΔHR defined as HR_{exerc}—HR_{rest}, ΔHR_{5min} defined as HR_{5min}—HR_{rest}, ΔHR_{10min} defined as HR_{10min}—HR_{rest}, $HR_{max\%}$ Maximum heart rate expressed as a percentage of the predicted maximum heart rate, *95% CI* 95% confidence intervals; *: nominally significant *p*-value (<0.05); **: significant *p*-value (<0.00625) after Bonferroni correction

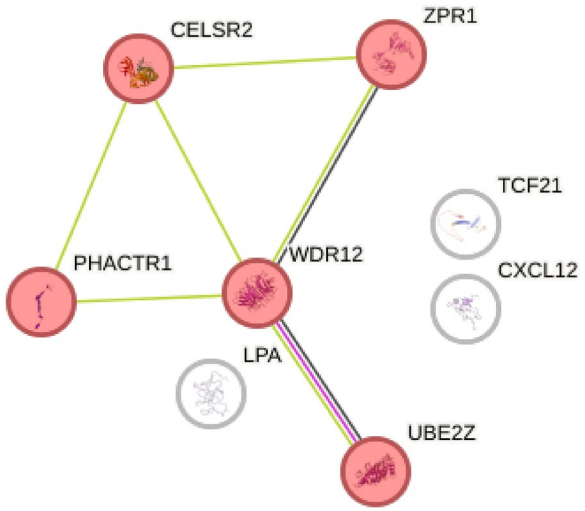

Fig. 1 STRING-based interaction network of oGRS genes showing functional connectivity, clustering, and evidence-type–specific link colors. Nodes represent individual genes; pink nodes indicate the MCL-identified cluster, white nodes denote ungrouped genes. Link colors indicate interaction evidence (green = coexpression, blue = curated database, purple = text mining)

STRING-based network clustering and RegulomeDB evaluation of oGRS components

Based on STRING network analysis, the algorithm identified a single cluster of five genes: *CELSR2*, *PHACTR1*, *UBE2Z*, *WDR12,* and *ZPR1*. These genes demonstrated sufficient connectivity or shared functional context to be grouped under the selected clustering conditions (see Fig. 1).

The remaining three genes (*CXCL12*, *LPA,* and *TCF21*) did not form part of any cluster, indicating that they had limited or no detectable interaction with the others under the current network and confidence settings.

The eight SNPs included in the oGRS were evaluated using RegulomeDB. All variants received high regulatory ranks (1b–1f). Furthermore, the rs9349379 variant (*PHACTR1*) received the highest regulatory score (rank 1b, score 0.99).

Six additional SNPs (rs12190287, rs646776, rs1746048, rs964184, rs46522 and rs6725887) were all ranked 1f, with scores ranging from 0.55 to 0.67. ChIP-seq data indicated binding sites for key transcriptional regulators, including *GATA2*, *POLR2A*, *EP300*, *RELA,* and *ZNF816*. The variant rs10455872 (*LPA*) received the lowest score (rank 1f, score 0.22) and had limited regulatory annotations.

Discussion

This study was the first to examine the effect of genetic variants associated with coronary heart disease on acute heart rate response in a Hungarian population sample, with a particular focus on autonomic cardiovascular flexibility. The results confirm that SNPs associated with CHD influence not only the development of atherosclerosis, but may also be functionally relevant in the regulation of heart rate dynamics.

The four genetic variants found to have significant effect on heart rate dynamics in this study, rs6725887 (*WDR12*), rs964184 (*ZPR1*), rs9349379 (*PHACTR1*), and rs1746048 (*CXCL12*), all showed a positive association with ΔHR. This suggests that these CHD-associated SNPs may also be functionally relevant in autonomic regulation dynamics and physical activity-induced cardiovascular responsiveness.

