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Is depression a risk factor for heart complaints?

Longitudinal aspects in the Zurich study

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Abstract *Background* The objective of this longitudinal study was to assess the association between major depression and heart complaints in a population of young and healthy adults. *Methods* Starting at the age 20/21, participants of the Zurich Study underwent 6 structured, psychological interviews during a span of 20 years. We evaluated longitudinal data from 277 persons who participated in all 6 interviews including questions about heart complaints. *Results* Over 20 years, heart complaints were reported by two thirds of participants, and the frequency of depression was 11.4%. At the age of 40/41, heart complaints were significantly associated with earlier heart complaints and major depression, both more often in women. Recurrent brief depression

showed a tendency, but neither minor depression nor depressive symptoms were predictive for later heart complaints. *Conclusions* This study suggests that major depression is a predictor for heart complaints at the age of 40 and that the severity of depressive disorder in younger age has an effect on subsequent heart complaints. Follow-up data will help to elucidate whether these subjective heart complaints show any correlation with a later coronary heart disease.

Key words epidemiology · heart complaints · major depression · minor depression · recurrent brief depression

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Introduction

Depressive syndromes, including major depression, are common. In the National Comorbidity Study, lifetime prevalence rates of major depression were reported to be 13% [16], in the Epidemiologic Catchment Area Study 6% [15]. Minor depressive disorder is also common both in the community [15] and in primary care clinics [21].

Coronary heart disease (CHD) is the leading cause of death and a major cause of morbidity and disability in Western industrialized countries. Depressive syndromes in persons with cardiovascular disease (coronary artery disease or coronary heart disease being one form of it) are rarely diagnosed, even if the prevalence of major depression is nearly 20% in persons with CHD [8, 13, 14, 25]. Depressive disorders are now recognized as a predictor of poor outcome in individuals with established cardiovascular disease [12, 13]. In a recent review [28], depressive disorders were found to be an independent risk factor for new events in patients with pre-existing coronary disease. Possible pathophysiological mechanisms, including cardiovascular autonomic dysregulation, by

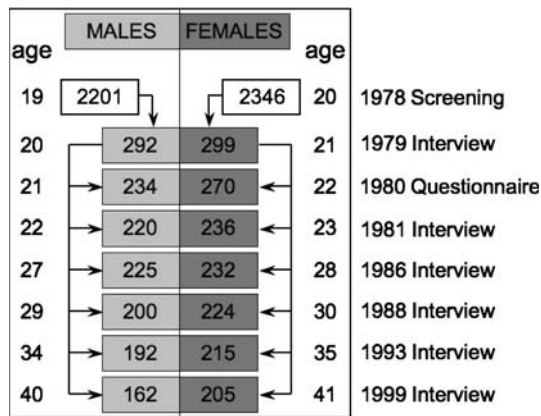


Fig. 1 Design of the Zurich Study 1978–1999

which depression may contribute to CHD were described previously by Musselmann et al. [19] and Carney [7]. However, traditional risk factors, such as tobacco use, hypertension, and obesity, explain at least 75% of the occurrence of new cases of cardiovascular disease [26].

Although “heart complaints” do not have the status of a disease and are not a defined predictor for CHD, they can be associated with depression. We thus hypothesized that if a correlation could be established between heart complaints and depression in a young population, it might stimulate further research into the prognostic link between heart complaints, depression, and the subsequent development of CHD.

The aim of this study was therefore to conduct the first quantitative assessment of the association between major depression and heart complaints in a population of young adults. We addressed this question by analyzing 20 years of longitudinal data of the Zurich Study. For conceptual clarity we focused on depressive disorders as there is ample evidence that depression and coronary disease are strongly associated with each other [11, 23, 24, 28]. Quantitative estimates of the magnitude of depression’s effect on heart complaints will allow comparison with known risk factors, such as smoking, caffeine intake, obesity, physical inactivity and previous heart complaints as well as psychosocial factors such as social class, mastery, hostility and anxiety [17] and coping strategies.

