Original Contributions

Hopelessness and 4-Year Progression of Carotid Atherosclerosis

The Kuopio Ischemic Heart Disease Risk Factor Study

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Abstract The importance of hope has long been recognized, whereas a lack of hope, or "giving up," is generally believed to have a negative impact on psychological well-being and physical health. Recently, hopelessness has been identified as a strong, independent predictor of cardiovascular disease morbidity and mortality in both American and Finnish populations. In this study we examined the association between high levels of hopelessness and progression of carotid atherosclerosis in participants (n=942) in the Kuopio Ischemic Heart Disease Study, a population-based study of middle-aged men from eastern Finland who underwent carotid ultrasonography at baseline and 4 years later. Men reporting high levels of hopelessness at baseline had faster progression of carotid atherosclerosis, assessed by four measures of intima-media thickening (IMT), than men reporting low to moderate levels of hopelessness. Further analyses revealed significant interactions between hopelessness and initial level of atherosclerosis, such that the effects of high hopelessness on progression were greatest among men who had baseline mean IMT values at or above the median. Moreover, progression was greatest among men reporting high levels of hopelessness at both baseline and follow-up. Traditional coronary risk factors and use of cholesterol-lowering and antihypertensive medications did not account for much variance in the observed relationships. These findings indicate that hopelessness contributes to accelerated progression of carotid atherosclerosis, particularly among men with early evidence of atherosclerosis, and that chronically high levels of hopelessness may be especially detrimental. Additional research is needed to identify the contributory pathways and/or mechanisms underlying these relationships. *(Arterioscler Thromb Vasc Biol.* **1997:17:1490-1495.)**

Key Words • hopelessness • intima-media thickening • progression • risk factor • atherosclerosis

A growing body of clinical and empirical evidence[1-6] supports the long-held belief that giving up hope has adverse physical and mental health consequences.[7-9] Anda and colleagues[4] recently reported that hopelessness significantly predicted fatal and nonfatal IHD after 12 years of follow-up in a cohort of more than 2800 initially healthy men and women from the National Health Examination Follow-Up Survey. Similarly, we found that a high level of hopelessness was consistently associated with increased risk for incident myocardial infarction and cardiovascular mortality, as well as other outcomes, after 6 years of follow-up in middle-aged men from eastern Finland.[5] In both studies, controlling for traditional cardiovascular risk factors had relatively little impact on the observed associations between hopelessness and cardiovascular morbidity and mortality, suggesting that hopelessness operates through other, as yet unidentified, mechanisms or earlier in the causal pathway.

To better understand the relationship between hopelessness and cardiovascular disease morbidity and mortality, it may be useful to examine the influence of hopelessness earlier in the disease process, eg, in relation to progression of atherosclerosis. No prior research has addressed this issue; however, animal and human studies offer suggestive evidence that psychosocial, behavioral, and/or environmental influences may potentiate atherosclerosis.[10] Accordingly, we examined the association between levels of hopelessness and 4-year progression of carotid atherosclerosis in a sample of middle-aged men participating in the KIHD study, a population-based study examining the effects of psychosocial characteristics and traditional and promising coronary risk factors on IHD and other outcomes.[11] The KIHD study enabled us to examine the influence of various behavioral and biological variables on the association between hopelessness and atherosclerotic progression.

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Methods

Study Population

The KIHD study is an ongoing population-based study designed to investigate previously unestablished risk factors for carotid atherosclerosis, IHD, mortality, and other outcomes among middle-aged men from the Kuopio region in eastern Finland, an area with high coronary morbidity and mortality.[12] A total of 2682 42-, 48-, 54-, and 60-year-old men (82.9% of those eligible) were recruited in two cohorts. The first cohort consisted of 1166 54-year-old men (83.3% of those eligible), enrolled between March 1984 and August 1986; the second cohort included 1516 42-, 48-, 54-, and 60-year-old men (82.6% of those eligible), enrolled between August 1986 and December 1989. A total of 1229 men from the second cohort

