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# Past, present and future of cardiovascular twin studies

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SOUHRN

Narůstající výskyt kardiovaskulárních onemocnění ukazuje na zásadní potřebu intenzivního výzkumu v oblasti prevence těchto onemocnění a screeningu vrozených kardiovaskulárních poruch a rizikových faktorů. Studie u dvojčat nabízí možnost zhodnotit vliv genetických faktorů a faktorů prostředí a také interakcí mezi nimi. U krevního tlaku a jeho složek, tuhosti cévní stěny a intimomediální šíře arteria carotis je dědičnost jen malá, ale tvorba karotického plátu a koronární ateroskleróza jsou silně geneticky podmíněné. Tyto nálezy podpořily důležitost identifikace specifických genetických faktorů a screeningu osob s vysokým rizikem v důsledku dědičnosti. Další studie by pak měly zhodnotit přínos případných screeningových programů. Významnou příležitostí v genetickém výzkumu jsou páry monozygotních dvojčat, z nichž jen jedno má určité onemocnění. Takový výzkum může pomoci zhodnotit význam určitých prenatálních a postnatálních (epigenetických, stochastických) faktorů prostředí ve vývoji daného onemocnění. Longitudinální studie dvojčat představují ideální model ke studiu epigenetického driftu uvnitř páru (např. DNA metylace, modifikace histonů) během času. V budoucnosti by tyto studie dvojčat mohly pomoci rozplést epigenetické změny spojené s kardiovaskulárními biomarkery rizika onemocnění, což by mohlo napomoci při identifikaci těch osob, které mají zvýšené riziko pro budoucí kardiovaskulární onemocnění. Jelikož ve většině studií dvojčat je zjišťován významný vliv specifických faktorů prostředí, je i nadále důležitý tradiční koncept deterministické úlohy modifikovatelných faktorů prostředí, jako je kouření, nezdravá strava nebo omezená fyzická aktivita.



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ABSTRACT

The increasing burden of cardiovascular disorders highlights the crucial need to research efforts in the prevention and screening of heritable disorders or cardiovascular risk factors. Twin studies offer an opportunity to assess the influence of genetic and environmental factors and gene-environment interactions as well. Blood pressure and its components, arterial stiffness, carotid intima-media thickness were found to have a moderate heritability, whereas carotid plaque formation and coronary atherosclerosis seemed to be strongly genetically determinated. These findings so far underlined the importance of identification of the specific genetic factors and screening of high-risk individuals due to genetic transmission, therefore, further studies should investigate the benefits of a possible screening program. Beyond this „classical" model, monozygotic twin pairs discordant for a disease are important research opportunity since this method is able to assess the role of prenatal and postnatal environmental (epigenetic, stochastic) factors in the development of a disease. Longitudinal twin studies provide an ideal model to investigate the within-pair epigenetic drift (e.g., DNA methylation, histone modification) over time. In the future, these twin studies might unravel the underlying epigenetic changes associated with cardiovascular disease-risk biomarkers, which can help in the identification of those individuals who have higher risk for future cardiovascular disorders. Since in most twin studies a considerable role is found for unique environmental factors, the "traditional" concept of the deterministic role of individual-specific modifiable environmental factors, such as smoking, unhealthy nutrition or reduced physical activity, still remains important.

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## Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide, assuming an increasing role as a major cause of morbidity and mortality [1]. Between 1990 and 2020, the proportion of worldwide deaths from CVD is projected to rise from 29% to 36% [1,2]. This tendency has been mainly related to alarming trends in the increasing prevalence of cigarette smoking and obesity and decrease of physical activity [1]. The increasing burden of CVD in developed countries, the alarming trends in cardiovascular risk factors and the emerging pandemic of CVD all underscore the crucial need to research efforts in treatment and prevention [2].

Therefore, studies, which offer an opportunity to assess the influence of genetic and environmental factors and gene-environment interactions, are necessary. Heritability is the proportion of the phenotypic variance in the population that is attributed to genetic variation. If heritable effects are demonstrated in case of a trait, identification of the specific genetic factors is recommended. Furthermore, prevention of the related disorder might be highlighted if the specific environmental factors are also identified. Heritability estimates are traditionally obtained by comparing the extent of similarity between relatives in classical twin studies, twin-adoption studies, sib/half-sib studies, and transgenerational family studies. Each has weaknesses, but for most traits twin studies are generally regarded as the most reliable because they are unbiased by age effects and offer the ability to separate common environment from genetic effects [3–5]. The family design is useful in the determination of inter-generation resemblance or difference, but in contrast to the twin study design it does not tangibly express the mechanism through which resemblance emerges, such as genetic effect vs. socialized environment [6].