Methods

The Zurich Study is a longitudinal epidemiological study that started in 1979 with a sample of 591 participants (292 men born in 1959 and 299 women born in 1958). The participants were selected from a representative sample of 4,547 young adults from the Canton Zurich in Switzerland according to scores of the SCL-90R Global Severity Index (GSI) [9] obtained from screening interviews carried out in 1978. Two thirds of the sample scored above the 85th percentile (high scorers) and one third below (low scorers).

The mean GSI of the 591 participants in the Zurich study in 1978 was 0.8 (SD = 0.53), whereas the mean GSI of the original representative screening sample ($N = 4547$) was 0.4 (SD = 0.39).

The study participants were interviewed in 1979, 1981, 1986, 1988, 1993, and 1999, thus covering a period of 20 years from age 20/21 to age 40/41 (see Fig. 1). Overall, 278 (47.0%) participants of the initial sample underwent all six interviews. In 1999, 367 participants (62.5%) could be interviewed. Compared with the initial sample, the proportions of high scorers and low scorers did not change significantly [10].

Participants were interviewed at their homes by trained clinical psychologists and psychiatric residents. The instrument used was SPIKE (Structured Psychopathological Interview and Rating of the Social Consequences of Psychic Disturbances for Epidemiology), a semi-structured diagnostic interview developed for the Zurich Study [3]. SPIKE collects information on psychiatric and somatic syndromes, including questions on heart complaints, depression and the use and abuse of various substances.

From the beginning in 1979, the presence of heart complaints as subjectively perceived by the participants was assessed. The assessment of heart complaints started with the probe question: “During the last 12 months, have you suffered from heart problems (cardiac irregularity, strong palpitation)?” For heart complaints as well as for all other syndromes covered in SPIKE, symptoms, duration, frequency, subjective degree of suffering, treatment, and partly social consequences were assessed for the last twelve months prior to the interview. Additionally, two potentially cardiac symptoms of the SCL-90 R were included: pain in the heart or chest region, and heart pounding or racing. In contrast to the SPIKE, SCL-90R answers refer to the last month prior to the interview.

Depression was assessed starting with the probe question: “During the last 12 months, have you ever felt lack of energy, depressed, sad, sick of life, or have you experienced loss of productivity, feeling of inferiority, no interests at all? Or simply spoken spiritless?”. Major depressive disorder was defined according to DSM-IV [1] criteria, and recurrent brief depression (RBD) according to criteria by Angst et al. [4, 5]. RBD was defined by the same number of symptoms as MDD, but having a duration of at least 1 day but less than 2 weeks, and a total duration of at least 1 month over 1 year, and by work impairment. Minor depression (MinD) was defined as a depressive syndrome with 2–3 of the nine criterial symptoms for MDE and a minimum duration of 2 weeks [2].

For categorical data, statistical analyses were based on chi-square statistics and logistic regression analysis. Of the features selected for use as explanatory variables, 5 referred to information assessed during 1988 (namely nicotine intake, body mass index, circulatory problems, coping/rumination, heart complaints), and 3 referred to information assessed during 1986 (namely practicing sports, caffeine intake, and mastery meaning control beliefs about health). Another four features referred to socio-economic information (namely father’s occupation, education, social class, social support) assessed in 1979. For each interview wave, assessments of MDD, RBD and MinD were also made.

Results

Overall, 278 participants participated in all interviews from 1979 to 1999. The following results are based on the 277 participants who answered the probe question within the syndromal section heart complaints in 1999.

In 1999, 83 participants (30%) of this sample reported heart complaints. Half of them complained of pain in the heart or chest region (chest pain), three-quarters of palpitations. Women showed slightly higher rates of heart complaints than men (33.5% vs. 25%, n.s.). Weighted by high versus low scorer status, 32.5% of participants are expected to suffer from