Selected Abbreviations and Acronyms

BMI = body mass index
CCA = common carotid artery
IHD = ischemic heart disease
IMT = intima-media thickness
KAPS = Kuopio Atherosclerosis Prevention Study
KIHD = Kuopio Ischemic Heart Disease Risk Factor Study
SBP = systolic blood pressure

underwent ultrasound examination of the right and left carotid arteries at baseline. This group was invited to participate in a follow-up study, which was conducted between March 1991 and December 1993. Of the 1229 men who were eligible for follow-up examination, 1038 (88.2%) participated; 107 refused; 52 could not participate because of death, severe illness, or relocation; and 32 could not be contacted. Average time to follow-up was 4.2 years (range=3.8 to 5.2 years). The present study includes data from the 942 men who had complete information from the baseline and follow-up ultrasound examinations and on the measures of hopelessness and all covariates. Persons with missing data who were excluded from the present study (n=96) did not differ from participants with respect to baseline or follow-up levels of carotid atherosclerosis, although nonparticipants were slightly older ($P<.002$).

Baseline and Follow-up Examinations

Examinations were carried out over 2 days, 1 week apart, at both baseline and follow-up, and consisted of a wide variety of biochemical, physiological, anthropometric, and psychosocial measures (see Salonen[11] for complete details). Medical history and medication use were checked during a medical examination at both baseline and follow-up.

Hopelessness Scale

Hopelessness, defined as negative expectancies about oneself and the future, was measured by two items from a battery of psychosocial questionnaires administered at the baseline examination. The items were "I feel that it is impossible to reach the goals I would like to strive for" and "The future seems to me to be hopeless, and I can't believe that things are changing for the better." Responses were on a 5-point Likert scale (0, absolutely agree; 1, somewhat agree; 2, cannot say; 3, somewhat disagree; or 4, absolutely disagree). Items were reverse-scored and summed to create a hopelessness score, with a range of 0 to 8. Three groups were formed according to low, moderate, or high scores on the hopelessness scale, based on meaning of the scores and response options, as follows: 58.3% of men had low scores (0, 1, or 2), indicating general disagreement with each of the two statements; those with scores in the middle range of the scale (3, 4, or 5) formed a "moderately hopeless" group (32.9%) (moderate scores reflected a mixed response to the items); and men with high scores (6, 7, or 8) formed a "highly hopeless" group (8.8%) (high scores were indicative of general agreement with both statements).

Measurement of Carotid Atherosclerosis

Extent of carotid atherosclerosis was assessed by high-resolution B-mode ultrasonography of the right and left CCAs in a 1.0- to 1.5-cm section at the distal end of the CCA, proximal to the carotid bulb. Images were focused on the posterior wall of the right and left CCA and recorded on videotape for later analysis. Near-wall images were not obtained because of their greater measurement variability.[13] Ultrasound examinations were conducted by one of four trained sonographers and were performed with the subject in a supine position after a 15-minute rest.

At baseline, CCA images were obtained using a duplex ultrasound system with a 10-MHz sector transducer. At follow-up, images were obtained with a scanner equipped with a 10-MHz annular array probe.[14] Wedge phantom studies of this system, calibrated against an RMI 414B tissue phantom, have demonstrated measurement precision of ± 0.03 mm.[14,15]

Baseline and follow-up IMT measurements were made via computerized analysis of the videotaped ultrasound images using Prosound software (University of Southern California, Los Angeles, Calif). This software uses an edge-detection algorithm, specifically designed for use with ultrasound imaging,[16] that allows automatic detection, tracking, and recording of the intima/lumen and media/adventitia interfaces. IMT, calculated as the mean distance between these interfaces, was estimated at approximately 100 points in both the right and left CCAs.

