QUARTERLY FOCUS ISSUE: PREVENTION/OUTCOMES

Early-Onset Depression, Anxiety, and Risk of Subsequent Coronary Heart Disease

37-Year Follow-Up of 49,321 Young Swedish Men

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Objectives	The purpose of this study was to investigate the long-term cardiac effects of depression and anxiety assessed at a young age, when reverse causation is not feasible.
Background	Most prospective studies found a relatively strong association between depression and subsequent coronary heart disease (CHD). However, almost exclusively, only middle-age or older participants were examined, and subclinical atherosclerosis might contribute to the observed association. The prospective association between anxiety and CHD was less evident in previous studies and has been subjected to similar methodological concerns on the possibility for a reverse causation.
Methods	In a nationwide survey, 49,321 young Swedish men, 18 to 20 years of age, were medically examined for military service in 1969 and 1970. All the conscripts were seen by a psychologist for a structured interview. Conscripts reporting or presenting any psychiatric symptoms were seen by psychiatrists. Depression and anxiety was diagnosed according to International Classification of Diseases-8th Revision (ICD-8). Data on well-established CHD risk factors and potential confounders were also collected (i.e., anthropometrics, diabetes, blood pressure, smoking, alcohol consumption, physical activity, socioeconomic position, family history of CHD, and geographic area). Participants were followed for CHD and for acute myocardial infarction for 37 years.
Results	Multiadjusted hazard ratios associated with depression were 1.04 (95% confidence interval [CI]: 0.70 to 1.54), 1.03 (95% CI: 0.65 to 1.65), for CHD and for acute myocardial infarction, respectively. The corresponding multiadjusted hazard ratios for anxiety were 2.17 (95% CI: 1.28 to 3.67) and 2.51 (95% CI: 1.38 to 4.55).
Conclusions	In men, aged 18 to 20 years, anxiety as diagnosed by experts according to ICD-8 criteria independently predicted subsequent CHD events. In contrast, we found no support for such an effect concerning early-onset depression in men. (J Am Coll Cardiol 2010;56:31–7) © 2010 by the American College of Cardiology Foundation

Most prospective studies found a relatively strong association between depression and subsequent coronary heart disease (CHD) events in initially CHD-free populations (1–9). However, previous research has had several potential limitations concerning causal inference.

It was noted that the greatest challenge in the research on a prospective association between depression and CHD is the possibility that both depression and subsequent CHD are caused by subclinical manifestations of cardiovascular disease (7). Atherosclerosis, the underlying pathophysiological mechanism of CHD, is known to develop during the

decades before the first clinical symptoms. However, most often the average length of follow-up was <15 years, and almost all studies included only middle-aged or older adults. Thus, individuals free of clinical CHD included in the aforementioned prospective studies may not have been free of atherosclerosis. Atherosclerosis may facilitate depressive symptoms even before clinical CHD symptoms (8,9).

Furthermore, very few population-based studies relied on expert diagnosis of depression. Questionnaires used for assessing depressive symptoms in previous investigations may not be specific for depression, but rather reflect a general distress. Thus, it could be difficult to separate depressive symptoms measured by these instruments from symptoms of a physical illness (5,6). On the other hand, studies relying on expert

Abbreviations and Acronyms

AMI = acute myocardial infarction

CHD = coronary heart disease

CI = confidence interval

ICD-8 = International Classification of Diseases-8th Revision

diagnosis of depression using selected clinical samples of psychiatric patients generally lack comparable reference groups (6,10,11). Moreover, previous reports inadequately controlled for the well-known cardiovascular risk factors (1).

A prospective relationship has been suggested between anxiety and CHD as well, although with less evidence of an association and with similar concerns over causality, especially concerning the possibility of a reverse causation (1,3,12,13).

It is imperative that we understand the issues relating to the potential cardiovascular implications of affective disorders exceedingly well. However, due to uncertainty concerning causal inference in previous research, depression and anxiety are not widely accepted as established risk factors for CHD (14–16).

The possibility of reverse causation could be minimized or eliminated using a healthy young population whose affective problems are unlikely to be influenced by subclinical or clinical cardiovascular disease. Therefore, we followed 49,321 young Swedish men for 37 years, an almost complete birth cohort of males born from 1949 to 1951, who were extensively examined for both somatic and psychological conditions before their military service at age 18 to 20 years. Depression and anxiety were evaluated by specialists, and major cardiovascular risk factors were also recorded.