In twins, heritability estimates compare concordance rates or intra-class correlations in monozygotic (MZ) and dizygotic (DZ) twins. Twin estimates of heritability compare phenotypic similarities in MZ and DZ twins, because MZ twins are genetically identical and share nearly 100% of their germline sequence variation, whereas DZ twins are not genetically identical and share only on average 50% of germline sequence variants. In addition, MZ and DZ twins share the same uterus and birth date, and are exposed to very similar environmental factors in early development. The advantage of the classical twin study is that it is possible to estimate and distinguish between the contributions of genetic, shared environmental, and unique environmental components to the phenotype [5]. If we assume that the environment shared by twins is roughly the same for monozygotic and dizygotic pairs, then any greater observed similarities in monozygotic than dizygotic pairs should reflect the action of genes. This "equal environments assumption" is open to criticism since there is some evidence that monozygotic pairs report greater environmental similarities (such as dressing the same, sharing friends and environment in utero) than do dizygotic pairs, especially during childhood [7]. Despite this criticism, twin studies still remain one of the milestones of genetic studies which offers an excellent opportunity for investigation of genetic and environmental contribution of a trait.

The classic twin model assumes absence of gene-environment (GxE) interaction, which is the genetic control of sensitivity to the environment and refers to the fact that different genotypes respond differently to the same environment. However, since the introduction of the GxE twin model in a seminal paper by Purcell [8], this situation has changed and many twin studies including those for CVD risk factors have explored GxE interaction. GxE interaction can be incorporated in variance components twin analyses in which at least 600 MZ and 600 DZ twins are necessary to have the power to detect quite appreciable GxE effects [9].

In this review, we aim to summarize the findings of some interesting and important cardiovascular twin studies. Studies on most frequent cardiovascular disorders, such as carotid and coronary atherosclerosis will be described, and future role of twin studies in cardiovascular research will be discussed. In Hungary, we established the Hungarian Twin Registry (HTR) in 2007, which includes over 600 twin pairs nowadays [10]. Thanks to the HTR, in the recent years we were able to organise many twin studies to determine the heritability of some traits [11]. Some of these results will also be described in this report.

## Cardiovascular risk factors

### *Blood pressure and arterial stiffness variables*

It is widely known that blood pressure (BP) has a multifactorial origin arising from an interaction between susceptibility genes and environmental factors. Genetics of hypertension is complex since many genes contribute to it each with mild effects on blood pressure [12]. Twin studies and nuclear family studies have demonstrated that a sizeable proportion of systolic blood pressure (SBP) and diastolic blood pressure (DBP) variance is due to genetic effects [13–16]. Most of these studies documented a 30–50% of heritability of blood pressure and around 50% effect of unique environmental factors. These studies highlighted that hypertension has a moderate heritable background which underlines the importance of identification of the specific genetic factors for this trait. Shared family environment (e.g., alcohol use, nutrition habits) is responsible for a negligible portion of the total variance [17].

McCaffery et al. investigated the GxE interaction in self-reported hypertension in over 7 000 male Vietnam-era twins and showed that educational attainment modifies the heritability of hypertension, since nongenetic pathways may differentially contribute to risk among those with fewer years of education [18]. Another GxE interaction twin study demonstrated that higher BMIs may reduce SBP heritability through a larger impact of environmental effects whereas this is not the case for DBP in which the heritability remains unchanged at higher BMI levels [19].