For the present study, four measures of IMT were used: (1) mean IMT, calculated as the mean of all IMT estimates from the right and left CCAs and considered an overall measure of the atherosclerotic process; (2) maximum IMT, the average of the points of maximum thickness from the right and left CCAs and indicative of the depth of intrusion of IMT into the lumen in this part of the CCA; (3) plaque height, the average of right and left CCA measurements of plaque height, calculated as the difference between maximum and minimum thickness, and an assessment of how steeply atherosclerotic lesions protruded into the lumen; and (4) surface roughness, a measure of variability in IMT, calculated as the SD of all IMT measurements from the right and left CCAs, and hypothesized to be a measure of sensitivity of the vessel wall to thrombus or plaque formation and hemodynamic turbulence and shear stress. Progression of atherosclerosis was estimated as follow-up minus baseline values for each of these IMT measures.

Baseline Covariates

Biological Factors

Biological risk factors included resting SBP, measured with a random-zero sphygmomanometer and calculated as the average of four SBP measurements obtained on the first baseline examination day (two readings taken at minutes 10 and 15 of a 15-minute supine rest, followed by two readings taken at minutes 5 and 10 of a 10-minute seated rest); HDL and LDL cholesterol, separated from fresh plasma using ultracentrifugation and precipitation and measured enzymatically (CHOD-PAP cholesterol method, Boehringer Mannheim, Mannheim, Germany); and BMI, calculated as weight divided by height squared (kg/m^2).

Behavioral and Education Factors

Behavioral covariates included alcohol consumption, assessed by a questionnaire on drinking behavior over the previous 12 months and by a 4-day instructed dietary record, and cigarette smoking, assessed by self-report of never, former, and current smoking (pack-years). Education was assessed by self-report of completed years of schooling.

Medications

Use of medications for hypertension or hyperlipidemia was assessed at baseline via interview.

Data Analyses

To examine the association between hopelessness and progression of atherosclerosis over 4 years, we estimated the mean change in each measure of IMT (mean, maximum, plaque height, surface roughness) by level of hopelessness. Because preliminary analyses suggested a threshold effect rather than a gradient of increasing change in IMT with increasing levels of hopelessness and because we were specifically interested in examining the influence of high levels of hopelessness on atherosclerotic progression, we combined the data from the low and moderate hopelessness groups for our analyses. Analyses were performed using the general linear model procedure

in SAS, version 6.09, installed on a Sun SPARCstation 20. This procedure estimated least-square mean values of IMT and performed F tests examining the effect of hopelessness on atherosclerotic progression while simultaneously controlling for age and other covariates in the model. In addition to age, the initial model included adjustments for baseline IMT, zooming depth of the ultrasound scan, sonographer, and participation in the placebo or treatment arm of a clinical trial of pravastatin.[17]

A subset of 136 KIHD participants from the present study also participated in the KAPS study, a clinical trial that showed that pravastatin effectively reduced cholesterol levels in hyperlipidemic men.[17] Two dummy-coded variables representing randomization in the placebo or treatment arm of KAPS, versus nonparticipation, were included in all models; however, these covariates were nonsignificant, indicating that patients' participation in KAPS did not affect the results of this study.

To examine the influence of potential risk factors, we then calculated a second model that included all variables in the initial model plus variables representing SBP, HDL, LDL, BMI, education, cigarette smoking, alcohol consumption, and use of antihypertensive or antihyperlipidemic medications as covariates. Analyses for the four measures of IMT used in this study were conducted separately.

To determine whether the associations between hopelessness and atherosclerotic progression varied according to initial level of IMT, we then repeated the analyses, stratifying at the median level of mean IMT at baseline (0.731 mm). Finally, because it is plausible that hopelessness may have more pronounced and deleterious effects on health if it is chronic rather than acute, we repeated the analyses comparing men who reported high levels of hopelessness at both baseline and follow-up (n=49) to those reporting low to moderate levels of hopelessness at both examinations (n=627). Men who reported different levels of hopelessness at baseline and follow-up also were included in these analyses as a separate group (n=228). Thirty-eight subjects with missing data on the hopelessness scale at follow-up were excluded from these tertiary analyses.