Methods

The study was based on data from a nationwide survey of 49,321 young Swedish males, 18 to 20 years of age, born from 1949 to 1951, who were conscripted for compulsory military service in 1969 and 1970. Participants of this survey were extensively examined for somatic and psychological problems for 2 days. The examination team included several specialists such as cardiologists, psychologists, and psychiatrists. The background of the Swedish conscription surveys and the variables included were presented previously in more detail (17–22).

Diagnosis of depression and anxiety. All conscripts were seen by a psychologist for a structured interview (18). Those who reported or presented any psychiatric symptoms were seen by a psychiatrist and any diagnoses, primary or secondary, were recorded according to International Classification of Diseases-8th Revision (ICD-8) (23). Depression was defined as having a diagnosis of psychotic (296) or neurotic (300.4) depression. Anxiety was defined as anxiety neurosis (300.0).

During the years preceding this survey, efforts had been made to improve the quality of the psychological and psychiatric assessments during the military examinations (20). The psychiatrists were instructed to uniformly adopt the ICD-8

criteria for diagnostic conclusions, and the psychological examinations were regularly checked for inter-rater variability to maintain high quality and reliability (24). The threshold for referral to a psychiatrist was low, so that any psychiatric disorder could have been detected. Nearly one fifth of the conscripts were examined by a psychiatrist. The psychiatric evaluation took place at the end of the second day of the examination.

Follow-up. The health care system in Sweden provides virtually complete follow-up information for all patients by matching their unique 10-digit person identification numbers to health care registers. Hospitalization and mortality for CHD and acute myocardial infarction (AMI) were identified by the Swedish health registers (25).

In Sweden, the registration of hospital diagnoses started in 1964, but did not cover the whole country until January 1, 1987. However, participants were very young for CHD before 1987. Therefore, lack of full coverage is unlikely to modify our results.

Participants who emigrated from Sweden were censored at the date of emigration. Follow-up was closed on December 31, 2006. To this date, data with the necessary quality check were available. The average follow-up was 37 ± 1 years for the censored cases.

Covariates. INFORMATION COLLECTED AT THE CONSCRIPT EXAMINATION. Information on smoking was collected through a questionnaire, and all men were classified into 1 of 5 levels (nonsmokers, 1 to 5 cigarettes/day, 5 to 10 cigarettes/day, 11 to 20 cigarettes/day, >20 cigarettes/day).

Alcohol consumption was also assessed by a questionnaire. Participants were queried about the usual frequency and quantity of intake of the main beverage types (i.e., medium and strong beer, wine, and spirits). Average weekly alcohol intake was calculated in grams based on the estimated alcohol content of these beverages. Participants were categorized as abstainers or very low consumers (<1 g/week) and consumers of 1 to 100 g, 101 to 250 g, and >250 g of alcohol/week.

Height and weight was measured, and body mass index was calculated. However, because our analyses indicated that body height was a stronger confounder for the association between psychiatric diagnosis and outcome than was body mass index, we used it in our multivariable analyses instead of body mass index.

Blood pressure was measured on the first day of the conscript examination, after 5 to 10 min of rest. Only 1 measurement was performed unless systolic blood pressure exceeded 145 mm Hg or diastolic blood pressure was outside the range of 50 to 85 mm Hg. In that case, a second measurement was made on the next day and the resulting value was used in the subsequent analyses.

All conscripts were seen by a physician who diagnosed any disorders according to ICD-8. The diagnosis of diabetes was derived from these records.

We used active membership in sport clubs as a proxy for physical activity.

Geographic area was classified into 2 categories based on a northern or southern location of the county of residence in Sweden.

INFORMATION FROM REGISTERS ON PARENTS. Family history of CHD was defined as death known from CHD at age 55 years or younger for the father and 65 years or younger for the mother, as provided by the National Cause-of-Death Register. Biological parents were identified by the Swedish Multigeneration Register.

The conscripts and their fathers or other heads of household when different from the fathers were linked to each other through their personal identification numbers by Statistics Sweden. Information on childhood socioeconomic position was obtained from the National Population and Housing Census of 1960 (response rate: 99%) (i.e., when the participants were 9 to 11 years of age). The classification, into the following 6 socioeconomic groups, was based on information on the occupation of the father or the other head of the household: unskilled worker, skilled worker, farmer, nonmanual (lower level), nonmanual (medium level), nonmanual (higher level).