In the recent years, further blood pressure components, such as pulse pressure (PP), a measure of the pulsatile component of BP, have also been recognized as important predictors of future cardiovascular events [20]. In addition, central BP has been emphasized as a more direct measure than peripheral BP of the hemodynamic stress imposed on the myocardium and the coronary

and cerebral circulation [21,22]. Our working group has shown that the heritability of central BP components was also moderate, and generally higher than the corresponding brachial pressure values. Central SBP was heritable in 60% versus 51% concerning peripheral SBP. PP had a 47% genetic background centrally vs 30% peripherally [23]. A possible explanation for the greater heritability of central BP might be that it is influenced by major determinants with potential genetic components, including wave reflections, vascular stiffness, left ventricular contractility and heart rate [24]. Pulse pressure is influenced by systolic blood pressure, which is an important cardiovascular parameter in terms of pulsatile stress on vessel wall. An English twin study certified similar heritability of PP compared to our findings (43%) [25]. A Chinese twin study provided both epidemiological and molecular genetic evidence for the genetic dissection of pulse pressure, which could help in fine mapping and in characterizing genes that are involved in the regulation of PP [26]. A recent Chinese twin study assessed eight metabolic factors (body mass index, waist circumference, waist-to-hip ratio, total serum cholesterol, serum triglycerides, serum uric acid besides systolic and diastolic blood pressure) in 508 twin pairs aged 8–17 years and reported that the effect of genetic factors on most metabolic traits decreased from childhood to adolescence [27]. Similarly, decreasing heritable effects were demonstrated in case of BP variability so that it is likely that BP variability in younger and older age groups may reflect different pathological phenotypes [28]. These findings further highlight a possible role of epigenetic factors in aging by decreasing heritable effect of the investigated traits.

In case of two heritable traits with a significant phenotypic correlation between them, twin studies are able to decompose if the correlation is related to common genetic or environmental background. For instance, in our study, blood pressure components were moderately correlated with BMI, largely because of shared genetic factors [29]. In addition, shared genetic factors were demonstrated between resting and stress BP levels [30].

In the recent decade, great emphasis has been put on arterial stiffness, a dynamic property which is determined by vascular function like vascular smooth muscle tone and by the structure of the vessel wall as elastin/collagen content. Pulse wave velocity (PWV), a direct marker of arterial stiffness, is a strong vascular risk factor for prediction of mortality [31]. In addition, augmentation index (AIx) is recognised as an indicator of wave reflection and peripheral vascular resistance [32].

Twin studies have shown moderate genetic influence on these measures. For instance, heritability for carotid--femoral PWV was 36% in a genetically isolated Dutch population [33, whereas the genetic effects on aorto--radial and aorto-dorsalis-pedis PWV were reported 43% and 53% in young American twins [34]. Heritability of AIx in women has indicated 37% [14]. Our working group found a moderate genetic effect on arterial stiffness in a relatively large wide-age ranged twin sample: 50% for aortic PWV, 49% for aortic and 47% for brachial AIx [23]. In addition, genetic covariance models have proved a moderate common genetic link between aortic PWV and central SBP, PP, brachial SBP [23]. An English GxE interaction twin study demonstrated that physical activity reduces genetic predisposition to increased AIx [35].

Overall, heritability of aortic stiffness was found to be of the same magnitude as that of BP, although arterial stiffness is influenced by the cumulative effects of blood pressure and additional risk factors on the stiff and elastic components of the arterial wall [23]. These findings underline the importance of identification of the specific genes and environmental factors related to these traits, and the screening of high-risk individuals due to the moderate genetic transmission. Therefore, further studies should investigate the benefits of a possible screening program based on arterial stiffness measurements.

### *Body mass index, body composition*

Heritability estimates of body mass index (BMI) have been derived also from twin studies, indicating usually a strong genetic component [36,37]. In contrast, family studies suggested that high BMI has a relatively small contribution from additive genes unique in families with premature coronary heart disease, highlighting the role of lifestyle and environmental factors, or gene-environment interactions in the development of overweight and obesity [38]. Twin studies have demonstrated variation in the heritability of obesity, which can be attributed to various population characteristics, such as sex, age, time period of observation and average BMI, and social-environmental factors, e.g. country-level gross domestic product (GDP) per capita and GDP growth [36]. Genetics have an important impact in the variation of weight, height, and BMI not only in adults but also from early childhood to late adolescence, and gene-environment correlation and interaction is also likely [39]. Interestingly, physical activity can modify the effect of the genes responsible for predisposition to obesity, whereas the protein content of the diet has no such influence [40]. High heritability (74%) of body composition was also shown in our recent study in case of body fat percentage and fat-free mass [37]. Increased BMI has been strongly associated with many individual cardiovascular risk factors and with increased overall cardiovascular risk in many epidemiological studies [41].