Results

Table 1 presents the mean (and SD) or prevalence (%) for scores on the hopelessness scale, age, baseline levels of IMT, and other covariates by level of hopelessness.

Results from the initial models examining the influence of hopelessness on progression revealed a consistent pattern of findings across the measures of mean and maximum IMT, plaque height, and surface roughness. Compared to men with low to moderate scores on the hopelessness scale, highly hopeless men had a 19.2% greater increase in maximum IMT (+0.31 versus +0.26 mm, $P<.03$) and a significantly greater increase in variation of IMT along the walls of the CCA (surface roughness) (+0.03 versus +0.021 mm, $P<.04$). The most hopeless group also showed a 21.8% larger increase in mean IMT (+0.134 versus +0.11 mm) and a 10% greater progression in plaque height (+0.296 versus +0.269 mm) relative to those with lower hopelessness scores; however, these latter differences did not reach conventional levels of significance ($P<.20$). Similar results were seen after additional adjustments for biological and behavioral risk factors and medication use.

Stratifying by extent of atherosclerosis at baseline revealed that hopelessness was related to progression of carotid atherosclerosis only among men with baseline mean IMT values at or above the median. Given this pattern of findings, we recalculated the general linear models to test the interactive effects of baseline mean IMT and hopelessness on progression. Table 2 presents the means (and SEs) for 4-year changes in mean IMT, maximum IMT, plaque height, and surface roughness by level of hopelessness and mean IMT at baseline and the F and P values for the interactions from both the initial and fully adjusted models. Important interactions were identified for all four measures of progression in the initial age-adjusted models. Subsequent paired t tests revealed that among participants with median or higher levels of baseline mean IMT, those reporting high levels of hopelessness experienced significantly larger increases in mean IMT ($P<.024$), maximum IMT ($P<.006$), plaque height ($P<.049$), and surface roughness ($P<.0003$) than those reporting lower levels of hopelessness. Hopelessness was unrelated to progression in men with less than the median level of baseline mean IMT ($P>.4$). Additional adjustments for resting SBP, LDL, HDL, BMI, smoking, alcohol consumption, education, and use of medications for hypertension and hypercholesterolemia did not alter these findings.

Table 3 presents the data from the analyses examining the influence of chronic hopelessness on atherosclerotic progression. Compared to men with low to moderate levels of hopelessness at both examinations, men experiencing chronically high levels of hopelessness had a 32.7% larger increase in mean IMT, a 27.3% greater change in maximum IMT, and more than an 18% larger increase in plaque height, as well as a significantly greater increase in surface roughness of the CCA. Men whose reported level of hopelessness differed at baseline and follow-up showed an intermediate level of progression. Results were relatively unchanged in the models that included adjustments for behavioral and biological risk factors and medication use. (The models shown in Table 3 did not test the potential interactive effects of basal level of atherosclerosis and chronic hopelessness because the relatively small number of chronically hope-

TABLE 1. Mean (SD) or Prevalence (%) of Covariates by Level of Hopelessness

	Low/Moderate (n=859)	High (n=83)
Hopelessness score*	2.1 (1.5)	6.4 (0.7)
Age, y	51.7 (6.73)	52.5 (6.20)
Education, y*	9.4 (3.60)	8.1 (2.25)
IMT, mm		
Mean	0.76 (0.18)	0.77 (0.14)
Maximum	0.95 (0.24)	0.96 (0.20)
Plaque height, mm	0.38 (0.18)	0.38 (0.15)
Surface roughness, mm	0.09 (0.04)	0.09 (0.04)
SBP, mm Hg	132.1 (15.7)	131.9 (18.6)
HDL, mmol/L	1.31 (0.30)	1.25 (0.29)
LDL, mmol/L	3.87 (0.95)	3.77 (0.95)
BMI, kg/m^2	26.7 (3.31)	26.5 (3.14)
Alcohol consumption, %		
None	11.42	13.25
>2 drinks/d†	20.63	34.94
Smoking, %		
Never	27.5	20.5
Former	39.7	39.8
Current	32.8	39.8
Medication use, %		
Antihyperlipidemics	0.9	1.2
Antihypertensives	19.9	25.3

*$P<.0001$.
†$P<.003$.