Statistical analyses. We used Cox proportional hazard models to examine the association between depression, anxiety, and cardiac outcomes. Unadjusted and multivariable-adjusted models, adjusted for smoking, body height, diabetes, systolic blood pressure, alcohol consumption, physical activity, father's occupation, family history of CHD, and geographic area, were performed. We evaluated the proportionality of hazards using formal 2-sided tests of interaction with time or log-time (all p values >0.10).

To assess possible effect modification, we conducted stratified analyses according to variables included in the multiadjusted models. Statistical analyses were performed using SAS version 9 for Windows (SAS Institute Inc., Cary, North Carolina).

Results

Characteristics of men who received a diagnosis of depression or anxiety during the conscript examination and of the rest of the cohort are presented in Table 1. In general, both depressed and anxious men were physically less active and smoked more cigarettes. Moreover, depression was associated with higher alcohol consumption, and anxiety was associated with higher blood pressure and higher prevalence of low childhood socioeconomic position in terms of having unskilled workers as fathers or other heads of households.

Table 2 shows the study characteristics in relation to future CHD events. Those in whom CHD developed had higher

Table 1	Characteristics of the Population				
	Depression			**Anxiety**	
	Yes	**No**		**Yes**	**No**
n	646	48,675		162	49,159
Systolic blood pressure, mm Hg	126 ± 13	126 ± 12		129 ± 13	126 ± 12
Body mass index, kg/m^2	20.7 ± 2.6	21.0 ± 2.6		20.3 ± 2.3	21.0 ± 2.6
Body length, cm	178 ± 7	178 ± 7		177 ± 6	178 ± 7
No. of cigarettes per day					
0	165 (26.1)	19,938 (41.6)		58 (36.3)	20,045 (41.4)
1–5	74 (11.7)	5,358 (11.2)		14 (8.8)	5,418 (11.2)
6–10	101 (16.0)	9,956 (20.8)		29 (18.1)	10,028 (20.7)
11–20	207 (32.8)	10,983 (22.9)		41 (25.6)	11,149 (23.1)
>20	85 (13.5)	1,660 (3.5)		18 (11.3)	1,727 (3.6)
Diabetes	2 (0.31)	39 (0.08)		0 (0)	41 (0.08)
Physically active	147 (22.8)	17,871 (36.8)		30 (18.5)	18,008 (36.6)
Alcohol consumption, g/week					
Abstainer, <1 g	39 (6.2)	2,742 (5.8)		15 (9.6)	2,766 (5.8)
1–100 g	342 (54.6)	33,184 (70.7)		91 (58.0)	33,435 (70.5)
101–250 g	188 (30.0)	9,359 (19.9)		46 (29.3)	9,501 (20.0)
>250 g	57 (9.1)	1,667 (3.6)		5 (3.2)	1,719 (3.6)
Childhood socioeconomic level*					
Unskilled worker	210 (33.5)	16,141 (33.9)		69 (44.0)	16,282 (33.9)
Skilled worker	145 (23.1)	10,402 (21.9)		32 (20.4)	10,515 (21.9)
Farmer	35 (5.6)	5,384 (11.3)		9 (5.7)	5,410 (11.3)
Nonmanual					
Lower level	85 (13.6)	4,912 (10.3)		16 (10.2)	4,981 (10.4)
Medium level	124 (19.8)	8,182 (17.2)		24 (15.3)	8,282 (17.2)
Higher level	28 (4.5)	2,556 (5.4)		7 (4.5)	2,577 (5.4)
Family history of CHD	14 (2.2)	996 (2.1)		2 (1.2)	1,008 (2.1)

Values are mean ± SD or n (%). *Father's occupation or occupation of the other head of household if it was not the father.
CHD = coronary heart disease.

