

Major Depression and Coronary Artery Disease in the Swedish Twin Registry

Phenotypic, Genetic, and Environmental Sources of Comorbidity

Kenneth S. Kendler, MD; Charles O. Gardner, PhD; Amy Fiske, PhD; Margaret Gatz, PhD

Context: Major depression (MD) and coronary artery disease (CAD) frequently co-occur. The mechanisms of comorbidity are uncertain.

Objective: To clarify sources of MD-CAD comorbidity.

Design: Major depression was assessed at the time of the personal interview, and CAD from hospital discharge records and death certificates.

Setting: Swedish population-based twin registry.

Participants: The study included 30 374 twins with a mean age of 57 years.

Main Outcome Measure: Modified *DSM-IV* diagnosis of MD or diagnosis of CAD.

Results: Lifetime association between MD and CAD was modest (odds ratio, ~1.3). In time-dependent Cox analyses, onset of CAD produced concurrent and ongoing hazard ratios for MD of 2.83 and 1.75. These risks increased if the diagnosis of CAD was restricted to myocardial infarction. Onset of MD increased the concurrent and on-

going hazard ratios for CAD to 2.53 and 1.17. The ongoing CAD risk was strongly associated with depressive severity and recurrence. Twin models showed that the modest comorbidity between MD and CAD in women arose primarily from shared genetic effects, although the genetic correlation was small (+0.16). In men, the source of comorbidity was moderated by age, being environmental in older members and largely genetic in younger members of the sample.

Conclusions: Although the MD-CAD relationship across the lifespan is modest, time-dependent models reveal stronger associations. The sustained effect of CAD onset on MD risk is much stronger than vice versa. The effect of MD on CAD is largely acute, and the longer-term effects are apparently mediated via depressive recurrence. When examined separately, in men, environmental effects, which are often acute, play a large role in MD-CAD comorbidity, whereas in women, chronic effects, which are in part genetic, are more important. In men, genetic sources of MD-CAD comorbidity are more important in younger members of the sample.

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Author Affiliations: Virginia Institute for Psychiatric and Behavior Genetics, Departments of Psychiatry (Drs Kendler and Gardner) and Human and Molecular Genetics (Dr Kendler), Virginia Commonwealth University School of Medicine, Richmond; Departments of Psychology, West Virginia University, Morgantown (Dr Fiske), and University of Southern California (Dr Gatz), Los Angeles; and Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden (Dr Gatz).

WHILE AN ASSOCIATION between major depression (MD) and coronary artery disease (CAD) has long been noted¹⁻³ and recently confirmed,⁴⁻⁸ the direction and cause of this association remain unclear. Because genetic factors are etiologically important in MD^{9,10} and CAD,¹¹⁻¹³ shared genetic risk factors may contribute to comorbidity. However, alternative causal mechanisms might be operative.¹⁴ The physiologic concomitants of MD, which include hypercortisolemia, inflammation, autonomic arousal, and altered platelet function¹⁵⁻¹⁷ might increase CAD risk. Coronary artery disease as a stressful event might increase MD risk^{18,19} or might reflect atherosclerosis processes that increase risk for MD via cerebrovascular dis-

ease.²⁰ A common set of environmental risk factors could predispose to both MD and CAD.²¹ Major depression could reduce treatment seeking for CAD or treatment compliance. To clarify the causal relationship between MD and CAD, predicted to be the 2 leading causes of morbidity worldwide by 2020,²² is important to help inform approaches to prevention and treatment.

In the Vietnam Era Twin registry, a substantial association was observed between depression and CAD, as assessed by self-report questionnaire, mediated entirely by genetic factors with a genetic correlation of +0.42.⁵ However, these twins (mean age, 42 years) were substantially younger than the median age of CAD onset.

We attempted to further elucidate the causal relationship between MD and CAD by the use of epidemiologic, longitudinal,

and twin modeling in the Swedish Twin Registry. A lifetime history of MD was assessed at personal interview at the mean age of 57 years. A history of CAD was assessed from hospital discharge information and death certificates. We also examined men and women separately because of prevalence differences between them for MD and CAD^{23,24} as well as previous evidence for sex differences in genetic influences on MD^{10,25} and on important precursors of CAD which include body mass index, insulin resistance, and dyslipidemia.²⁶

METHODS

SAMPLE

This sample originated from the population-based Swedish Twin Registry.²⁷ In the Screening Across the Lifespan Twin (SALT) Study, telephone interviews were conducted between March 1998 and January 2003 with all cooperative living members of the Registry who chose to participate and were born in 1958 or earlier. The project was approved by the Swedish Data Inspection Authority and the Ethics Committee of Karolinska Institute. The participation rate was 73.6%.