TABLE 2. Progression of Carotid Atherosclerosis (mm) at 4-Year Follow-up by Levels of Hopelessness and Baseline Mean IMT Values*

	Model 1 Level of Mean IMT at Baseline		Model 2 Level of Mean IMT at Baseline	
	Below Median Mean (SE)	At or Above Median Mean (SE)	Below Median Mean (SE)	At or Above Median Mean (SE)
Mean IMT change				
Low/moderate	+0.132 (0.007)	+0.088 (0.007)	+0.136 (0.007)	+0.086 (0.007)
High	+0.134 (0.022)	+0.135 (0.020)	+0.132 (0.022)	+0.130 (0.020)
Statistics for interaction	F=2.1, *P*<.15		F=2.47, *P*<.12	
Maximum IMT change				
Low/moderate	+0.255 (0.011)	+0.266 (0.011)	+0.260 (0.011)	+0.263 (0.011)
High	+0.262 (0.032)	+0.349 (0.029)	+0.254 (0.032)	+0.338 (0.029)
Statistics for interaction	F=2.91, *P*<.09		F=3.28, *P*<.07	
Plaque height change				
Low/moderate	+0.232 (0.009)	+0.307 (0.009)	+0.237 (0.009)	+0.304 (0.009)
High	+0.214 (0.030)	+0.362 (0.027)	+0.209 (0.030)	+0.351 (0.027)
Statistics for interaction	F=3.02, *P*<.08		F=3.29, *P*<.07	
Surface roughness change				
Low/moderate	+0.016 (0.002)	+0.027 (0.002)	+0.017 (0.002)	+0.026 (0.002)
High	+0.011 (0.006)	+0.046 (0.005)	+0.011 (0.006)	+0.044 (0.005)
Statistics for interaction	F=9.3, *P*<.0024		F=9.42, *P*<.0022	

*n=942. Values shown are calculated as follow-up minus baseline value. Model 1 included adjustments for age, baseline IMT, sonographic zooming depth, sonographer, and participation in a clinical trial of pravastatin. Model 2 included the model 1 covariates plus adjustment for SBP, HDL, LDL, BMI, education, alcohol consumption, cigarette smoking, and use of antihyperlipidemic and antihypertensive medications.

less men did not provide adequate power to test this interaction.)

Discussion

This study demonstrates that a high level of hopelessness exacerbates the atherosclerotic process in middle-aged men. We observed accelerated progression in the small number of men who reported strong feelings of hopelessness at the baseline examination. The consistency of associations across measures of IMT in this study is especially noteworthy in light of the fact that less than 10% of our sample was in this highly hopeless group.

Interestingly, our analyses that examined the association between hopelessness and atherosclerotic progression by basal level of atherosclerosis indicated that hopelessness exerted its effect primarily among those men with IMT levels in the upper half of the distribution at baseline. Indeed, significant interactions between hopelessness and baseline mean IMT were noted for all four measures of IMT progression. This finding suggests

TABLE 3. Chronicity of Hopelessness and Progression of Carotid Atherosclerosis (mm) at 4-Year Follow-up*