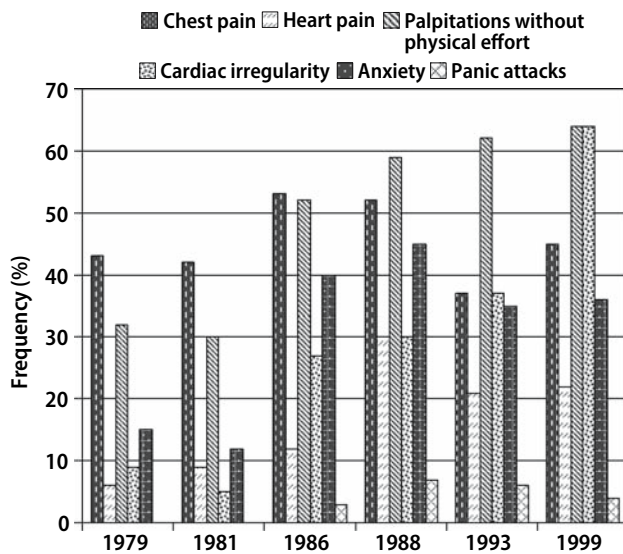


Fig. 2 Heart symptoms reported by Zurich Study participants with positive answer to the probe question between 1979–1999

heart complaints (95% CI: 30.5–34.6). Pain in the heart or chest region as assessed by cardiac symptoms of the SCL-90R was reported by 45 participants (57.7%) with positive answer to the probe question, heart pounding or racing by 38 participants (48.7%). Within the syndromal section anxiety, agoraphobia and/or panic disorder, palpitations were indicated by 32 participants (38.5%) of the sample (Fig. 2).

During the entire study period, 14 participants (16.9%) suffering from heart complaints sought professional help: 13 consulted a practicing physician, two were hospitalized, and two required medical help from other sources (psychologists, naturopathic physicians). Medication prescribed by physicians to counteract heart complaints was reported by two subjects. Medication consisted in analgetics, sedatives and betablockers. In regard to social consequences, 11

participants (13.2%) considered themselves as impaired at work.

The number of participants who reported heart complaints at one of the interviews between 1979 and 1999 was 77 (27.8%), at two interviews 40 (14.4%), and at least at three interviews 61 (22%). Overall, two thirds of participants reported heart complaints at least in one of the interviews.

In bivariate analyses, heart complaints in 1999 were significantly correlated with smoking, body mass index (BMI), and previous heart complaints as well as with the SCL-90R factors hostility/anger and anxiety (Table 1). Participants with heart complaints reported slightly (n.s.) more often circulatory problems than participants without heart complaints (37.3% vs. 26.8%). No correlations were found with gender, caffeine intake, sport activity, coping/rumination, and mastery. Referring to socio-economic variables, only social class correlated significantly with heart complaints.

Of the 83 participants reporting heart complaints in 1999, 42 (50.6%) were given a diagnosis of MDD at least at one of the six interviews 1979–1999, 33 (39.8%) at least one diagnosis of RBD and 12 (14.5%) at least one diagnosis of MinD. Thus, participants with at least one diagnosis of MDD in their previous history reported significantly more often heart complaints in 1999 than participants without any diagnosis of MDD (50.6% vs. 37.6%, χ^2 (1, $N = 277$) = 4.030, $P = .031$). MDD occurred slightly more often in females than in males reporting heart complaints at age 40/41 years (57.4% vs. 37.9%, n.s.). In a bivariate logistic regression, the association between MDD and heart complaints was significant (OR = 1.7, 95% C.I. 1.01–2.85, $P < 0.05$). Adding the predictor variables smoking, BMI, previous heart complaints, social class and SCL anxiety to the model did not weaken the association, but the statistical significance of the overall model was marginal (OR = 1.7, 95% C.I. 0.93–2.94, $P < 0.09$). Moreover,

