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Heritability of death from coronary heart disease: a 36-year follow-up of 20 966 Swedish twins

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Abstract. Zdravkovic S, Wienke A, Pedersen NL, Marenberg ME, Yashin AI, de Faire U (Karolinska Institutet, Stockholm, Sweden; Max-Planck Institute for Demographic Research, Rostock, Germany; University of Pennsylvania School of Medicine, Philadelphia, PA, USA). Heritability of death from coronary heart disease: a 36-year follow-up of 20 966 Swedish twins. *J Intern Med* 2002; **252:** 247–254.

Objective. The aim of the present study was to evaluate and distinguish between environmental and genetic effects for death from coronary heart disease (CHD) as well as to determine whether the importance of genetic influences is changing with age.

Design. A cohort study with a follow-up time of 36 years.

Subjects. The cohort drawn for the present study includes 20 966 twins born in Sweden between 1886 and 1925 where both twins within a pair still lived within the country in 1961.

Methods. Concordances and correlated γ-frailty model were used to assess and distinguish between genetic and environmental influences as well as to evaluate *age-related* changes in genetic influences.

Results. A total number of 4007 CHD-deaths (2208 males, and 1799 females) was observed. The probability of dying from CHD given that one's twin partner already has died from CHD decreased with increasing age, particularly amongst males. The genetic variation in susceptibility to death from CHD was moderately large, and decreased slightly across time, particularly amongst males. The heritability was 0.57 (95% CI, 0.45–0.69) amongst male twins, and 0.38 (0.26–0.50) amongst female twins.

Conclusions. The genetic contribution to the variation in CHD-mortality was moderate both in females and males. Furthermore, although genetic effects appeared to be greater at younger ages of death, our findings clearly suggest that genetic factors are in operation throughout the entire life span.

Keywords: concordance, Coronary heart disease, frailty, heritability, twins

Abbreviations: CHD, coronary heart disease; AIC, Akaike information criterion.

Introduction

Twin, family, and adoption studies suggest an impact of genetic factors on the occurrence of coronary heart disease (CHD), particularly at early ages [1–10]. In a previous study on the Swedish Twin Registry it was demonstrated that the relative risk to die from CHD was influenced by genetic factors that were evident up to the age of 75 years [9] both in women and men, and that the genetic effects decreased gradually at older ages. The relative importance of the genetic influences, however, was not resolved from those data, but the relative hazards for CHD-mortality were only marginally reduced when other risk factors for CHD were included in the calculations of relative hazards [9]. Furthermore, a study on premature death in adult adoptees [10] suggested that premature death in adults as a result of infectious and vascular causes have a strong genetic background. It is therefore of

Table 1 Mortality caused by coronary heart disease in the old cohort of the Swedish twin registry, by sex and zygosity

Age at death due to coronary heart disease	Men Monozygotic twins ($n = 3280$)	Dizygotic twins ($n = 5956$)	Women* Monozygotic twins ($n = 4008$)	Dizygotic twins ($n = 7722$)
36–55 years	20	39		
56–65 years	95	200	(36–65) 48	(36–65) 76
66–75 years	235	561	138	313
76–85 years	324	530	291	546
>85 years	83	121	141	246
Total	757	1451	618	1181

*The age categories of 36–55 and 56–65 years were merged into the age category of 36–65 years for female twins because of the small number of deaths.

great interest to further quantify the genetic contribution to the variation in risk. Different analytical procedures/methods regarding quantitative genetics [11] have been used during the years to estimate the relative importance of genetic (heritability [12]) and environmental influences on susceptibility to death. For the purpose of estimating heritability we applied the correlated γ-frailty model [13–17], a particularly useful model in analysis of dependent duration data such as twin lifetimes. The aim of the present study was to evaluate and distinguish between environmental and genetic effects for death from CHD as well as to determine whether the importance of genetic influences are changing with age, using information on 20 966 twins born between 1886 and 1925.