	Model 1		Model 2	
	Mean (SE)	*P*	Mean (SE)	*P*
Mean IMT change				
Low/moderate at baseline, follow-up	+0.107 (0.005)		+0.109 (0.005)	
Differing levels at baseline, follow-up	+0.110 (0.008)	<.78	+0.107 (0.008)	<.82
High levels at baseline, follow-up	+0.142 (0.018)	<.06	+0.134 (0.018)	<.18
Maximum IMT change				
Low/moderate at baseline, follow-up	+0.253 (0.008)		+0.256 (0.008)	
Differing levels at baseline, follow-up	+0.274 (0.013)	<.16	+0.269 (0.013)	<.42
High levels at baseline, follow-up	+0.322 (0.027)	<.016	+0.307 (0.028)	<.08
Plaque height change				
Low/moderate at baseline, follow-up	+0.264 (0.007)		+0.268 (0.007)	
Differing levels at baseline, follow-up	+0.285 (0.012)	<.15	+0.278 (0.012)	<.49
High levels at baseline, follow-up	+0.313 (0.026)	<.074	+0.298 (0.026)	<.27
Surface roughness change				
Low/moderate at baseline, follow-up	+0.021 (0.001)		+0.021 (0.001)	
Differing levels at baseline, follow-up	+0.025 (0.002)	<.09	+0.024 (0.002)	<.29
High levels at baseline, follow-up	+0.035 (0.005)	<.006	+0.033 (0.005)	<.03

*n=904. Values shown are calculated as follow-up minus baseline value. Model 1 included adjustments for age, baseline IMT, sonographic zooming depth, sonographer, and participation in a clinical trial of pravastatin. Model 2 included the model 1 covariates plus adjustment for SBP, HDL, LDL, BMI, education, alcohol consumption, cigarette smoking, and use of antihyperlipidemic and antihypertensive medications. Probability values are from paired *t* tests comparing the groups with differing and high levels of hopelessness to the group with low to moderate hopelessness at baseline and follow-up.

that hopelessness exacerbates the mechanisms that contribute to increased arterial wall thickening but may be less important in the initial atherosclerotic process. The lack of a cross-sectional association between reported hopelessness and IMT values at baseline (Table 1) is consistent with this conclusion. Reasons why hopelessness may have fewer atherogenic effects among men without initial thickening or be less significant in the early stages of atherosclerosis are unknown. The mechanisms underlying the association between hopelessness and atherosclerotic progression remain to be identified in humans. However, animal studies have shown that exposure to uncontrollable stressors and learned helplessness, phenomena that can be considered precursors to and/or correlates of hopelessness, have adverse autonomic, neuroendocrine, and immunologic effects,[18-20] all of which may potentiate atherogenesis.

Our observed pattern of results was consistent across the four measures of carotid atherosclerosis but strongest for the measures of maximum IMT and surface roughness. These findings indicate that hopelessness influences the overall atherosclerotic process but may be particularly pathogenic with respect to the development and/or progression of focal lesions and arterial wall roughness, thereby increasing the likelihood of plaque fissuring or rupture. Moreover, although the differential pathological and clinical significance of the four parameters of carotid atherosclerosis used in this study remain to be determined, cross-sectional data from the entire KIHD sample revealed that each 0.10-mm difference in maximum IMT was associated with an 11% increase in risk of acute myocardial infarction ($P<.001$).[21]

Our previous study showed that hopelessness was strongly and consistently related to all-cause and cause-specific mortality and incidence of cancer and myocardial infarction, independent of classic risk factors.[5] These findings are consistent with the concepts of generalized resistance[22] and allostatic load,[23] notions that suggest that individuals in interaction with their environment develop a set of behavioral, social, psychological, and physiological adaptations that have a cumulative, generic effect on health. Hopelessness appears to be one such maladaptive, psychological response. The present study is consistent with this interpretation.