Table 1 Variables representing risk factors for heart complaints in 1999

		With HC (%)	without HC (%)	
Smoking	Non-smoker	47 (58.8)	109 (62.0)	χ^2 (2, $N = 256$) = 6.573, $P = .037$
	1–10 cigarettes/day	4 (5.0)	24 (13.6)	
	>10 cigarettes/day	29 (36.3)	43 (24.4)	
		100%	100%	$N = 256$
Previous heart complaints	With	24 (28.9)	20 (10.5)	χ^2 (1, $N = 273$) = 14.449, $P = .000$
	Without	59 (71.1)	170 (89.5)	
BMI	<25	77 (92.8)	161 (84.7)	χ^2 (1, $N = 273$) = 3.336, $P = .047$
	>25	6 (7.2)	29 (15.3)	
Social class	Student	22 (26.5)	42 (21.6)	χ^2 (3, $N = 277$) = 9.515, $P = .023$
	Employee	27 (32.5)	52 (26.8)	
	Apprentice/skilled worker	16 (19.3)	73 (37.6)	
	Unskilled worker	18 (21.7)	27 (13.9)	
Hostility/anger (SCL-90R)	Low	19 (24.4)	69 (36.3)	χ^2 (1, $N = 268$) = 3.585, $P = .039$
	High	59 (75.6)	121 (63.7)	
Anxiety (SCL-90R)	Low	22 (28.2)	82 (43.2)	χ^2 (1, $N = 268$) = 5.207, $P = .015$
	High	56 (71.7)	108 (56.8)	

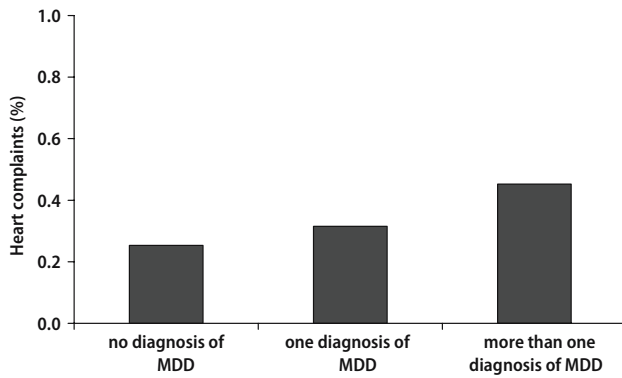


Fig. 3 Percentage of participants indicating heart complaints in 1999 (χ^2 (2, $N = 277$) = 6.425, $P < .05$)

an association between the number of diagnoses of MDD and heart complaints reported in 1999 can be observed (Fig. 3). There was no analogous difference for diagnosis of RBD and MinD.

Discussion

This 20-year-long follow-up of young subjects provides unique data regarding the development of heart complaints and depression over time and their correlation with each other. We found that both heart complaints and MDD remained relatively constant over time, with MDD showing a trend toward higher frequency with older age. The fact that heart complaints were themselves predicted by prior heart complaints indicates that the same participants complained of them repeatedly. The main finding of this study is that heart complaints were significantly associated with major depression, and the association was reduced only little when adjusted for other risk factors. Recurrent brief depression showed a non-significant trend towards association with heart complaints, but no other (minor) depressive disorders or depressive symptoms predicted subsequent heart complaints.

The somatic value of the term “heart complaints” cannot be ascertained because the complaints represent the subjective perception of the participants, as reported during the interviews. Because the last interview reported here took place at the age of 40/41 years, it is not surprising that only few participants had reported diagnosed somatic heart disease by the end of the study period. Since the population presented in the study is relatively young, we cannot expect that traditional risk factors for CHD will already have made a considerable impact at this young age. Although smoking was correlated with heart complaints, body mass index showed an unexpected, negative correlation. These relationships must be interpreted with caution, because somatic correlates are lacking. Complaints reported by the partic-

ipants, such as heart pain, palpitations, or irregular heart beat can be caused by a variety of somatic diseases or have no physical correlation at all, and this study was not designed to ascertain the somatic correlates of the subjectively reported complaints. We are not aware of any predictive association between general heart complaints and subsequent development of CHD or other somatic problems. Nonetheless, subjective heart symptoms can be extremely disturbing, can affect the quality of life, and even lead to hospitalization in some cases. Our data suggest that the influence of depression on heart complaints occurs without a concurrent somatic disease and independently of the traditional risk factors for CHD, at least until the age of 40.

The frequency of depression in our sample is with 11.4% (lifetime prevalence) in the expected range. MDD has been reported in 11.8% of unselected young adults [27].

