JOURNAL OF WOMEN'S HEALTH
Volume 13, Number 1, 2004

Why Eve Is Not Adam: Prospective Follow-Up in 149,650 Women and Men of Cholesterol and Other Risk Factors Related to Cardiovascular and All-Cause Mortality

HANNO ULMER, Ph.D.,[1,4] CECILY KELLEHER, M.D.,[2,4] GÜNTER DIEM, M.D.,[3,4] and HANS CONCIN, M.D.[3]

ABSTRACT

Purpose: **To assess the impact of sex-specific patterns in cholesterol levels on all-cause and cardiovascular mortality in the Vorarlberg Health Monitoring and Promotion Programme (VHM&PP)**

Methods: **In this study, 67,413 men and 82,237 women (aged 20–95 years) underwent 454,448 standardized examinations, which included measures of blood pressure, height, weight, and fasting samples for cholesterol, triglycerides, gamma-glutamyl transferase (GGT), and glucose in the 15-year period 1985–1999. Relations between these variables and risk of death were analyzed using two approaches of multivariate analyses (Cox proportional hazard and GEE models).**

Results: **Patterns of cholesterol levels showed marked differences between men and women in relation to age and cause of death. The role of high cholesterol in predicting death from coronary heart disease could be confirmed in men of all ages and in women under the age of 50. In men, across the entire age range, although of borderline significance under the age of 50, and in women from the age of 50 onward only, low cholesterol was significantly associated with all-cause mortality, showing significant associations with death through cancer, liver diseases, and mental diseases. Triglycerides > 200 mg/dl had an effect in women 65 years and older but not in men**

Conclusions: **This large-scale population-based study clearly demonstrates the contrasting patterns of cholesterol level in relation to risk, particularly among those less well studied previously, that is, women of all ages and younger people of both sexes. For the first time, we demonstrate that the low cholesterol effect occurs even among younger respondents, contradicting the previous assessments among cohorts of older people that this is a proxy or marker for frailty occurring with age.**

INTRODUCTION

IT HAS BEEN WELL ESTABLISHED that there are sex-specific differences in trends of cardiovascular diseases, although the precise mechanisms remain unclear.[1,2] The three cardinal risks factors are blood pressure, smoking, and total cholesterol as an indicator of lipoprotein profile. However, the role of total cholesterol in predicting cardiovascular disease is still discussed controversially, as it is not a strong predictor in older people, particularly women.[3–7] Mortality rates from heart

[1]Institute of Biostatistics and Documentation, Leopold Franzens University of Innsbruck, Innsbruck, Austria.
[2]Department of Public Health Medicine and Epidemiology, University College Dublin, Dublin, Republic of Ireland.
[3]Agency for Social- and Preventive Medicine, Bregenz, Austria.
[4]Participant in European Union-funded Health Risk Monitoring Program (EHRM) (*www.ktl.fi/ehrm*).

disease in women and men differ over the course of life, attributed by some investigators to alterations in lipoprotein and hemostatic systems occurring in the postmenopausal period in women.[8] The precise temporal relationships between changes in risk factor profile and shifts in incidence and mortality patterns have not been well delineated in women, in part because long-term epidemiological data on women are not as readily available as for men. Although cohort data on women have become available,[9] very few studies contain adequate numbers of both men and women to allow direct comparisons using a comparable methodology.[10–19] It has long been known from ecological data that men have higher cumulative mortality rates than women,[20] but it has been asserted recently that the widespread variations in epidemic patterns of heart disease across countries seen in men apply little, if at all, to women and that environment or lifestyle, rather than constitutional factors, provides the paramount explanation.[21]

The significance of low cholesterol level as a predictor of health status has been reappraised.[22] This interest began first with the evidence that iatrogenic lowering of the cholesterol level was associated with unexpected mortality from causes other than cardiovascular disease.[23,24] The question is whether a low cholesterol level is a marker for underlying ill health, as for instance, from wasting diseases, such as cancer,[25–28] or is a cause of ill health in itself. This clearly has implications for public health policy, particularly in advocating health promotion nutrition guidelines at a population level. There are too few long-term epidemiological studies of healthy women that can assess over time how cholesterol level relates to health status and how this contrasts with the situation in men. Two large-scale meta-analyses in 1999 have contributed some information,[10,29] but these were concerned largely with individuals at high relative risk, were not primarily concerned with women, and dealt mainly with middle-aged people.

The Vorarlberg Health Monitoring and Promotion Programme (VHM&PP)[30] in Austria is a large-scale longitudinal database consisting of repeatedly measured risk factors linked to disease-specific mortality outcomes. Participants are free-living citizens across the adult age spectrum (20–95 years), and both sexes are represented. The objectives of this paper, therefore, are to examine how level of cholesterol across the age spectrum relates to longer-term risk outcome, taking into account other known risk factors, and to document differences in patterns according to sex.

VHM&PP Working Group

Hans-Peter Bischof and *Elmar Bechter*
Government of Vorarlberg, Austria
Leopold Bischof, *Josef Bachmann*, *Karl Huber*, *Klaus Zitt*, *Paul Gmeiner*, *Johann Brändle*
Agency for Social- and Preventive Medicine, Bregenz, Austria
Larry Brant
National Institute on Aging, Baltimore, MD
Michael Kunze and *Anita Rieder*
Institute of Social Medicine, University of Vienna, Austria
Rudolf Bruppacher
Institute of Social- and Preventive Medicine, University of Basel, Switzerland

MATERIALS AND METHODS

Participants

In Vorarlberg, the westernmost province of Austria, population-based documentation of cardiovascular risk factors has been performed routinely since 1970 by the Agency for Social- and Preventive Medicine. From the outset, this ongoing extensive risk factor surveillance and treatment referral program has conducted medical examinations of more than two thirds of the entire population of this province.