Table 2	Characteristics of the Population According to Future Hospitalization and Mortality for CHD	
	CHD	
	Yes	**No**
n	1,894	47,427
Systolic blood pressure, mm Hg	127 ± 12	126 ± 12
Body mass index, kg/m²	22 ± 3.1	21.0 ± 2.5
Body length, cm	177 ± 6	178 ± 7
Number of cigarettes per day		
0	498 (26.8)	19,605 (42.0)
1–5	166 (8.9)	5,266 (11.3)
6–10	436 (23.5)	9,621 (20.6)
11–20	631 (34.0)	10,559 (22.6)
>20	126 (6.8)	1,619 (3.5)
Diabetes	9 (0.48)	32 (0.07)
Physically active	616 (32.5)	17,422 (36.7)
Alcohol consumption, g/week		
Abstainer, <1 g	90 (5.0)	2,691 (5.9)
1–100 g	1,234 (67.8)	32,292 (70.6)
101–250 g	410 (22.5)	9,137 (20.0)
>250 g	85 (4.7)	1,639 (3.6)
Childhood socioeconomic level*		
Unskilled worker	717 (39.1)	15,634 (33.7)
Skilled worker	438 (23.9)	10,109 (21.8)
Farmer	190 (10.4)	5,229 (11.3)
Nonmanual		
Lower level	164 (8.9)	4,833 (10.4)
Medium level	255 (13.9)	8,051 (17.4)
Higher level	71 (3.9)	2,513 (5.4)
Family history of CHD	96 (9.5)	914 (1.9)

Values are mean ± SD or n (%). *Father's occupation or occupation of the other head of household if it was not the father.
   Abbreviation as in Table 1.

blood pressure and body mass index, were shorter, physically less active, smoked more cigarettes, and more often had diabetes, a family history of CHD, and a lower childhood socioeconomic position.

Table 3 presents the relationship between depression, anxiety, and cardiac outcomes. The relative risk associated with depression for CHD and AMI was relatively weak and statistically nonsignificant and further decreased by multivariable adjustment. In contrast, anxiety was strongly associated with CHD and AMI, in both the unadjusted and multiadjusted models.

Among the covariates used in the multiadjusted models, smoking, alcohol consumption, physical activity, and blood pressure might be on the causal pathway between depression, anxiety, and cardiac events. Therefore, in additional multiadjusted analyses, we controlled for body length, father's occupation, family history of CHD, and geographic area (i.e., for factors that cannot possibly be mediators for the association). The hazard ratios for CHD hospitalization and AMI were 1.18 (95% confidence interval [CI]: 0.80 to 1.75) and 1.20 (95% CI: 0.75 to 1.90) for depression and 2.44 (95% CI: 1.44 to 4.14) and 2.82 (95% CI: 1.56 to 5.11) for anxiety in these models.

In our stratified analyses, we found no evidence of effect modification from the covariates included in this study.

Discussion

Our results did not suggest that depression, diagnosed by a psychiatrist in men at ages 18 to 20 years, would be a major risk factor in men for subsequent cardiac events later in life. When controlled for well-established vascular risk factors, we observed virtually null associations between depression and cardiovascular outcomes. In contrast, anxiety was relatively strongly associated with cardiac outcomes in all models.

A recent meta-analysis (2) of 21 prospective studies, including 124,509 participants and 4,016 events with a mean follow-up of 10.8 years, showed a pooled relative risk of 1.81 (95% CI: 1.53 to 2.15) for future CHD events associated with depression at baseline. The adjusted relative risk was 1.90 (95% CI: 1.49 to 2.42) in those 11 studies in which adjustments for cardiac risk factors were made. However, the authors concluded that depression cannot yet be included among the established independent CHD risk factors. They raised concerns about the possibility of a reverse causation and also of incomplete adjustment for conventional CHD risk factors.

Table 3	Depression, Anxiety, and Risk of CHD and AMI			
	Depression		**Anxiety**	
	Yes	**No**	**Yes**	**No**
n	646	48,675	162	49,159
CHD				
Cases	30 (4.6)	1,864 (3.8)	14 (8.6)	1,880 (3.8)
Unadjusted HR	1.26 (0.88–1.81)	1.00	2.30 (1.36–3.89)	1.00
Multivariable-adjusted HR	1.04 (0.70–1.54)	1.00	2.17 (1.28–3.67)	1.00
AMI				
Cases	22 (3.4)	1,273 (2.6)	11 (6.8)	1,284 (2.6)
Unadjusted HR	1.36 (0.89–2.07)	1.00	2.56 (1.46–4.80)	1.00
Multivariable-adjusted HR	1.03 (0.65–1.65)	1.00	2.51 (1.38–4.55)	1.00

Values are n (%) or hazard ratio (HR) (95% confidence interval). *Multivariable adjusted HR indicates HR adjusted for smoking (in 5 categories), body length, diabetes, systolic blood pressure, alcohol consumption (in 4 categories), physical activity, father's occupation (6 categories), family history of coronary heart disease (CHD), and geographic area (2 categories).
   AMI = acute myocardial infarction.