Material

The Swedish Twin Registry

The Swedish Twin Registry [18] is the largest population-based twin registry in the world. The registry includes information on all twins born in Sweden between 1886 and 1990. This study is based on the oldest cohort from the Registry, that is, all like-sexed pairs born between 1886 and 1925, where both twins still lived within the country in 1961, and responded to a questionnaire in 1961. The cohort was annually matched with the Swedish Cause of Death Registry to obtain International Classification of Death codes (ICD) [19] for information from death certificates, with a follow-up time of 36 years (through 1996). During the follow-up period three different revisions of ICD were used: ICD7, ICD8 and ICD9. Codes classified as CHD-deaths between 1961 and 1968 (ICD7) were 420.00–420.99 and 422.1. Between 1969 and 1986 and 1987 and 1996 (ICD8 and ICD9, respectively) the death codes were 410.00–414.99. The cohort drawn for the present study contains 21 884 same sexed twins or 10 942 twin pairs. For this study, we excluded all twins with unknown zygosity, a total of 439 pairs, and additionally 20 pairs because of missing information in the cause of death registry. The final sample contained 10 483 twin pairs or 20 966 twins (Table 1). Of the total sample, 9236 were male twins, 11 730 were female twins. Of the 7288 monozygotic (MZ) twins, 3280 were male and 4008 female. Of 13 678 dizygotic (DZ) twins, 5956 were male and 7722 female.

Methods

Information on life span (considered as a time scale) and CHD-mortality were our primary variables. In order to distinguish whether the index twin's (the first twin within a pair to die from CHD) age at CHD-death (considered as a time point) influence the genetic risk of dying from the disease, the age at CHD-death of the index twin was divided into the intervals 36–55, 56–65, 66–75, 76–85 and over or equal to 86. For females the intervals 36–55 and 56–65 were merged into one interval because of smaller number of cases. Within these age intervals, each twin pair was only included once in the age at death dependent analysis, given that at least one twin in a pair died from CHD. In order to determine whether genetic effects are changing across time, we analysed the cohort based on several follow-up times, until the year 1987, 1992 and 1996, respectively. In this way we maintained the same number of twins in the analysis and the extended

follow-up times included increasing numbers of older cases. By defining the follow-up time until the year 1987 all deaths (observed in the cohort) that occurred before the age of 62 were included whereas by defining the follow-up time until the year 1992 all deaths that occurred before the age of 67 were included. Finally, the follow-up time until the year 1996 included all deaths that occurred before the age of 71. If the hypothesis that the genetic contribution to the variation of risk decreases with age is true, one could expect the heritability to decrease over the extended follow-up times. Statistical software used for the present study was SAS [20], SPSS [21] and GAUSS [22].

Analysis of proband-wise concordances

The proband-wise concordance rate is the probability that a twin gets the disease given that his or her twin partner already had developed the disease. The rate is obtained by taking twice the number of concordant pairs divided by the number of discordant pairs and twice the number of concordant pairs. The aim of conducting these calculations was to determine how age at death from CHD of the index-twin influences the survival of the second twin regarding CHD. If higher concordances are observed amongst MZ-twins (completely identical for all genetic factors) than DZ-twins (who shares, on average, half of their genes) the difference is interpreted to be caused by genetic factors. Furthermore, in order to calculate proband-wise concordance rates [23] we defined concordant pairs as those pairs where both twins died from CHD. Discordant pairs were defined as those pairs where one twin died from CHD. All other twin pairs (i.e. one or both died from other causes) were excluded from the analyses of concordance. Significant differences between concordance rates for MZ and DZ-twins were determined by the chi square test with 1 degree of freedom.

Genetic and environmental analysis of frailty

Correlated γ-frailty model. In order to analyse variability in susceptibility to CHD-mortality we used the correlated γ-frailty model. The key idea behind the concept of frailty (susceptibility to CHD-mortality) is that individuals have different susceptibilities, in the present study to CHD-mortality, and that those who are most susceptible or frail have an increased risk to die earlier than others. The relationship between susceptibility to death and longevity is modelled by the notion of random hazard. In such models susceptibility is represented by an unobserved random variable called liability in biometrical genetics [24] and frailty when the random variable acts multiplicatively on the baseline hazard. Furthermore, frailty describes the effect of nonobserved covariates. Univariate frailty models assume subjects in the study population to be independent, and do not reflect the association between the life spans of twins. A *correlated* γ-frailty model is therefore particularly useful [13–17] when dependent life times are analysed. The model allows dealing with censored and truncated observations, and application of survival analysis and methods of quantitative genetics.