The epidemiologic and twin analyses used the 15 284 twin pairs with known zygosity and valid MD diagnosis in both members. Their mean age was 57.3 years, and 53.4% were women. The zygosity breakdown was as follows: 14.8% monozygotic (MZ) FF, 20.5% dizygotic (DZ) FF, 11.6% MZ MM, 16.7% DZ MM, and 36.4% DZ MF. The survival analyses required age-at-onset data, which were available for all CAD onsets because they were based entirely on registry data. Some participants with MD were missing valid age-at-onset data; thus, our survival analyses were based on 30 374 subjects from 15 284 pairs (15 090 complete and 194 with 1 twin). These 30 374 subjects were divisible into 6 categories: (1) no history of MD or CAD, $n=21\,894$; (2) MD and no CAD, $n=5275$; (3) CAD but no MD, $n=2751$; (4) both with onset of MD before CAD, $n=348$; (5) both with onset of CAD before MD, $n=82$; and (6) both with CAD and MD with onset in the same year, $n=24$. Our Mx models used twin pairs in which both were alive and eligible for the SALT Study and at least 1 twin was interviewed. This data set contained 21 180 complete pairs (42 360 individuals, of whom 36 046 had valid MD diagnoses). Of these pairs, 15 285 had complete information, whereas 5476 were missing a valid MD diagnosis in 1 twin and 419 were missing a valid MD diagnosis in both twins.

SOURCES OF DATA

Information was obtained from the SALT Study interview and linkages to the Swedish Inpatient Discharge Register (IDR) and the Cause of Death Register (CODR). The IDR, which contains primary and secondary hospital discharge diagnoses for all public hospitals in Sweden, was established in 1964 on a regional basis and expanded to complete coverage by 1987. The IDR uses *International Classification of Diseases (ICD)*²⁸ coding and also contains surgical procedure codes from the Classification of Operations (versions 1-7; 1964-1996) and the Nordic Medico-Statistical Committee Classification of Surgical Procedures (version 1.9; in use since 1997; revised in 2004²⁹). The CODR, (in place since 1749) is a nationwide register that contains underlying and contributing causes of death as classified by ICD code.

Major depression was assessed in the SALT Study by the Composite International Diagnostic Interview–Short Form.^{10,30,31} We used the recommended cutoff of 4 or more of 8 assessed criteria. Information about CAD was obtained from diagnoses and surgical codes in the IDR and cause of death codes in the

COD register by the use of the following *ICD-10* diagnoses (and equivalent diagnoses from earlier *ICD* versions): myocardial infarction (MI), acute, including old MI in *ICD-9* or subsequent MI in *ICD-10*; angina pectoris; other acute ischemic heart disease; chronic ischemic heart disease that includes coronary atherosclerosis (*ICD-9*); and asymptomatic ischemic heart disease (*ICD-8*) with the exclusion of complications after acute MI (*ICD-10*) or aneurysm and dissection of heart (*ICD-9*).

Surgical procedures indicative of CAD included: coronary artery bypass graft, coronary thromboendarterectomy, and all types of expansion and recanalization of the coronary artery (dilation, percutaneous transluminal coronary angioplasty with or without stenting, embolectomy, removal of a foreign body from the coronary artery, expansion using patch, and other recanalization). Excluded were repair of the coronary artery, closure of a coronary fistula, and other operations on coronary arteries. Age at onset for CAD was defined as the age at first diagnosis in the IDR. For some types of CAD such as angina, onset might precede the first hospital diagnosis by years. Therefore, we also conducted all of our survival models using “MI only” under the assumption that for this subform of CAD, onset and age at first hospital diagnosis will be similar in most cases.