The rs6725887 variant resides in the *WDR12* gene, a PeBoW complex component involved in ribosomal biogenesis and cell cycle regulation [43]. Elevated *WDR12* expression in proliferating vascular smooth muscle cells suggests a role in vascular remodeling [44]. Although its direct link to autonomic regulation remains unclear, genotype-dependent modulation of vascular tone and peripheral resistance may explain the observed association with heart rate dynamics during physical exertion [45].

The rs964184 variant lies near *ZPR1*, a gene consistently linked to triglyceride levels and lipoprotein profiles [46]. Although *ZPR1* is not a canonical lipid gene, its proximity to the *APOA5-A4-C3-A1* cluster and its role in transcriptional regulation suggest metabolic relevance [47]. Its interaction with peroxisome proliferator-activated receptor gamma (PPARγ) signaling may influence myocardial energy supply [48]. The observed ΔHR increase among carriers supports a lipid-related genetic contribution to autonomic cardiovascular responsiveness [49, 50].

The rs9349379 variant in *PHACTR1* modulates endothelial function via actin cytoskeleton and phosphatase regulation [51]. Acting as a distal enhancer of *EDN1*, it influences the expression of endothelin-1, a key vasoconstrictor involved in autonomic regulation [51]. Carriers of the G allele show elevated endothelin-1 levels and increased risk of coronary microvascular dysfunction, potentially contributing to reduced myocardial perfusion and altered heart rate response during physical exertion [8].

The rs1746048 variant near the *CXCL12* gene, a chemokine involved in progenitor cell recruitment and myocardial regeneration [52], has been linked to coronary artery disease and vascular integrity [53]. Although direct evidence is limited, altered *CXCL12* signaling may affect myocardial repair and angiogenesis, potentially modulating heart rate dynamics during exertion [54].

Overall, these findings confirm that genetic variants associated with CHD play a role not only in the structural components of atherosclerosis, but also in the functional aspects of autonomic regulation and heart rate variability. Although impaired heart-rate response to exercise may reflect underlying cardiovascular vulnerability, CHD-associated genetic variants do not necessarily exert parallel effects on autonomic regulation, as these pathways are partly independent.

The oGRS presented in the study was closely associated with several dynamic heart rate variability parameters, particularly ΔHR, ΔHR_{5min} and ΔHR_{10min}. These parameters are considered objective indicators of autonomic nervous system function and cardiovascular flexibility. They reflect cardiac performance and the speed and efficiency of autonomic regulation, especially after physical exertion.

Beyond statistical robustness, the oGRS demonstrated biological coherence: STRING analysis revealed a functional cluster (*CELSR2*, *PHACTR1*, *UBE2Z*, *WDR12*, and *ZPR1*) involved in endothelial regulation, lipid metabolism, cytoskeletal dynamics, and ubiquitin signaling [35, 55]. This supports the oGRS as a mechanistically interpretable construct rather than a purely statistical aggregation.

CXCL12, *LPA*, and *TCF21* genes did not cluster in the STRING network, reflecting functional heterogeneity. *CXCL12* mediates progenitor cell recruitment and myocardial regeneration [56]; *LPA* encodes apolipoprotein(a), a genetically determined CHD risk factor [57]; and *TCF21* regulates mesodermal differentiation [58]. Their distinct pathways suggest that while each gene contributes to cardiovascular phenotypes, they act through divergent molecular mechanisms.

The partial clustering of oGRS genes aligns with systems genetics, which views CHD as a polygenic condition driven by multiple, largely independent yet potentially interacting pathways. Systems-level analyses have identified 30–40 CAD-related mechanisms [59, 60], including extracellular matrix remodeling, immune signaling, TGF-β/SMAD cascades, and oxidative stress, highlighting the complexity of CAD pathogenesis and the context-dependent effects of genetic variants.

The functional diversity of oGRS components enables a deeper insight into the genetic basis of heart rate responses and informs precision strategies. Clustered genes may serve as shared targets for prevention and/or therapeutic targets, while non-clustered variants may require individualized approaches for biomarker development and intervention.