Quantitative genetics. The correlation coefficients ρ_{MZ} and ρ_{DZ} calculated for MZ and DZ twins are useful for analyses of genetic and environmental factors. These correlations provide information about genetic and environmental influences on frailty. For example, under the assumption of equal environments for both MZ and DZ twins, differences in the two correlation coefficients reflect the influence of genetic factors. Using these coefficients, estimates of heritability may be obtained. Standard assumptions about the quantitative genetics yield the following relations:

$$\rho_{MZ} = a^2 + d^2 + c^2,\ \rho_{DZ} = 0.5a^2 + 0.25d^2 + c^2$$
$$\text{and } 1 = a^2 + d^2 + c^2 + e^2$$

[note that a^2 corresponds to the proportion of total variance associated with additive genetic effects (A), d^2 corresponds to the proportion of total variance associated with dominant genetic effects (D), c^2 corresponds to the proportion of total variance associated with shared environmental effects (C), and e^2 corresponds to the proportion of total variance associated with nonshared environmental effects (E)]. The components are assumed to be independent. Five genetic models based on different assumptions about genetic structure were fit to variance estimates produced by the γ-frailty model. From the estimation point of view no more than three components can be simultaneously represented in a model for MZ and DZ twins. Additional

components could be added if data on twins reared apart was available. For example, an ADE model refers to decomposition of frailty $Z = A + D + E$, and an AE model refers to decomposition of frailty $Z = A + E$. ACE, DE and CE models are similarly defined. Dominant genetic factors and shared environmental factors cannot be estimated simultaneously because they are confounded in the classical twin study of twins reared together [25]. In standard biometric practice the models assume no epistasic (genetic interlocus interaction), no gene–environment interaction and no assortative mating. Selection of the best fitting nested model was based on the likelihood ratio test and selection of the best fitting non-nested model was based on Akaike information criterion [26] (AIC).

Results

Death from CHD

A total number of 4007 CHD-deaths (2208 male, and 1799 female CHD-deaths) was observed during the follow-up period until 1996. With regard to censored observations (death due to other causes or alive at the end of the 36 years of follow-up), the number of deaths due to other causes was 4071 amongst male and 4866 amongst female twins. The total number of twins alive at the end of the follow-up was 2957 male and 5065 female twins.

Analysis of proband-wise concordances

Concordance rates are presented in Table 2. The proportion of concordant MZ pairs was greater than the corresponding proportion of DZ pairs in both sexes. The difference in concordance rates between MZ and DZ male pairs was statistically significant ($P < 0.05$). This suggests a possible role of genetic factors on death from CHD amongst males. The MZ concordance rate amongst female twins was greater than the corresponding rate for DZ female twins although the difference was not statistically significant. Age-specific concordance rates in male and female twins (presented in Fig. 1) showed successively lower concordance rates with increasing age at death in male twins both amongst MZ and DZ twins. As the difference in concordance rates between MZ and DZ male twins is almost the same for all age-intervals it seems as if genetic influences are fairly stable over the age-at-death-intervals. In female twins, on the other hand, no decreasing trend was apparent but the data suggested that genetic influences on CHD-mortality were more important amongst female twins whose twin partners died from CHD before the age of 65 years than those whose partners died after 65 years of age.

Genetic and environmental analysis of frailty

In the analyses of the correlated γ-frailty model (presented in Table 3) the model with an additive genetic component and a nonshared environmental component gave the best fit to the data according to the AIC- for both male and female twins. The purely environmental CE-model gave the worst fit to data, for both male and female twins, suggesting that the susceptibility to die from CHD is not purely environmental. The heritability estimate for the best fitting model, AE, was approximately 0.38 (95% CI, 0.26–0.50) amongst female twins. Amongst male twins the heritability estimate was 0.57 (0.45–0.69), which is larger (borderline significant, $P = 0.06$) than the corresponding estimate amongst female

Table 2 The number of concordant and discordant twin pairs and proband-wise concordance rates for death caused by coronary heart disease, by sex and zygosity

Coronary heart disease	Monozygotic twin pairs men	Dizygotic twin pairs	Monozygotic twin pairs women	Dizygotic twin pairs
Total number of CHD-dead twin pairs	604	1203	521	1026
Concordant pairs	153	248	97	155
Discordant pairs	451	955	424	871
Proband-wise concordance rate	40.4*	34.2*	31.4	26.2

*Differences between proband-wise concordance rates (in percentage) in MZ and DZ twins are statistically significant ($P < 0.05$).