STATISTICAL METHODS

Our survival analyses were based on the Cox proportional hazards model with time-dependent covariates.³² Because of strong cohort effects with both MD and CAD, data were stratified into 5-year birth cohorts. Thus, individuals were compared only with other members of their 5-year birth cohort, and age effects within the cohort are an inherent part of the time-to-event approach of the Cox model. Genetic influences were modeled with coding that reflects additive genetic effects (-1 and -0.5 for unaffected MZ or DZ co-twin and $+0.5$ or $+1.0$ for affected DZ or MZ co-twin, given that MZ twins share all their genes in common, whereas DZ twins share, on average, 50% of their genes by descent). The effect codes and covariate values were centered on the grand mean; thus, baseline represents an overall average set of risk factors. Tests of the proportional hazards assumption, that is, that the proportional effect of the key covariate variable on the hazard for the outcome variable was stable over time, were performed for each risk factor and covariate. Nonproportional hazards models, which permit the effect on the outcome variable to decay over time, were fit where appropriate. We adjusted our standard errors and test statistics for clustering of twin pairs using the method developed by Binder.³³

In our Cox models, onset of 1 disorder (MD or CAD) was the outcome variable, and onset of the other disorder was a time-dependent covariate. Therefore, in the analysis of, for example, the effect of CAD on MD risk, individuals would have a baseline hazard function that would increase in the year of CAD onset. In this model, individuals with MD onset before CAD are censored; thus, the time-dependent CAD risk applies to those who have no history of MD at the time of CAD onset, not to the population as a whole. Two forms of this time-dependent hazard ratio (HR) are calculated: a concurrent HR, which reflects the risk for MD in the year of CAD onset, and an ongoing HR, which represents the increase in MD risk in subsequent years. Our estimates of the concurrent HRs are based on only 24 individuals who report MD and CAD onset in the same year and, thus, are not known with high precision. To summarize, the Cox model is evaluated at each possible time point, and at each point, a subject is compared only with those uncensored members of his or her birth cohort.

Our twin models, fitted in Mx,³⁴ decomposed the variance and covariance in liability between MD and CAD into that due to additive genetic (A), shared environmental (C), and unique environmental (E) influences. We examined both quantitative

Table 1. Cox Model With Time-Dependent Covariates and Genetic Risk: Prediction of Major Depression

Variable	Study Participants								
	All			Men			Women		
	χ^2 ^a	P Value	HR (95% CI)	χ^2 ^a	P Value	HR (95% CI)	χ^2 ^a	P Value	HR (95% CI)
Prediction of MD									
Sex ^b	659.1	<.001	2.07 (1.96-2.18)
Zygoty ^c	0.7	.25	1.03 (0.96-1.10)	0.1	.79	1.02 (0.90-1.15)	0.5	.46	1.03 (0.95-1.11)
CAD concurrent	26.2	<.001	2.83 (1.90-4.21)	21.0	<.001	3.56 (2.07-6.13)	9.0	.003	2.43 (1.36-4.35)
CAD subsequent	24.1	<.001	1.75 (1.40-2.19)	16.8	<.001	1.96 (1.42-2.69)	12.4	.004	1.77 (1.29-2.44)
Genetic risk for MD	226.1	<.001	1.55 (1.46-1.64)	50.7	<.001	1.47 (1.32-1.64)	191.5	<.001	1.58 (1.48-1.69)
Genetic risk for CAD	0.3	.59	0.98 (0.91-1.06)	0.4	.53	0.96 (0.84-1.10)	0	.93	1.00 (0.91-1.10)

Abbreviations: CAD, coronary artery disease; CI, confidence interval; ellipses, no data available; HR, hazard ratio; MD, major depression.

^aAll *df*=1.

^bHR >1.0 indicates increased risk in women.

^cHR <1.0 indicates decreased risk in monozygotic twins.

Table 2. Cox Model With Time-Dependent Covariates and Genetic Risk: Prediction of Coronary Artery Disease

Variable	Study Participants								
	All			Men			Women		
	χ^2 ^a	P Value	HR (95% CI)	χ^2 ^a	P Value	HR (95% CI)	χ^2 ^a	P Value	HR (95% CI)
Prediction of CAD									
Sex ^b	403.7	<.0001	0.48 (0.45-0.52)
Zygoty ^c	1.9	.17	1.06 (0.98-1.15)	0.2	.67	0.98 (0.87-1.09)	4.1	.04	1.15 (1.00-1.31)
MD concurrent	20.7	<.001	2.53 (1.70-3.78)	17.5	<.001	3.16 (1.85-5.43)	6.2	.01	2.11 (1.17-3.83)
MD subsequent	7.2	.008	1.17 (1.04-1.31)	2.5	.12	1.15 (0.97-1.36)	3.9	.05	1.17 (1.00-1.37)
Genetic risk for CAD	84.9	<.001	3.06 (2.41-3.89)	68.9	<.001	3.32 (2.50-4.41)	23.0	<.001	2.78 (1.83-4.23)
Decay genetic risk for CAD	30.1	<.001	0.98 (0.98-0.99)	26.6	<.001	0.98 (0.97-0.99)	7.3	.007	0.99 (0.98-1.00)
Genetic risk for MD	0.3	0.57	1.02 (0.95-1.11)	0.7	.41	0.95 (0.85-1.07)	2.8	.10	1.10 (0.98-1.22)