### *Diabetes mellitus*

Twin studies have confirmed the multifactorial aetiology of type II diabetes, since genetic predisposition was demonstrated in the development of abnormal glucose tolerance. However, environmental factors also play a predominant role in controlling whether a genetically predisposed individual progresses to overt Type II diabetes [42]. Twin studies also confirmed a shared genetic effect between BMI and type 2 diabetes, which suggested that these traits are partly influenced by the same genetic factors [43].

### *Dyslipidaemia*

The role of both environmental and genetic factors were demonstrated in the etiology of dyslipidemia [44]. In our own study, shared and unique environmental influences had the highest proportion of total phenotypic variance in serum total cholesterol, serum HDL-cholesterol and triglycerides, underscoring the role of lifestyle habits in

the prevention [45]. In other studies, heritability varied between 8–72% for total cholesterol, 21–79% for HDL--cholesterol and 19–72% for serum triglycerides [46].

### *Smoking habits and alcohol consumption*

Twin studies have shown that smoking habits are highly heritable. A Chinese twin study demonstrated that current smoking is heritable in 75% with no evidence for a significant contribution of shared environmental effects. In addition, heavy smoking was even more heritable [47]. Another study found that the way in which smoking patterns develop in adolescence has also a high heritability [48]. Current alcohol consumption and its amount is also strongly influenced by genetic effects (60% and 42%, retrospectively) [47].

### *Physical activity*

Similarly to most of the cardiovascular risk factors mentioned above, physical activity has been also linked to genes, ranging from 0% to 78% in twin studies [49]. A recent twin study confirmed with objective assessment that additive genetic factors explain 47% of the variance in physical activity energy expenditure and time spent in moderate--to-vigorous intensity physical activity, suggesting that innate biological processes may be driving some of our daily physical activity [49].

## Cardiovascular diseases

### *Carotid artery disease*

Carotid intima-media thickness (IMT), the distance between the hyperechoic layers of intima and media, is regarded a surrogate marker for atherosclerosis, prevalent CVD [50], unfavorable levels of established cardiovascular risk factors, and atherosclerosis. Carotid IMT can be easily measured by B-mode ultrasound, and automatic softwares are also available for proper analysis.

Most studies reported that genetic factors account for a moderate variance of carotid IMT variation (25–60%) [51–53. An Italian twin study reported a substantial genetic and unshared environmental influences on carotid IMT by confirming the relevant role of age in the aetiology of these traits [54]. An English twin study has shown that aortic stiffening relates to aortic calcification, and this relation is driven by common genes [55]. Since carotid IMT seems to be only partly genetically determined, these studies may provide further support for prevention and health promotion strategies based on modifiable lifestyle factors due to their moderate influence on this trait. Of note, an American twin study failed to establish a genetic link between carotid IMT and Cardiovascular Health Index, which is a health metric consisting of 7 modifiable risk factors [56].

Carotid artery plaque formation has been associated with multiple complications such as cardiovascular events, retinal or cerebral ischemia and all-cause mortality [57]. A limited number of family studies have investigated, indeed partially and contradictory, the genetic determinants of carotid plaque characteristics [33,58,59]. Moskau reported no genetic base for the carotid plaque score (a dimensionless plaque score ranging from 0 to 8), but demonstrated a moderate heritability of maximal carotid stenosis [58]. A moderate (23–28%) heritability of the presence of carotid plaques was reported in the San Antonio Family Heart Study [59], and a similar magnitude of heritability of the carotid plaque score was found in the Erasmus Rucphen Family [33. In a large international twin study (275 twin pairs) performed by our working group, heritability of carotid plaque characteristics was much higher than previously reported in family studies, ranging between 66 and 78% [60]. It can be attributable to the fact of age dependent expression of genetic effects as twins always have the same age, which may explain the often observed decrease in familial correlations as age differences become larger (rDZ > rSIBs > rparent-offspring). Age-, sex- and country-adjusted heritability in this twin study was 78% for the presence of carotid plaque, 74% for plaque echogenicity (hypoechoic, hyperechoic or mixed), 69% for plaque size, 74% for plaque sidedness (unilateral or bilateral), 74% for plaque numerosity, 68% and 66% for the presence of plaque in carotid bulbs and proximal internal carotid arteries [60]. Unique environmental factors were responsible for the remaining variance (22–34%) [60]. Cecelja and coworkers reported similarly high heritability (61%) on calcified aortic plaques assessed by computed tomography [61].