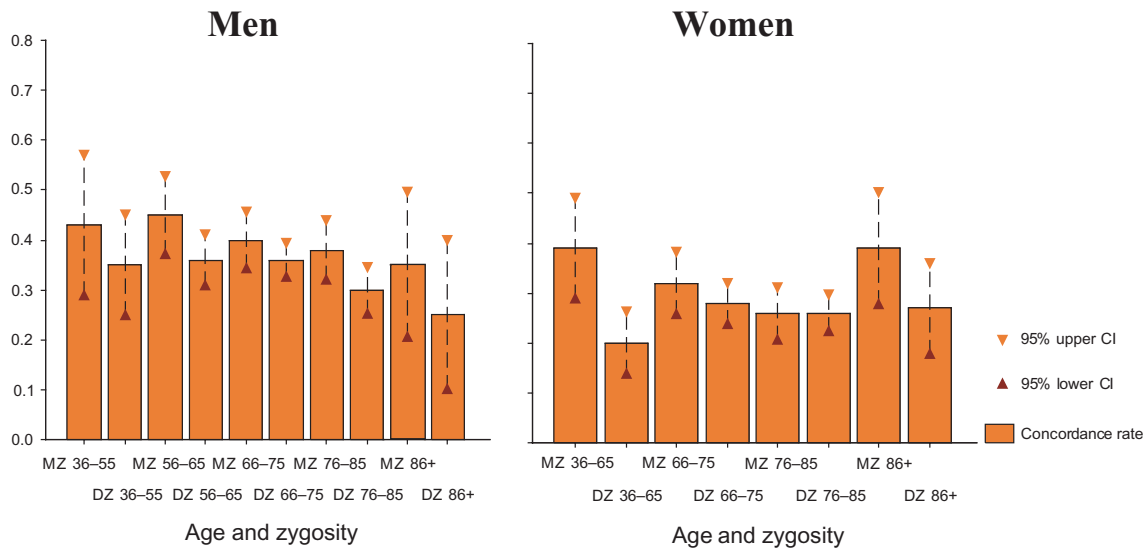

Fig. 1 Proband-wise concordance rates dependent on the age at death of the index-twin, by sex and zygosity.

Table 3 Estimates of the components of variance in frailty to mortality due to coronary heart diseases, follow-up time to 1996

	σ	a^2	c^2	d^2	e^2	Log-likelihood	AIC
Males							
ACE	2.48 (0.31)	0.57 (–)	0.00 (–)		0.43 (–)	−2.4040	22215.5287
AE	**2.48 (0.31)**	**0.57 (0.06)**			**0.43 (0.06)**	**−2.4040**	**22213.5287**
ADE	2.52 (0.32)	0.43 (0.16)		0.16 (0.17)	0.41 (0.07)	−2.4039	22214.6051
DE	2.63 (0.34)			0.60 (0.06)	0.40 (0.06)	−2.4047	22220.5480
CE	2.50 (0.34)		0.38 (0.05)		0.62 (0.05)	−2.4074	22245.3929
Females							
ACE	3.15 (0.45)	0.38 (–)	0.00 (–)		0.62 (–)	−1.6262	19087.4433
AE	**3.15 (0.45)**	**0.38 (0.06)**			**0.62 (0.06)**	**−1.6262**	**19085.4433**
ADE	3.14 (0.46)	0.37 (0.14)		0.02 (0.16)	0.61 (0.07)	−1.6262	19087.3260
DE	3.00 (0.46)			0.45 (0.07)	0.55 (0.07)	−1.6267	19091.6602
CE	3.41 (0.45)		0.24 (0.04)		0.76 (0.04)	−1.6278	19105.0324