Examining the influence of long-term hopelessness on progression showed that men who reported high levels of hopelessness at both their baseline and follow-up examinations experienced the largest increases in carotid atherosclerosis relative to men reporting low to moderate hopelessness at both points in time. Men whose reported level of hopelessness either increased or decreased during the 4 years of follow-up showed an intermediate level of progression. This pattern of findings suggests that long-term, pronounced feelings of hopelessness may be particularly pathogenic. Nevertheless, our study was not designed to examine chronicity of emotions, so our results can only be considered suggestive. The correlation between hopelessness scores at baseline and follow-up was .51 ($P<.0001$), indicating a moderate degree of consistency in individuals' reported sense of hopelessness across time. However, we did not obtain information on how long respondents had experienced feelings of hopelessness before their baseline examination. Given that atherosclerotic lesions begin to develop early in life,[24] it would be useful to gather such information in future studies to more fully examine the impact of long-term hopelessness on the atherosclerotic process. Additionally, given the interaction between hopelessness and extent of atherosclerosis at baseline identified in this study (see Table 2), it will be important to determine whether long-term hopelessness also shows a synergistic relationship with atherosclerosis. Our findings suggest that sustained feelings of extreme hopelessness may be especially atherogenic in individuals with early evidence of atherosclerotic thickening.

The associations between hopelessness and progression of carotid atherosclerosis reported herein were relatively unchanged after adjustments for established cardiovascular disease risk factors, including HDL and LDL cholesterol levels, resting SBP, BMI, education, cigarette smoking, and alcohol consumption. This may reflect a lack of confounding by known cardiovascular risk factors, or it may be that the impact of these risk factors on disease progression was not adequately assessed because we considered only basal levels rather than changes in risk factor levels. Alternatively, it may be that the cumulative effect of these variables on atherosclerosis was taken into account by baseline level of IMT, which was a highly significant covariate in all models. It may also be the case that risk factors not measured in the present study (eg, homocysteine) or presently unidentified risk factors are contributing to the association between hopelessness and progression of carotid atherosclerosis.

The present study was conducted in middle-aged white men. It remains to be seen whether similar associations between hopelessness and progression of atherosclerosis will be evident in female or nonwhite populations and among different age groups. It will also be informative to determine whether other long- or short-term negative emotional states have similar effects on atherosclerosis or whether the findings presented here are unique to the construct of hopelessness.

In summary, the present study demonstrates that hopelessness contributes to accelerated progression of carotid atherosclerosis, particularly among men with early evidence of atherosclerosis, and that chronically high levels of hopelessness may be especially atherogenic. This study thus contributes to the growing literature[1-6,25-27] that provides empirical support for the long-held belief that a lack of hope has adverse health effects. Future research needs to more thoroughly examine the mechanisms underlying the observed relationships and to identify the social, psychological, and physiological factors that lead to hopelessness as well as the factors that help to alleviate it.

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References

1. Pettingale KW, Morris T, Greer S, Haybittle J. Mental attitudes to cancer: an additional prognostic factor. *Lancet*. 1985;3:750. Letter.
2. Jensen M. Psychobiological factors predicting the course of breast cancer. *J Pers*. 1987;55:317-342.
3. Stein S, Linn MW, Stein EM. Psychological correlates of survival in nursing home cancer patients. *Gerontologist*. 1989;29:224-228.