Abbreviations: CAD, coronary artery disease; CI, confidence interval; ellipses, no data available; HR, hazard ratio; MD, major depression.

^aAll *df*=1.

^bHR <1.0 indicates increased risk in men.

^cHR >1.0 indicates decreased risk in monozygotic twins.

and qualitative sex effects including genetic correlations within disorder across sex, across disorder within sex, and across disorder across sex. Because of the large changes in prevalence, especially in CAD, with increasing age, our models used birth year as a moderator variable centered on the mean (SD): 1941.2 (11.5) years. The range of birth years was from 1900 to 1958. To adjust for cohort effects, birth year was used to adjust thresholds via linear regression and also to modify the variances of and correlations between the latent variables as linear adjustments to the square root of the variance and to correlations. These models require the constraint of the variances of the latent variables to unity at some specified value of the moderator, in our case, the mean. We tested both whether the estimates of A, C, and E and the genetic and environmental correlations between sexes, and especially between disorders, varied with birth year.

RESULTS

OVERALL ASSOCIATION OF MD AND CAD

Controlling for birth year, the Mantel-Haenszel odds ratio (OR) and 95% confidence interval (CI), and tetrachoric correlation and standard error between MD and CAD was 1.31 (1.15-1.49) and +0.08 (±0.02) in women.

The figures for men were 1.34 (1.16-1.55) and +0.09 (±0.02), respectively.

Standard Cox Models With Time-Dependent Covariates and Genetic Risk: Prediction of Risk of MD

We first predicted onset of MD from occurrence of CAD. The model indicated a large increased risk for MD onset associated with female sex ($\chi^2=669.5$; *df*=1; *P*<.001; HR, 2.13; 95% CI, 2.01-2.25), a substantial spike in the concurrent risk for depressive onset in the year of CAD onset ($\chi^2=26.5$; *df*=1; *P*<.001; HR, 2.84; 95% CI, 1.91-4.22), and a stable subsequent elevation in the ongoing rate of onset of MD ($\chi^2=24.4$; *df*=1; *P*<.001; HR, 1.75; 95% CI, 1.40-2.19). We found no evidence for the nonproportionality in these effects.

We then added to this model a control variable for zygoty and our weighted index of genetic risk to MD and CAD (**Table 1** and **Table 2**). Monozygoty did not predict risk for MD. Genetic risk for MD significantly predicted risk for depressive onset (HR, 1.55). However, controlling for the twins' own history of CAD, genetic risk for CAD did not further affect risk for MD (HR, 0.98).

Despite the strong predictive power of genetic risk for MD, its addition to the model did not affect the magnitude of the association between MD and CAD either in the year of CAD onset (HR, 2.83) or in subsequent years (HR, 1.75). That is, genetic risk factors for MD and a personal history of CAD independently affect risk for depressive episodes.

We ran this model separately for men and women (Tables 1 and 2). The pattern of results was broadly similar between the 2 sexes. However, the spike in risk for MD in the year of CAD onset was stronger in men (HR, 3.56) and greater than the elevated risk for MD in subsequent years (HR, 1.96). In women, the concurrent risk was more modest (HR, 2.43) and only modestly in excess of that noted subsequent to CAD onset (HR, 1.77).

Because age at onset may not be accurately dated from hospital data for all cases of CAD, we repeated the main analyses using only the diagnosis of MI. The pattern of findings was broadly similar to that for CAD. The spike in risk for depressive onset in the year of MI onset was substantially greater than that for CAD ($\chi^2=26.7$; $df=1$; $P<.001$; HR, 3.95; 95% CI, 2.35-6.66), whereas the stable subsequent elevation in rate of MD onset was more modestly increased ($\chi^2=18.7$; $df=1$; $P<.001$; HR, 1.95; 95% CI, 1.44-2.64).