A = additive genetic effects, D = dominant genetic effects, C = shared environmental effects, E = nonshared environmental effects. Standard errors were not given for the ACE model since 0 is the boundary of the parametric space. The variance for the ACE-model is depicted as follows: Var $(Z) = \sigma^2 = \sigma^2_A + \sigma^2_C + \sigma^2_E$ (Z = frailty). The variance components are $a^2 = \sigma^2_A/\sigma^2$, $c^2 = \sigma^2{}_C/\sigma^2$, $e^2 = \sigma^2{}_E/\sigma^2$ [where Var $(Z) = \sigma^2$, Var $(A) = \sigma^2{}_A$, Var $(C) = \sigma^2{}_C$, Var $(D) = \sigma^2{}_D$] The variance components for the other four models are depicted in a similar way. Values shown in bold are those obtained by the best fitting genetic model.

twins. Analyses based on the three follow-up times (presented in Fig. 2) indicated that the highest heritability estimates were noted for follow-up through 1987 (i.e. the shortest period of follow-up time). The small but noticeable decrease in heritability over extended follow-up times confirms the hypothesis that the heritability decreases slightly over time, and that genetic effects seem to be stronger in early phases of life, although the decrease may not be considered as statistically significant.

Discussion

The present study was based upon 36 years of follow-up of 20 966 Swedish twins in order to quantify the relative importance of age-related changes in genetic influences on death caused by CHD. In addition, the study contained the largest number of CHD-deaths (4007) ever presented from Twin registries. Using the classical twin approach, our results indicate the importance of genetic

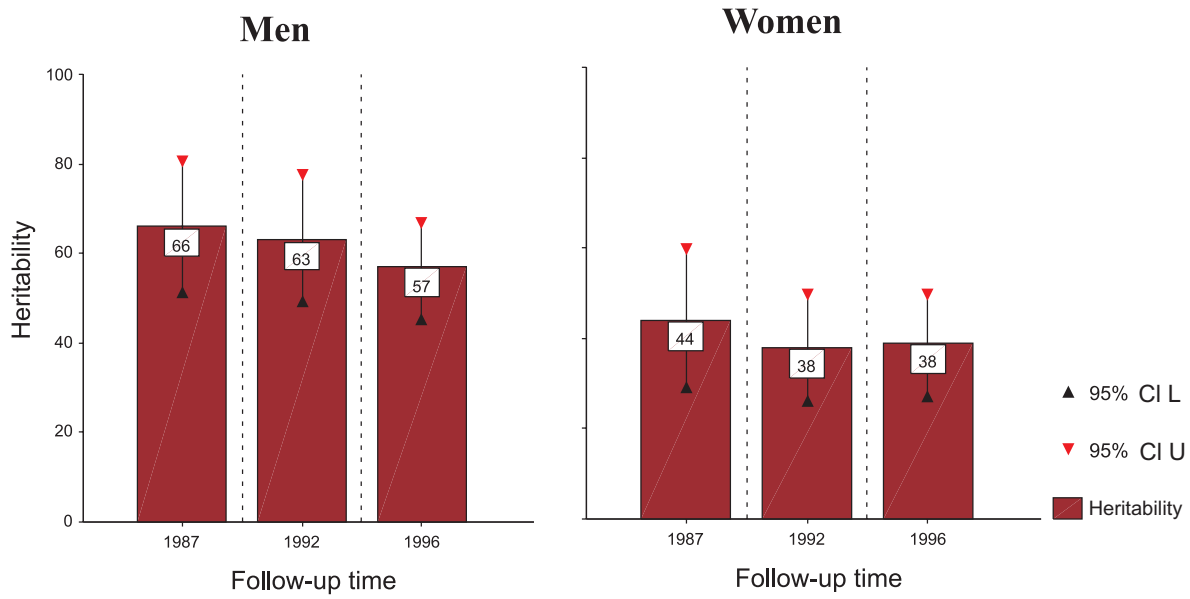

Fig. 2 Heritability estimates obtained from the best fitting model, the AE-model with regard to different follow-up times, by sex.

components on death from CHD, particularly amongst male twins. Heritability was estimated to be 0.57 (0.45–0.69) amongst male twins and 0.38 (0.26–0.50) amongst female twins. Both comparisons of concordance rates stratified by age at death of index proband and analyses of frailty with varying follow-up time indicate that genetic effects are in operation throughout the entire life span, although they are particularly important for earlier ages at death.