A genome-wide linkage analysis obtained a bit higher heritability estimates for plaque presence (50%) compared to the findings of family studies [62]; yet, the genome--wide association studies usually underreport heritability [63] since SNPs in total associated with a complex disease only explain a small proportion of the genetic variation in the population which is called "missing heritability." The two most plausible explanations for these observations are either the too small effect sizes at individual SNPs or the causal variants which are not in sufficient linkage disequilibrium with SNPs on the commercial arrays to be detected by association [6]. The same study identified loci on chromosomes 11p15, 14q32, and 15q23 which might influence heritability and stated that the SOX6 gene within the bone morphogenic protein pathway could be a candidate for carotid plaque formation [62].

### *Coronary heart disease in twins*

Although few data are available on genetic studies using twins in coronary heart disease (CHD), these twin studies played a pivotal role in the discovery of the genetic basis of coronary artery disease, myocardial infarction and most of their associated risk factors [65]. The knowledge of CHD in twins has been represented by case reports mainly. These papers also underlined the role of genetic factors, such as the onset of symptoms occured within a short time span between the twins, the coronary pathology was often very similar [66]. Therefore, these reports highlighted that asymptomatic twins of symptomatic counterparts require aggressive assessment and management for occult coronary artery disease [67]. In a coronary angiography case report, plaques were suggested to be at least partly independent of the human genome, whereas age at first cardiac event, type of cardiac event and risk factor profile appeared to be more heritable [68]. In contrast, a German report of 6 twin pairs obtained no evidence in support of the hypothesis that the location of coronary stenosis is

strictly determined by hereditary factors [69]. In addition, coronary blood supply and the right versus left dominance pattern was shown to be heritable [69]. Colleagues of the Swedish twin registry followed 21,004 Swedish twins for 26 years investigating the risk of death from CHD, and reported that at younger ages, death from CHD is influenced by genetic factors in both women and men, which genetic effect decreases at older ages [70]. This genetic contribution to the variation in CHD-mortality was moderate (57% in males and 38% in females) [71].

Other studies searched for risk factors of CHD. Classical CHD risk, lifestyle factors (e.g. smoking, sedentary lifestyle, alcohol intake and BMI) were significantly associated with increased CHD incidence [72]. In addition, an American twin study performed a longitudinal study in Vietnamese veteran twins and found that the incidence of CHD was more than double in twins with post-traumatic stress disorder (PTSD) than in those without PTSD, indicating that PTSD is a risk factor for CHD [73]. Postload plasma glucose levels have been associated with long-term coronary heart mortality risk largely by factors shared between co-twins [74]. Since twin studies supported the genetic basis for CHD and many inherited cardiovascular risk factors can be modified, early detection of CHD might lead to earlier intervention for genetically susceptible individuals [75]. Since current guidelines do not support the use of genetic profiles in risk assessment of CHD despite twin studies indicated a family transmission of this trait, further studies are needed to address aspects of genetic profiling in the primary prevention setting [76].

### *Lower limb peripheral artery disease*

Only few twin studies are available in the literature which assessed the contribution of genetic factors in twins to peripheral arterial disease (PAD). A study investigating the ankle-brachial index (ABI) has indicated that 48% of the observed variability in ABI values could be attributed to additive genetic effects [77]. A recent Swedish twin study also delineated that heritability (58%) and unique environmental factors (42%), and traditional risk factors could explain a major proportion of PAD heritability [78].