Standard Cox Models With Time-Dependent Covariates and Genetic Risk: Prediction of Risk for CAD

We began by predicting the onset of CAD from MD occurrence. The model indicated a strong reduced risk associated with female sex ($\chi^2=397.5$; $df=1$; $P<.001$; HR, 0.47; 95% CI, 0.44-0.51), a substantial spike in risk for CAD onset in the year of MD onset ($\chi^2=21.2$; $df=1$; $P<.001$; HR, 2.56; 95% CI, 1.72-3.82), and a stable but modest subsequent elevation in risk for onset of CAD from that time onward ($\chi^2=6.90$; $P=.01$; HR, 1.17; 95% CI, 1.04-1.31). We found no evidence for the nonproportionality in these effects.

We then added to this model a control variable for zygosity and our weighted index of genetic risk for MD and CAD (Tables 1 and 2). Monozygosity was unrelated to risk for CAD. Genetic risk for CAD strongly predicted CAD onset (HR, 3.06). However, controlling for the twins' own history of MD, genetic risk for MD produced only a modest and nonsignificant effect on further risk for CAD (HR, 1.02). Now, however, our proportionality assumption failed. The effect of genetic risk for CAD, as indexed by CAD in co-twins, on risk for CAD onset declined with increasing age (HR, 0.98 per year). Of note, in this combined model, the effect of the history of MD on the concurrent (HR, 2.53) and subsequent (HR, 1.17) risk for CAD was nearly unchanged from the previous model.

We ran this model separately in men and women (Tables 1 and 2). The pattern of results had several important differences. The spike in risk for CAD in the year of MD onset is stronger in men (HR, 3.16) than in women (HR, 2.11). Controlling for personal history of MD, genetic risk for MD weakly predicted risk for CAD in women at a trend level (HR, 1.10) but had no such effect in men (HR, 0.95).

We then explored whether clinical features of MD, particularly severity and recurrence, were related to the prediction of CAD. We focused on the prediction of long-term CAD risk because these estimates are considerably more stable than those for year of onset. These Cox models control for zygosity, sex effects, birth cohort, and risk in year of onset. We found a strong relationship between clinical severity of MD and future risk for CAD. Twins who met the minimal number of symptomatic criteria for MD in the Composite International Diagnostic Interview–Short Form (4 criteria) had no significant increase in their long-term risk for CAD ($\chi^2=2.6$; $df=1$; $P=.11$; HR, 0.46; 95% CI, 0.07-3.27). Those who met 5 criteria had a nearly significant ongoing risk ($\chi^2=3.6$; $df=1$; $P<.06$; HR, 1.22; 95% CI, 0.99-1.51), and those who met 6 or more criteria had the highest ongoing risk ($\chi^2=14.4$; $df=1$; $P<.001$; HR, 1.33; 95% CI, 1.15-1.54). Individuals who reported a single depressive episode had no increased future risk for CAD ($\chi^2=0.1$; $df=1$; $P=.79$; HR, 1.03; 95% CI, 0.85-1.24); all risk for future CAD was concentrated in those who reported recurrent episodes ($\chi^2=7.3$; $df=1$; $P=.007$; HR, 1.32; 95% CI, 1.08-1.60).

TWIN MODELS

The first goal of our model fitting was to clarify the sources of resemblance of twins. We, therefore, began with an ACE model that included both qualitative and quantitative sex effects (model I: $-2LL=59\,235.4$; $df=78\,380$; Akaike information criteria [AIC]= $-97\,524.6$). We then dropped all shared environmental effects, and the resultant AE model had a much better AIC value (model II: $-2LL=59\,235.4$; $df=78\,387$; AIC= $-97\,538.6$). In contrast, the dropping of all genetic effects resulted in a much poorer fit (model III: $-2LL=59\,335.2$; $df=78\,389$; AIC= $-97\,442.8$). Next we constrained parameter estimates to equality across sexes; however, that also resulted in a poorer fit (model IV: $-2LL=59\,242.6$; $df=78\,389$; AIC= $-97\,535.4$).

We then added to model II 8 age moderation effects: for A and E each for men and women and for MD and CAD. This substantially improved the model fit (model V: $-2LL=59\,185.3$; $df=78\,379$; AIC= $-97\,572.7$), which indicated that genetic and environmental effects differed for MD and CAD as a function of age or birth cohort.