Key SNPs identified, rs9349379 (*PHACTR1*), rs964184 (*ZPR1*), rs6725887 (*WDR12*), and rs1746048 (*CXCL12*), received high RegulomeDB scores (1b–1f), indicating transcriptional activity in cardiovascular tissues. Notably, rs9349379 functions as a distal enhancer of EDN1, modulating endothelin-1 expression in endothelial cells [16] in response to hemodynamic stimuli [61], thereby influencing vascular tone and autonomic regulation, and may contribute to the pathogenesis of multiple vascular diseases [8].

Epigenetic data further support the regulatory relevance of the key SNPs. *H3K27ac* enrichment [62], a marker of active enhancers [63], has been observed at the *PHACTR1* locus in endothelial cells, confirming transcriptional activity [64]. Similarly, hypoxia-induced enhancer activation near the *CXCL12* locus suggests a role in myocardial regeneration and progenitor cell recruitment [56], linking genetic variation to cardiovascular repair mechanisms.

Combined RegulomeDB and histone acetylation quantitative trait locus (haQTL) data confirm that the SNPs associated with ΔHR reside in transcriptionally active regions of cardiovascular tissues, supporting their functional relevance beyond statistical association.

Including both Hungarian and Roma populations enabled analysis of gene–environment interactions. The bimodal distribution of ΔHR categories, particularly in the Roma group, suggests that oGRS effects are modulated by lifestyle and social factors such as physical activity, diet, and stress, consistent with the framework of context-dependent genetic influence [65].

Recent evidence from Emirati cohorts highlights the importance of population-specific genomic profiling, with over 20% of detected CVD variants absent from global databases [66]. This parallels findings in the Roma population, underscoring that oGRS not only captures genetic predisposition to heart rate response but also reflects ethnic and environmental influences, reinforcing the need for inclusive genomic resources and tailored risk models.

It should also be noted that the YMCA 3-Minute Step Test uses age-adjusted normative categories; therefore, older adults may be classified as ‘good/excellent’ relative to their own age group.

This study has several limitations that warrant consideration. Its cross-sectional design precludes causal inference between genetic variants and heart rate dynamics. Although the inclusion of both Hungarian and Roma populations enhances epidemiological relevance, subgroup sizes may limit statistical power for ethnicity-specific effects. The SNP panel was restricted to previously reported CHD-associated variants, potentially omitting other relevant loci. Heart rate measurements were obtained manually via radial pulse palpation, introducing observer variability, and physical activity data were self-reported, raising concerns about recall bias. The oGRS was not

externally validated, limiting generalizability. RegulomeDB and epigenetic annotations support transcriptional relevance, functional validation in cardiovascular tissues remains necessary. Finally, although abnormal heart rate dynamics may occur both before and after the development of CHD, our cross-sectional design does not allow formal mediation analysis of the potential pathways. Mediation testing requires temporally ordered measurements and an explicit CHD outcome variable, which were not available in the present dataset. Nevertheless, mediation analysis could provide valuable mechanistic insight in future longitudinal studies.

Despite these limitations, the study employs a multi-layered analytical framework—combining statistical association testing, oGRS optimization, functional network clustering, and regulatory annotation—that enables biologically interpretable insights into heart rate dynamics. The oGRS demonstrated statistical robustness and mechanistic coherence, with several variants mapping to interconnected cardiovascular pathways. The inclusion of diverse populations facilitated the exploration of gene–environment interactions and emphasized the importance of population-specific risk profiling. Heart rate responses were assessed using a standardized step-test protocol, capturing real-world autonomic flexibility. Moreover, the identification of regulatory variants supported by epigenetic data (e.g., *H3K27ac* enrichment) underscores the study's translational relevance in precision cardiovascular medicine.

This study demonstrates that genetic variants associated with coronary heart disease influence the acute heart rate response to exercise in a Hungarian population. The optimized genetic risk score captures the cumulative effect of genetic variants and correlates with multiple autonomic parameters, including heart rate variability. Functional network clustering, regulatory annotations, and epigenetic enrichment support the biological plausibility of these associations. Including ethnically diverse cohorts emphasizes the importance of population-specific profiling and gene-environment interactions. These findings contribute to our growing understanding of the genetic basis of autonomic cardiovascular traits and may inform future personalized risk assessment and precision intervention strategies.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1186/s40246-026-01035-5.