Depression has been found to be a significant risk factor for primary CHD or for mortality in patients already suffering from CHD [6, 11, 20, 22, 29]. After adjustment for other risk factors, depression increased the risk for CHD events by 1.15–3.9 times in persons without previous CHD, and by 1.4 to over 6 times in persons with CHD [18]. Non-adherence to risk factor modification, abnormal platelet function, endothelial dysfunction, reduced heart rate variability, and overall cardiovascular autonomic dysregulation have all been associated with depression and may be pathophysiologically responsible for the association between depression and CHD (reviewed by Zellweger [29], Carney [7], and Nicholson [20]). However, the role of depression as an independent risk factor for CHD is still debated, particularly because of incomplete risk factor adjustments in many studies and the possibility of reverse causality [20]. Our sample is younger than most of the other populations studied. As our cohort of study participants ages, new cases of CHD are likely to occur, and those in whom MDD has been diagnosed must nevertheless be considered at higher risk for such events. This will continue to be assessed within the study. The association between heart complaints, depression, and the possible subsequent development of CHD continues to require further study.

There are several limitations to our study that should be discussed. First heart complaints were self-reported and were not verified objectively. The heart complaints were not assessed exactly the same way in the six interview waves, but the key questions remained constant. Second, although the SPIKE has been shown to have good reliability and validity for depression and anxiety, there is a possibility of misclassification of exposure. Third, we were unable to look at mortality from heart disease, but as there are only 16 persons at the time of writing of this manuscript who died, the small number can be neglected. We also were unable to study specific medication (as

only two persons were medicated), to adjust for length of time of medication use and dosage and finally, the ascertainment of medication was by self-report. Fourth, as in most community based cohort studies, losses to follow-up did occur in our study, but those missing did not differ significantly from those successfully re-interviewed. Information on coronary risk factors such as RR measures or cholesterol levels would strengthen our study but is missing.

Conclusions

The Zurich Study has several strengths. It is a population-based investigation consisting of two cohorts, men being 20-years-old, women 21 years of age. The study is prospective in design, has its focus on young people, following them for 20 years. This allows some confidence in our assessment of temporal relationship of heart complaints and MDD. The study investigated not only mental disorders but from the beginning on also collected data on subjective heart symptoms and other somatic syndromes.

We conclude that MDD is significantly associated with heart complaints and that heart complaints tend to re-occur in the same people. Complaints of heart symptoms in young people should prompt for the diagnostic evaluation of a possible depression. Further study is needed to elucidate the potential predictive value regarding the development of a later CHD.