4. Anda R, Williamson D, Jones D, et al. Depressed affect, hopelessness, and the risk of ischemic heart disease in a cohort of U.S. adults. *Epidemiology*. 1993;4:285-294.
5. Everson SA, Goldberg DE, Kaplan GA, et al. Hopelessness and risk of mortality and incidence of myocardial infarction and cancer. *Psychosom Med*. 1996;58:113-121.
6. Greene SM. The relationship between depression and hopelessness: implications for current theories of depression. *Br J Psychiatry*. 1989;154:650-659.
7. Scheier MF, Carver CS. Optimism, coping, and health: assessment and implications of generalized outcome expectancies. *Health Psychol*. 1985;4:219-247.
8. Snyder CR, Irving LM, Anderson JR. Hope and health. In: Snyder CR, Forsyth DR, eds. *Handbook of Social and Clinical Psychology*. Elmsford, NY: Pergamon Press; 1991:285-305.
9. Scheier MF, Carver CS. Effects of optimism on psychological and physical well-being: theoretical overview and empirical update. *Cogn Ther Res*. 1992;16:201-228.
10. Kaplan JR, Pettersson K, Manuck SB, Olsson G. Role of sympathoadrenal medullary activation in the initiation and progression of atherosclerosis. *Circulation*. 1991;84[suppl VI]:VI-23-VI-32.
11. Salonen JT. Is there a continuing need for longitudinal epidemiologic research? The Kuopio Ischemic Heart Disease Risk Factor Study. *Ann Clin Res*. 1988;20:46-50.
12. Keys A. *Seven Countries: A Multivariate Analysis of Death and Coronary Heart Disease*. Cambridge, Mass: Harvard University Press; 1980.
13. Wikstrand J, Wendelhag L. Methodological considerations of ultrasound investigation of intima-media thickness and lumen diameter. *J Int Med*. 1994;236:555-559.
14. Salonen R, Salonen JT. Intima-media changes in a population study: KIHD. In: Boccalon H, ed. *Vascular Medicine*. Amsterdam: Elsevier Science Publishers, 1993;301-304.
15. Salonen JT, Korpela H, Nyyssönen K, Salonen R. Precision and reproducibility of ultrasonographic measurement of progression of common carotid artery atherosclerosis. *Lancet*. 1993;341: 1158-1159.
16. Blankenhorn DH, Selzer RH, Crawford DW, et al. Beneficial effects of colestipol-niacin therapy on the common carotid artery: two- and four-year reduction of intima-media thickness measured by ultrasound. *Circulation*. 1993;88:20-28.
17. Salonen R, Nyyssönen K, Porkkala E, et al. Kuopio Atherosclerosis Prevention Study (KAPS): a population-based primary preventive trial of the effect of LDL lowering on atherosclerotic progression in carotid and femoral arteries. *Circulation*. 1995;92:1758-1764.
18. Seligman MEP, Maier SF, Solomon RL. Unpredictable and uncontrollable aversive events. In: Brush FR, ed. *Aversive Conditioning and Learning*. New York: Academic Press; 1971.
19. Weiss JM, Goodman PA, Losito BG, Corrigan S, Charry JM, Bailey WH. Behavioral depression produced by an uncontrollable stressor: relationship to norepinephrine, dopamine, and serotonin levels in various regions of rat brain. *Brain Res Rev*. 1981;3:167-205.
20. Weiss JM, Sundar S. Effects of stress on cellular immune responses in animals. In: Tasman A, Riba M, eds. *Review of Psychiatry*, vol 11. Washington, DC: American Psychiatric Press; 1992.
21. Salonen JT, Salonen R. Ultrasound B-mode imaging in observational studies of atherosclerotic progression. *Circulation*. 1993; 87(suppl II):56-65.
22. Cassel J. The contribution of the social environment to host resistance. *Am J Epidemiol*. 1976;104:107-123.
23. McEwen BS, Stellar E. Stress and the individual. *Arch Intern Med*. 1993;153:2093-2101.
24. Stary HC, Chandler AB, Dinsmore RE, et al. A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis. *Arterioscler Thromb Vasc Biol*. 1995;15: 1512-1531.
25. Appels A, Falger PR, Schouten EG. Vital exhaustion as risk indicator for myocardial infarction in women. *J Psychosom Res*. 1993;37:881-890.
26. Appels A, Mulder P. Fatigue and heart disease: the association between "vital exhaustion" and past, present, and future coronary heart disease. *J Psychosom Res*. 1989;33:727-738.
27. Kop WJ, Appels A, de Leon CF, Swart HB, Far FW. Vital exhaustion predicts new cardiac events after successful coronary angioplasty. *Psychosom Med*. 1994;56:281-287.