We examined whether any of the genetic and environmental correlations between MD and CAD separately in men and women and in opposite sex twin pairs were themselves modified by birth cohort. A modest improvement in the model fit was seen only when the genetic correlation between MD and CAD was allowed to vary in men, which produced our best-fit model (model VI: $-2LL=59\,183.0$; $df=78\,378$; AIC= $-97\,573.0$).

Parameter estimates for the best-fit model VI are presented for birth years 1930 (Figure, A) and 1953 (Figure, B), which represent, respectively, 1 SD above and below the mean in the sample. As noted earlier in these data,¹⁰ heritability for MD is higher in women than in men. Heritability of MD increases in more recent birth cohorts in both men and women. Heritability for CAD is higher in men than in women and increases in more recent birth cohorts in men but declines in more recent cohorts in women.

The genetic correlation between MD and CAD in men varied across cohorts, being negative in older members of the sample but positive, albeit modestly (+0.12), in the younger twins. In our best-fit model, all other correlations were constant. In women, the genetic correlation between MD and CAD was modest and estimated at +0.16. The environmental correlation in women was low (+0.04), and was particularly lower than in men (+0.13). The genetic correlation between men and women for MD and CAD was estimated at +0.62 and +0.67, respectively.

From our best-fit model, we can estimate the percentage of the comorbidity between MD and CAD that results from genetic and environmental risk factors, respectively, that affect the 2 disorders in men born in 1953 (41 of 59) and women born in 1930 (69 of 31) and 1953 (71 of 29). In men born in 1930, all of the MD-CAD comorbidity arises from environmental risk factors because genetic factors act to reduce the level of comorbidity.

COMMENT

Using time-dependent Cox models and twin modeling, we sought to clarify the causal relationship between MD and CAD in a large population-based sample of Swedish twins in middle to late adulthood. Six findings are noteworthy. First, the lifetime association between MD and CAD in this sample was modest (OR, ~1.3) and did not differ substantially in men and women. Second, in more informative time-dependent analyses, CAD onset was associated with a nearly 3-fold increased risk for depressive onset in that year and a nearly 2-fold increase in subsequent years. The long-term effect of CAD on risk for MD did not attenuate over time. Because the reliability of the dating of CAD onset from hospital data may be limited, we repeated these analyses using the diagnosis of MI. Both associations strengthened, which suggested that we were more likely underestimating than overestimating the temporal MD-CAD association with our hospital-based CAD diagnoses.

Third, given an onset of MD, the risk for CAD onset was increased 2.5-fold in that year and much more modestly (OR, ~1.2) in subsequent years. The ongoing increased risk for CAD after MD onset did not attenuate over time. Although modest, this future risk for CAD was strongly related to the severity and recurrence of MD. Indeed, elevated future CAD risk was confined to individuals with recurrent episodes of MD or those who meet more than the minimal number of diagnostic criteria.

Fourth, the temporal pattern of the prediction of MD onset from CAD onset differed across sexes. In men, the increased risk for MD was much greater in the year of CAD onset than in subsequent years. Women had a smaller concurrent spike in risk for MD in the year of CAD onset, and the subsequent risk was of nearly the same magnitude. These differences became even more striking when we examined only MI. In men, the spike in concurrent risk for MD in the year of MI onset was far greater than the subsequent risk (5.40 vs 1.95); in women, the difference was much more modest (2.65 vs 2.29).