Moreover, they found some indication of a publication bias. Other authors also noted that reverse causation (i.e., the possibility that both depression and subsequent CHD are caused by subclinical manifestations of cardiovascular disease) is the greatest challenge in the research on a prospective association between depression and CHD (7).

The prospective association between anxiety and CHD is less evident in previous studies, but has been subjected to very similar methodological concerns about the possibility of a reverse causation (1). In the present study, early-onset anxiety was predictive of CHD and AMI in men. All participants underwent a detailed medical and psychological investigation, and anxiety was diagnosed by a psychiatrist. In these settings, a reverse causation is not feasible. It is also unlikely that a physical illness would be a common cause for anxiety symptoms and cardiovascular outcomes.

Sympathetic overactivity and autonomic dysfunction might explain the increased risk of cardiac events among participants diagnosed with anxiety. Several studies demonstrated a higher resting heart rate and decreased heart rate variability in association with anxiety (26). Hypertension might also mediate the relationship. Paterniti et al. (27) found a relatively strong graded association between hypertension and anxiety but not between hypertension and depression among older French men. The relationship was not found in women (27). In the present study, hypertension was slightly elevated among participants with anxiety, and controlling for hypertension somewhat decreased the observed association. One can hypothesize that the difference in hypertension increased between participants with and without anxiety during the follow-up. Furthermore, in addition to its contribution to coronary atherosclerosis, anxiety may also influence the risk of acute coronary events by triggering mechanisms (28).

In most previous studies, the average length of follow-up was <15 years and almost exclusively only middle age or older adults were included; thus, it is not possible to draw any inference regarding the cardiovascular importance of early-onset depression or anxiety. Participants free of clinical CHD at baseline were not necessarily free of subclinical CHD and atherosclerosis in these studies (7,8). Neuroimaging and neuropathological investigations suggest that otherwise silent cerebrovascular disease may predispose, precipitate, or perpetuate late-onset depression (29,30). Furthermore, extracranial manifestations of subclinical cardiovascular disease might also contribute to depressive symptoms and therefore to a spurious prospective association between depression and CHD. One possible pathway is the depressogenic actions of the increased inflammatory activity (31) that accompanies asymptomatic atherosclerosis (32).

Anxiety and depression are independent psychopathological conditions, although they share common symptoms and are very often comorbid (33). The self-report screening instruments used in most previous studies may not be very specific and perhaps reflect general distress. Furthermore, they may not be able to distinguish depression from anxiety (34), which, in light of our results, might have contributed to the observed

strong association between depression and subsequent cardiac events in these studies.

Study limitations. The psychiatric diagnoses were based on the ICD-8 classification system, and the diagnostic categories are not directly transferable to later ICD or to Diagnostic and Statistical Manual of Mental Disorders classifications. Concerning affective disorders, the concordance between ICD-8 and later diagnostic systems is generally good. The most relevant difference is that the latter ones are broader and able to identify more patients including the less severe cases (35). Anxiety neurosis defined in ICD-8 corresponds to both generalized anxiety and panic disorders but not to phobic anxiety disorders in contemporary classifications. Today, psychotic and neurotic depression per the ICD-8 would be included among depressive and bipolar disorders.

The prevalence of depression and anxiety was considerably lower in our sample than in previous prospective studies on affective disorders and cardiovascular risk, especially compared with studies relying on self-reported symptoms, but not largely different from the corresponding prevalence for adolescent males in Swedish and international samples relying on similar diagnostic methods (36–39). We also emphasize that the threshold for referral to a psychiatrist was low, so that any psychiatric disorder could have been detected. Nearly one fifth of the conscripts were examined by a psychiatrist. Nevertheless, we can assume that only severe cases would have been identified by today's standards.

Lower prevalence itself should not explain the null association for depression found in this study. As Nicholson et al. (2) concluded in their meta-analyses, studies with a low prevalence of depression found stronger depression-CHD associations, probably because a lower prevalence of depression also denotes more severe depression. Furthermore, we found a relatively strong effect for anxiety, although its prevalence was lower than that of depression. Nevertheless, direct comparison of our study with those of the prospective association between affective disorders defined by later diagnostic criteria or by applying questionnaires and cardiovascular outcomes should be done with caution. Moreover, the low prevalence of depression and anxiety did not allow us to analyze their joint effect on CHD.

Apart from the low prevalence of depression and anxiety and the relatively low number of cases of CHD and AMI, which is attributable to the young age of participants, our study was well powered. To the best of our knowledge, we analyzed a greater number of person-years than in any other studies, even greater than the aforementioned meta-analyses of the prospective association between depression and CHD (2), which summarized 21 previous prospective studies.