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References

- American Psychiatric Association (2000) Diagnostic and statistical manual of mental disorders: DSM-IV-TR. American Psychiatric Association, Washington
- Angst J, Dobler-Mikola A (1985) The Zurich study—a prospective epidemiological study of depressive, neurotic and psychosomatic syndromes. IV. Recurrent and nonrecurrent brief depression. *Eur Arch Psychiatry Clin Neurosci* 234:408–416
- Angst J, Dobler-Mikola A, Binder J (1984) The Zurich study—a prospective epidemiological study of depressive, neurotic and psychosomatic syndromes. I. Problem, methodology. *Eur Arch Psychiatry Clin Neurosci* 234:13–20
- Angst J, Hochstrasser B (1994) Recurrent brief depression—the Zurich study. *J Clin Psychiatry* 55:3–9
- Angst J, Merikangas K, Scheidegger P, Wicki W (1990) Recurrent brief depression—a new subtype of affective disorder. *J Affect Disord* 19:87–98
- Aromaa A, Raitasalo R, Reunanen A, Impivaara O, Heliövaara M, Knekt P, Lehtinen V, Joukamaa M, Maatela J (1994) Depression and cardiovascular diseases. *Acta Psychiatr Scand Suppl* 377:77–82
- Carney RM, Freedland KE, Veith RC (2005) Depression, the autonomic nervous system, and coronary heart disease. *Psychosom Med* 67:S29–S33
- Carney RM, Rich MW, Freedland KE, Saini J (1988) Major depressive disorder predicts cardiac events in patients with coronary artery disease. *Psychosom Med* 50:627–633
- Derogatis LR (1977) SCL-90R. Administration, scoring and procedures manual for the R (revised) version and other instruments of the psychopathology rating scale series. Johns Hopkins University School of Medicine, Chicago
- Eich D, Ajdacic-Gross V, Condrau M, Huber H, Gamma A, Angst J, Rössler W (2003) The Zurich study: participation patterns and symptom checklist 90-R scores in six interviews, 1979–1999. *Acta Psychiatr Scand* 108:11–14
- Ford DE, Mead LA, Chang PP, Cooper-Patrick L, Wang NY, Klag MJ (1998) Depression is a risk factor for coronary artery disease in men: the precursors study. *Arch Intern Med* 158:1422–1426
- Forrester AW, Lipsey JR, Teitelbaum ML, DePaulo JR, Andrzejewski PL, Robinson RG (1992) Depression following myocardial infarction. *Int J Psychiatry Med* 22:33–46
- Frasere-Smith N, Lesperance F, Talajic M (1995) Depression and 18-month prognosis after myocardial infarction. *Circulation* 91:999–1005
- Gonzalez MB, Snyderman TB, Colket JT, Arias RM, Jiang JW, O'Connor CM, Krishnan KR (1996) Depression in patients with coronary artery disease. *Depression* 4:57–62
- Johnson J, Weissman MM, Klerman GL (1992) Service utilization and social morbidity associated with depressive symptoms in the community. *JAMA* 267:1478–1483
- Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen H-U, Kendler KS (1994) Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. *Arch Gen Psychiatry* 51:8–16
- Kubzansky LD, Kawachi I (2000) Going to the heart of the matter: do negative emotions cause coronary heart disease? *J Psychosom Res* 48:323–337
- Lett HS, Blumenthal JA, Babyak MA, Sherwood A, Strauman T, Robins C, Newman MF (2004) Depression as a risk factor for coronary artery disease: evidence, mechanisms, and treatment. *Psychosom Med* 66:305–315
- Musselman DL, Evans DL, Nemeroff CB (1998) The relationship of depression to cardiovascular disease. *Arch Gen Psychiatry* 55:580–592
- Nicholson A, Kuper H, Hemingway H (in print) Depression as an aetiologic and prognostic factor in coronary heart disease: a meta-analysis of 6362 events among 146538 participants in 54 observational studies. *Eur Heart J*
- Ormel J, Koeter MWJ, van den Brink W, van de Willige G (1991) Recognition, management, and course of anxiety and depression in general practice. *Arch Gen Psychiatry* 48:700–706
- Penninx BW, Beekman AT, Honig A, Deeg DJ, Schoevers RA, van Eijk JT, van Tilburg W (2001) Depression and cardiac mortality: results from a community-based longitudinal study. *Arch Gen Psychiatry* 58:221–227
- Pratt LA, Ford DE, Crum RM, Armenian HK, Gallo JJ, Eaton WW (1996) Depression, psychotropic medication, and risk of myocardial infarction. *Circulation* 94:3123–3129
- Rugulies R (2002) Depression as a predictor for coronary heart disease. A review and meta-analysis. *Am J Prev Med* 23:51–61
- Schleifer SJ, Macari-Hinson MM, Coyle DA, Slater WR, Kahn M, Gorlin R, Zucker HD (1989) The nature and course of depression following myocardial infarction. *Arch Intern Med* 149:1785–1789
- Stamler J, Stamler R, Neaton JD, Wentworth D, Daviglius ML, Garside D, Dyer AR, Liu K, Greenland P (1999) Low risk-factor profile and long-term cardiovascular and noncardiovascular mortality and life expectancy. Findings for 5 large cohorts of young adult and middle-aged men and women. *JAMA* 282:2012–2018
- Wittchen H-U, Nelson CB, Lachner G (1998) Prevalence of mental disorders and psychosocial impairments in adolescents and young adults. *Psychol Med* 28:109–126

28. Wulsin LR, Singal BM (2003) Do depressive symptoms increase the risk for the onset of coronary disease? A systematic quantitative review. *Psychosom Med* 65:201–210
29. Zellweger MJ, Osterwalder RH, Langewitz W, Pfisterer ME (2004) Coronary artery disease and depression. *Eur Heart J* 25:3–9