Acknowledgements The authors would like to express their gratitude to János Sándor and Zsigmond Kósa for their invaluable work in coordinating the health survey, and to Zsuzsa Edit Tóth for preparing and managing the biological samples. Special thanks are extended to all the volunteers who participated in the study, as well as the general practitioners and health professionals who contributed to the data collection. The authors also acknowledge the use of Microsoft Copilot, an AI-powered language assistant, for providing editorial support in refining the structure, phrasing, and consistency of the manuscript during its preparation.

Author contributions Conceptualization, P.P.; Data curation, P.P.; Formal analysis, P.P.; Funding acquisition, R.A. and P.P.; Investigation, N.K. and S.F.; Methodology, H.A.A., N.K.H., N.K., G.T., and P.P.; Resources, R.A. and P.P.; Supervision, R.A. and P.P.; Validation, P.P.; Visualization, P.P.; Writing—original draft, H.A.A., N.K.H., N.K., G.T., and P.P.; Writing-review and editing, R.A. All authors have read and agreed to the final version of the manuscript.

Funding This project was cofounded by the European Regional Development Fund (GINOP-2.3.2-15-2016-00005), the Hungarian Academy of Sciences (TK2016-78), and the Hungarian Research Network—HUN-REN (TKCS-2021/32). Project No. 135784 has also been implemented with the support of the National Research, Development, and Innovation Fund of Hungary, financed under the K_20 program. P.P. and R.Á. also work as team members of the National Laboratory for Health Security, Hungary (RRF-2.3.1-21-2022-00006), supported by the National Research, Development, and Innovation Office (NKFIH). P.P. was supported by the Janos Bolyai Research Scholarship of the Hungarian Academy of Sciences (BO/00513/23/5). N.K. was supported by the EKÖP-24-4 University Research Scholarship Program of the Ministry for Culture and Innovation from the source of the National Research, Development and Innovation Fund. N.K.H was supported by the Stipendium Hungaricum Scholarship Programme, provided by the Tempus Public Foundation and the Hungarian Government. Supported by the University of Debrecen Program for Scientific Publication.

Data availability Due to data protection and ethical concerns, the dataset(s) supporting the conclusions of this article are available upon request from the study coordinators, Prof. Róza Ádány (adany.roza@med.unideb.hu) and Dr. Péter Pikó (piko.peter@med.unideb.hu).

Declarations

Ethics approval and consent to participate The study was conducted under the tenets of the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the Hungarian Scientific Council for Health (Reference No.: 61327–3/2017/EKU).

Consent for publication Informed consent was obtained from all subjects involved in the study.

Competing interests The authors declare no competing interests.

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Authors and Affiliations

Habib Al Ashkar[1,2] · Nihad Kharrat Helu[1] · Nora Kovacs[2,3] · Gergo Turi[4,5] · Szilvia Fiatal[3] · Roza Adany[2,3,4,6] · Peter Piko[3,4]

✉ Peter Piko
piko.peter@med.unideb.hu; piko.peter@semmelweis.hu

1 Doctoral School of Health Sciences, University of Debrecen, Debrecen 4032, Hungary

2 HUN-REN-UD Public Health Research Group, Department of Public Health and Epidemiology, Faculty of Medicine, University of Debrecen, 4032 Debrecen, Hungary

3 Department of Public Health and Epidemiology, Faculty of Medicine, University of Debrecen, 4032 Debrecen, Hungary

[4] National Laboratory for Health Security, Center for Epidemiology and Surveillance, Semmelweis University, 1089 Budapest, Hungary

[5] Synthesis Health Research Foundation, Budapest, Hungary

[6] Department of Preventive Medicine and Public Health, Semmelweis University, 1089 Budapest, Hungary