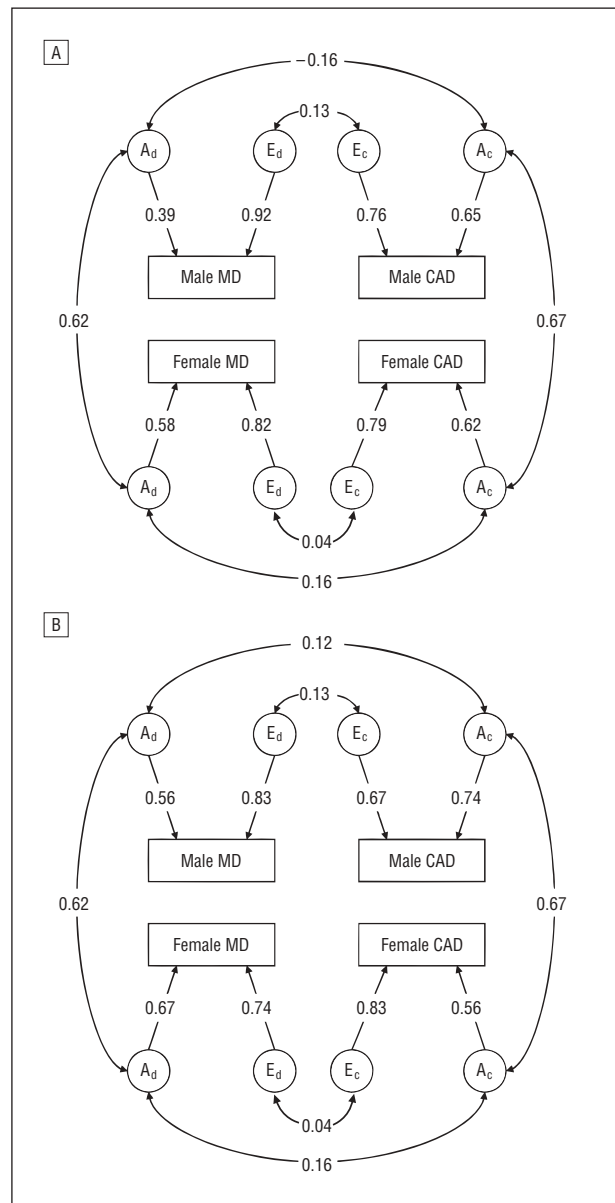


Figure. Best-fit twin models for birth years 1930 and 1953. Parameter estimates from our best-fit twin model (model VI) for major depression (MD) and coronary artery disease (CAD) estimated for birth year 1930, which is 1 SD below the mean birth year in the sample (A) and for birth year 1953, which is 1 SD above the mean birth year in the sample (B). Omitted from the models is the estimated genetic correlation between MD and CAD in opposite-sex twins of +0.09. A indicates additive genetic effects; E, individual specific environmental effects; subscripts d and c, MD and CAD, respectively.

Fifth, when genetic risk factors were added to these Cox models, there was consistently strong evidence for “within-disorder” genetic effects. Genetic risks for MD and CAD were, respectively, robust predictors of onset of MD and CAD. In contrast, “cross-disorder” effects were generally small and nonsignificant.

Sixth, our twin modeling provided the best picture of the genetic and environmental sources of comorbidity for lifetime MD and CAD. The results were relatively complex, with many of the model parameters showing variance by year of birth. Consistent with our lifetime association findings, the overall magnitude of the comorbidity between MD and CAD was modest. In confirmation of

our Cox results, differences were found in the source of this comorbidity by sex. In women, comorbidity was primarily owing to shared genetic effects, and this finding held across all age groups. In men, a similar pattern was seen only in the younger members of the sample. In the older men, genetic factors were, if anything, negatively correlated between the 2 disorders. Given the low prevalence rates for MD in these older men, this negative correlation should probably be regarded with some skepticism. Both our Cox and twin models, and the previous literature,¹¹ show that genetic factors are more potent in early- than in late-onset CAD. In men, therefore, it is the earlier onset and more genetically influenced forms of CAD that have a positive genetic correlation with MD.

INTEGRATION OF THE SURVIVAL AND TWIN MODELS

How can we integrate the Cox and twin-modeling results to develop a broader view of the etiologic interrelationship between MD and CAD and the way that that relationship is modified by sex? Unlike the twin models, the Cox model provided us with a temporally dynamic picture of the MD-CAD relationship. Two features of these results are noteworthy. First, we observed an important asymmetry in our prediction of enduring risk. The onset of CAD predicted ongoing risk for MD (HR, 1.75) much more strongly than the onset of MD affected long-term risk for CAD (HR, 1.17). Any complete understanding of the causes of this key comorbidity will have to explain this important finding.

Second, the concurrent association of MD and CAD was consistently stronger in men than in women. A similar pattern was not seen with the enduring risks. Putting these results together, we see that, compared with women, a larger proportion of the MD-CAD comorbidity in men arose from etiologic processes that were short-acting rather than enduring. This factor is of interest because genetic influences on comorbidity are likely to have long-lasting effects. Environmental effects, in contrast, can be short- or long-lived. Therefore, our Cox and twin models are congruent in pointing toward one key sex difference in MD-CAD comorbidity. While our twin models show that genetic factors are more important in MD-CAD comorbidity in women than in men, our Cox models show that enduring effects of each disorder on each other (which are likely genetic) are relatively more important in women than in men. Our Cox models show that short-term effects of MD on CAD risk and CAD on MD risk are more potent in men than in women. As we take all parts of our sample into consideration, our twin models show that environmental effects (which likely have short-term effects) play a greater role in MD-CAD comorbidity in men than in women.