When investigating the association between exposures at an early age and coronary events, which occur predominantly in middle age or later, long follow-up is inevitable. The lack of an association between depression and cardiovascular outcomes in the present study might be attributable to the length of follow-up (i.e., that the effect of depression was diluted during the long follow-up period). However, depression is a highly recurrent disease. The National Institute of Mental Health

Collaborative Depression Study found that the cumulative probability of recurrence is 60% at 5 years for patients with major depression and the risk of the recurrence of major depressive disorder progressively increases with each successive episode (40). Moreover, earlier onset of depression is related to greater risk of recurrence (41), and depression starting in childhood or adolescence is a particularly serious form (42). We emphasize that despite the lengthy follow-up, all established vascular risk factors, measured during the conscript examination at age 18 to 20 years, were related to outcomes with an effect size corresponding to previous investigations. Also, in contrast to the null effect on depression, anxiety was strongly associated with coronary events.

Although, we adjusted for a wide range of possible confounders and established cardiovascular risk factors, it should be emphasized that we did not include cholesterol, and controlling for physical activity was based on membership in sport clubs, which is only a proxy for the real exposure. Moreover, we had information on smoking and drinking habits only at late adolescence, which may poorly reflect the lifetime exposure. Smoking and drinking habits are candidate mediatory mechanisms for the association of affective disorders with CHD. Thus, the lack of repeated data limited our analyses of the intermediatory factors. We found that these lifestyle factors measured at late adolescence had similar associations with future cardiovascular outcomes to studies with shorter follow-up in older participants. However, it is important to emphasize that it was not possible to investigate and control for lifelong exposure to smoking and to other important coronary risk factors in this study.

Because we investigated exclusively only men, we cannot directly extrapolate our findings to women. The sexes differ in their risk of both cardiovascular and affective disorders. Previous studies found varying results concerning the effect of sex on the association between depression and CHD. Some studies concluded that depression is a risk factor only in men (43,44), whereas others (45) found the opposite.

Our study population was relatively young, even at the end of the follow-up. Therefore, we cannot exclude the possibility that depression is related to cardiovascular outcomes later in the follow-up. However, we emphasize that in the absence of a true biological interaction between depression and age on their association with cardiovascular risk, one would expect a higher relative risk of depression in younger populations because their underlying risk is lower than that for elderly individuals (46).

As with any null results, misclassification of the exposure or outcome is a potential explanation for the lack of association between depression and cardiac events. Due to the aforementioned conditions (i.e., detailed medical examination and the specialists' diagnosis of depression), the exposure is most probably less misclassified in the present study than in most previous studies. Moreover, the likelihood of a reverse causation is minimal in our study. We also claim that the ascertainment of outcome was generally more precise and the follow-up was more complete in the present study compared with earlier

investigations. Information on cardiovascular events was gathered by an automated search of the comprehensive Swedish health registers. The Swedish health registers provide high-quality information with a high degree of reliability (25). We also emphasize that in Sweden the health care system is equally accessible to all citizens and participation in the hospital registers is unavoidable. Consequently, all patients who sought help had the possibility of getting adequate treatment and consequently being registered. Therefore, together with our earlier notion of the replication of the expected relationships between conventional factors and subsequent cardiac events and the finding that anxiety predicted such events, we conclude that misclassification is an unlikely explanation for the lack of association between depression and cardiac outcome.

Our measurement of blood pressure also had limitations. The white-coat effect was recognized as a benign condition at that time and interest was focused on "true" hypertension. Recent data indicate that the risk of organ damage in patients with white-coat hypertension is higher than that of normotensive individuals but lower than that of patients with true hypertension (47). It is not clear whether white-coat hypertension is associated with anxiety. There are both positive (48) and negative (49) findings. The current circumstances (i.e., having data only for a second measurement for those showing high initial values) do not allow us to estimate the possible effect of stress due to the examination or the white-coat effect. Thus, we may underadjust for blood pressure as a mediating variable associated with anxiety.

Conclusions

We uniquely investigated the long-term relationship between depression and anxiety, diagnosed by experts in men at age 18 to 20 years and the subsequent long-term CHD outcome in a large sample of men. Anxiety but not depression was predictive for CHD events later in life in the present study. Our findings may indicate that only early-onset anxiety but not depression is a risk factor for CHD in men.

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