## Role of twin studies in the future of cardiovascular research

In cardiovascular research, twin studies played a pivotal role in the discovery of the contribution of genetic and environmental factors to various traits [65]. Beyond this "classical" model, numerous papers have been published in the past years on monozygotic twin pairs discordant for a certain disease since this method is able to assess the role of prenatal and postnatal environmental (epigenetic, stochastic) factors in the development of a disease. Antenatal environmental factors, such as maternal diet, smoking, xenobiotics exposure, stress and lifestyle factors can alter fetal gene regulation resulting epigenetic alterations, such as DNA methylation or histone modification. In addition, environment may affect expression of the genome through effects on epigenetic factors such as DNA methylation especially between twins with different lifestyle. These epigenetic modifications can switch on or off the gene transcription, leading to activation or deactivation of a disease. Monozygotic discordant twin study design combined with sequencing technologies will be possible to explore the complexity of the gene-environment relationships and individual variability to provide important insights into the pathogenesis of CVD in the future [65].

An additional interesting twin model is the longitudinal study which provides an ideal model to investigate the within-pair epigenetic drift (DNA methylation, histone modification, etc.) over time. Candidate gene and epigenome-wide association studies and transgenerational epigenetic inheritance of CVD are valuable fields which might serve with a potential for evidence-based interventions in the future [79]. As a good example for epigenetic mechanisms, early environmental effects have been shown to be markedly important in a Finnish study, in which migration of Finnish people (country with high CHD prevalence) at an early age and good integration were demonstrated to be beneficial to vascular health associated with moving from a high to a lower CHD risk country, suggesting that an environment-sensitive period influences atherogenesis before adulthood [80]. Furthermore, men originating from east Finland had a greater degree of subclinical atherosclerosis and they may be more susceptible to the impact of conventional cardiovascular risk factors than men originating from west Finland where CHD prevalence is lower [81]. Longitudinal epigenetic twin studies have shown evidence that DNA methylation changes over time, even between birth and 18 months of age thanks to non-shared stochastic and environmental factors [82]. These epigenetic modulating factors have been posited as the likely drivers of early-life programming of adult-onset CVD. Even slight differences in intrauterine environment can influence expression profile as demonstrated in a study of newborn twins, indicating that low birthweight (excluding the effects of circulation differences and twin to twin transfusion) is a predisposing factor for cardiovascular diseases [83]. In summary, if these epigenetic twin studies will unravel the underlying epigenetic changes associated with CVD-risk biomarkers, identification of those at risk for early-life interventions could aid to alter the risk trajectory and potentially reduce CVD incidence later in life [79].

## Conclusion

The increasing burden of cardiovascular disorders highlights the crucial need to research efforts in the prevention and screening of heritable disorders or cardiovascular risk factors. Twin studies offer an opportunity to assess the influence of genetic and environmental factors and also gene-environment interactions. If a trait is heritable, studies identifying specific genetic factors can be stimulated, and prevention of the related disorder or risk factor based on the family risk might be highlighted by efficient screening methods. In general, most of the investigated cardiovascular disorders or risk factors were found to have a moderate heritability based on findings of twin studies (blood pressure and its components, arterial stiffness, carotid intima-media thickness), whereas carotid plaque formation and coronary atherosclerosis seems

to be strongly genetically determinated. These findings so far underlined the importance of screening of high--risk individuals due to genetic transmission, therefore, further studies should investigate the benefits of a possible screening program. Of note, family history of CVD is already incorporated in the Framingham risk score. For further progress, identifying the specific genetic (or environmental) factors is a crucial step. Beyond this „classical" model, monozygotic twin pairs discordant for a disease are important research opportunity since this method is able to assess the role of prenatal and postnatal environmental (epigenetic, stochastic) factors in the development of a disease especially if combined with sequencing technologies. An additional interesting twin model is the longitudinal study which provides an ideal model to investigate the within-pair epigenetic drift (DNA methylation, histone modification, etc.) over time. In the future, these twin studies might unravel the underlying epigenetic changes associated with CVD-risk biomarkers, which can help in the identification of those individuals who have higher risk for future cardiovascular disorders. On the other hand, unique environmental contribution seems to have a considerable role in CVD. Therefore, the "traditional" concept of the deterministic role of individual-specific modifiable environmental factors, such as smoking, unhealthy nutrition or reduced physical activity, still remains important, since in societies where everyone is exposed to cardiovascular risk factors, genetics will become relatively more important in determining who will be affected by CVD (i.e. high heritability). Yet, management of cardiovascular risk factors remains cornerstone to eradicating the cardiovascular disease especially in genetically susceptible individuals.

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Authors declare no conflicts of interest.

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**Ethical statement**
The research was done according to ethical standards.

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