In a previous follow-up from our group encompassing 26 years of follow-up of twins from the Swedish Twin Registry [9], it was found that the relative hazards of death from CHD were largely influenced by genetic factors, especially amongst twins whose twin partner died from CHD at early ages. Estimating heritability was not the focus of this previous paper. The relative hazards [9] of CHD-mortality were marginally reduced by risk factors (self-reported in the early 1960s) such as hypertension, diabetes, smoking, and BMI. Of considerable interest are therefore findings on Swedish twins raised apart and together by Hong *et al.* [27], who found that one of the main risk factors for occurrence of CHD, hypertension (systolic blood pressure), was influenced by genetic factors and that the importance of those factors tended to decrease across age groups.

In a recent study on genetic influences behind death from heart diseases, Wienke *et al.* [28], noted in a subgroup-analysis that heritability (based on the correlated γ-frailty model as well) of death caused by CHD amongst twins in the Danish twin registry (a total number of 3231 CHD-deaths) was 0.53 (0.31–0.75) amongst male and 0.58 (0.31–0.85) female twins, respectively. These data are in agreement with our findings regarding male twins, but heritability was greater amongst Danish female twins than Swedish female twins.

Previous studies on the Swedish [1] and the Danish [2] twin registries suggested that genetic influence regarding CHD behind Danish and Swedish females might differ (higher heritabilities amongst Danish females). This may be partly explained by the selection criterion for twin pairs to be included in the Danish registry [2], which was that both twins born between 1870 and 1930 needed to survive the age of six. Furthermore, information regarding cause specific mortality as CHD-death is stored from 1943. Additionally, a larger number of younger CHD-deaths were represented in the Danish registry, although the number of observed CHD-deaths was greater amongst Swedish twins. This is in line with the present findings that genetic factors seem to play a more important role in earlier phases of life, particularly amongst female twins. Given our findings on age-related changes one might expect that the results

from Danish cohort would reflect a similar effect as those trends seen for our younger deaths.

We observed a slight decrease in heritability, particularly amongst male twins, dependent on the length of follow-up time (and hence inclusion of higher ages at death). As could be expected the heritability estimates were the largest for the follow-up time until 1987, when most of the cases were young (before the age of 62 years). Some part of the decrease in heritability may reflect age dependent expression of genes, and/or a change in the system's resilience to the more major effects of a genetic influence in early phases of life. Another possible explanation may be that the accumulation of environmental influences plays a larger role in older ages.

In the context of evolutionary theories of ageing [29, 30], genes, sex and ageing are often intricately intertwined. CHD is the consequence of an age-related underlying disorder, coronary atherosclerosis. The pathogenesis of the atherosclerotic process is a result of an interaction between ageing processes and disease-specific factors [31], both intrinsic and extrinsic. A large number of polymorphisms of genes such as APO-E, the LDL receptor, apolipoprotein (a) and genes of relevance for homocysteine metabolism as well as various cardiovascular risk factors such as dyslipoproteinaemia, hypertension, diabetes, smoking, diet high in saturated fats, physical inactivity, psychological stress, etc. are most likely involved.

The evolutionary theories of ageing and in that sense the role of chance at advanced ages [32, 33] are in line with our findings on increased influence of nonshared environment with increasing age. Furthermore, understanding that ageing represents a progressive and roughly synchronous decline in function of many different organs and that the decline might be influenced by chance, lifestyle as well as heredity is of great importance for further research concerning age-associated diseases such as CHD.

Concordances as well as heritability for CHD-mortality in the present study may well be underestimated, as twin pairs with premature CHD-death occurring before the establishment of the registry in 1961 were not included in the registry. Nevertheless, the frailty model takes censoring into account as well as truncation of data. Gene–environment interactions as well as genetic interlocus interactions were not determinable by the genetic model, which may have resulted in a slight biased estimation of the crude genetic or environmental influences. Had there been assortative mating (positive) the genetic estimates would have been underestimated and shared environmental influences overestimated. However, it is difficult to imagine the process by which mates would assort for a specific cause of death. The differences in heritability of CHD-mortality between sexes [35] may to some part be explained by the interaction between genes and environment: this interaction may be particularly of importance in older ages as the influence of non-shared environment increases across time [35–40].

Results presented in this study are based on unique data drawn from the largest population-based twin registry in the world with a follow-up time of 36 years, where information on 4007 validated [41] CHD-deaths have been used. Our quantitative genetic findings can therefore be used as a basis for further research on the genetic mechanisms involved in death from CHD at different ages.

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