PREVIOUS LITERATURE

The methods of this study were sufficiently different from those of most of the extensive previous literature on MD and CAD to render direct comparisons difficult. However, it is instructive to compare our findings with a recent study that addressed the MD-CAD relationship using

a different set of methods.³⁵ Surtees et al³⁵ assessed MD in 19 649 English subjects aged 41 to 80 years and followed them up for a median of 8½ years, and reported CAD-related deaths. First, they found that MD conveyed a 2.7-fold increased risk for CAD-related death, a figure somewhat higher than our concurrent HR (2.43). Our overall results, which combine our concurrent and persistent effects, are more in line with the OR of 1.60 estimated in a recent meta-analysis.⁸ Second, like us, Surtees et al³⁵ found no overall difference in MD-CAD association across sexes, and this was not found in the previous meta-analysis.⁸ Third, broadly consistent with our own findings, Surtees et al³⁵ reported a much greater risk for CAD when MD was reported to be present at the time of assessment vs in the past.

Our results do not agree with the one previous twin study of this issue,³ which found a stronger association between CAD and MD (OR, 4.03) and genetic correlation (+0.42) than we did. These differences could arise from several methodologic differences including the assessment of MD (diagnosis at personal interview vs symptom count), assessment of CAD (hospital summaries and death certificates vs self-report questionnaire), and age of the cohort (mean, 42 vs 57 years). In particular, onset of CAD before age 42 years is rare and atypical. Our results are broadly consistent with previous findings on the heritability of cardiac death,¹¹ angina,³⁶ and MI¹² in Swedish twins, and sex differences in heritability of precursors of CAD.²⁶

Our results have 2 implications for gene-finding efforts. First, given the modest genetic correlation, only a minority of risk genes for one of these disorders, that is, MD or CAD, are likely to affect risk for the other disorder. Although perhaps rare, such genes would be of great value in providing insight into the underlying pathophysiology of comorbidity. Second, if the goal is to uncover genes that affect MD-CAD comorbidity, it would be better to study women or early-onset CAD in men.

STUDY LIMITATIONS

Results of the present study must be interpreted in the context of 4 potential methodologic limitations. First, results are limited to Swedish twins and may not extrapolate to other ethnic groups. Second, in the upper age ranges of our cohort, a substantial percentage of the sample had died or were too ill to be interviewed. This attrition was nonrandom because MD³⁷ and CAD¹¹ predispose to premature death. Such attrition is more likely to attenuate than exaggerate the MD-CAD association. Our Mx models are more sensitive to this bias than our Cox models, in which all comparisons occur within 5-year cohorts. However, we were able to increase the generalizability of these models by the inclusion in all the analyses presented here of co-twins of interviewed twins who were eligible for the SALT Study interview but did not complete an interview either because they were too ill or they refused. The addition of these twins produced little change in parameter estimates. Third, in individuals with MD and CAD onset in the same year, we did not know which preceded the other. Thus, we have less ability to infer a causal relationship in our estimates of concurrent onset than of subsequent onset. Fourth, the validity of our conclusions rests substantially on the quality of the CAD di-

agnoses in the Swedish IDR and CODR. Previous studies have shown high positive predictive values for the diagnosis of MI (96%³⁸ and 86%³⁹) and other CAD diagnoses (81%³⁸ in the IDR and for CAD in the CODR (95%⁴⁰ and 92%⁴¹). Sensitivity has also been studied and found to be high for the diagnosis of MI in the IDR (94%³⁹) and for CAD in the CODR (94%⁴¹).

In conclusion, although the MD-CAD relationship across the lifespan is modest, time-dependent models reveal stronger associations. The sustained effect of CAD onset on MD risk is much stronger than vice versa. The effect of MD on CAD is largely acute, and the longer term effects are apparently mediated via depressive recurrence. When examined separately, in men, environmental effects, which are often acute, have a large role in MD-CAD comorbidity, whereas in women, chronic effects, which are in part genetic, are more important. In men, genetic sources of MD-CAD comorbidity are more important in younger members of the sample.

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Correspondence: Kenneth S. Kendler, MD, Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University, Box 980126, Richmond, VA 23298-0126 (kendler@vcu.edu).

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