A total of 149,650 individuals, 67,413 men (44.9%) and 82,237 women (55.1%), participated in the VHM&PP between 1985 and 1999. During this period, men underwent 191,629 examinations (42.2%), and women underwent 262,819 examinations (57.8%), a total of 454,448 in all. Informed consent to store and process the data was obtained from all participants at each examination time, and ethical approval was obtained. A total of 5,393 persons died in the course of follow-up, and cause of death was linked to the database using a validated record-linkage procedure.

Measurements

The VHM&PP participants underwent unequal numbers of repeated examinations, rang-

ing from 1 to 14 visits. The examinations were performed in a standardized way by trained general practitioners and internists and included a physical examination and recording of sociodemographic information. The methodology has been described previously.[31,32] The physical examination included a fasting blood sample and measurement of height, weight, and blood pressure. Systolic and diastolic blood pressure were measured with a mercury sphygmomanometer in the sitting position. Total cholesterol, triglyceride, gamma-glutamyl transferase (GGT), and blood glucose levels were determined enzymatically by two central laboratories. The two laboratories underwent a standardized internal and external quality procedure.

Statistical analysis

Risk factor values were summarized as means (standard deviations [SD]) and tabulated by 15-year age bands. Causes of death were coded according to the *International Classification of Diseases*, ninth revision (ICD-9) and classified into the subgroups of death from cardiovascular disease, stroke, cancer, and all other causes. Mortality rates were given both as crude rates and as direct age-standardized rates. A recently published standard proposed by the World Health Organization (WHO)[33] was used for age standardization. Cox proportional hazards models were used to assess the age-adjusted associations between the risk factors at first screening and mortality outcome. Variables for these models were selected according to their univariate association with mortality, evaluated by log-rank tests. In contrast to the other risk factors, cholesterol level and body mass index (BMI) did not show a simple unidirectional association with mortality but instead showed effects in both the lower and upper ranges (U-shaped relation with mortality). Therefore, these two variables were divided into quartiles, and the lowest and highest quartiles, respectively, were compared with the two medium quartiles in the models. In addition to the Cox models, to make use of the repeated measurements of the participants, multivariate regression models applying the general estimating equation (GEE) method[34] were also calculated. All analyses were performed separately for men and women. p values <0.05 were considered statistically significant. Statistical analysis was performed using Stata[35] statistical software.

RESULTS

Baseline sociodemographic characteristics of the participants in VHM&PP over the period 1985–1999 are shown in Table 1. In Table 2, the risk factor profiles for both men and women at their baseline examination are presented in 15-year age bands. These demonstrate different patterns according to sex. Whereas systolic blood pressure and glucose levels rise steadily with age in both sexes, and both diastolic blood pressure and gamma-gt show a plateau pattern in middle age, with a drop thereafter, triglycerides rise steadily in women. Total cholesterol level peaks in the 50–64-year age group in men but continues to rise in women. Table 3 shows causes of death during follow-up in each age band for men and women, including both absolute numbers and mortality rate. There is the expected rise in rates over time, with cardiovascular diseases other than stroke progressively accounting for most deaths in both sexes.

Figure 1 shows mean levels of cholesterol at 5-year intervals for both men and women. This shows definitively that males have higher average levels of cholesterol up to age 50, with

TABLE 1. SOCIODEMOGRAPHIC CHARACTERISTICS OF PARTICIPANTS, VHM&PP, 1985–1999

	Men		*Women*	
	n	%	n	%
Age group (years)				
20–24	7,893	11.7	12,561	15.3
25–34	18,619	27.6	20,601	25.1
35–44	14,503	21.5	16,037	19.5
45–54	12,563	18.6	14,037	17.1
55–64	8,610	12.8	10,370	12.6
≥65	5,225	7.8	8,631	10.5
Total	67,413	45.0	82,237	55.0
Marital status[a]				
Single	12,092	18.5	12,887	15.8
Married	48,232	73.7	52,511	64.4
Divorced	3,521	5.4	9,648	11.8
Widowed	1,602	2.4	6,444	7.9
Work status[b]				
White collar	33,883	52.3	42,976	54.2
Blue collar	23,899	36.9	30,034	37.9
Self-employed	7,056	10.9	6,275	7.9
Austrian	60,932	90.4	75,823	92.2
Number of deaths	2,942	4.4	2,451	3.0

[a]2,717 (1.8%) missing values.
[b]Including pensioners; housewives were classified according to their husbands' jobs; 5,531 (3.7%) missing values.

Table 2. Means and SD of Risk Factor Values by Sex and Age Group at First Examination, VHM&PP, 1985–1999

	Men				*Women*			
	20–34 years	*35–49 years*	*50–64 years*	*≥65 years*	*20–34 years*	*35–49 years*	*50–64 years*	*≥65 years*
Body mass index (kg/m^2)[a]	24.1 (3.3)[b]	25.8 (3.5)	26.4 (3.5)	25.8 (3.5)	22.3 (3.8)	24.7 (4.5)	26.5 (4.6)	26.1 (4.4)
Systolic blood pressure (mm Hg)	125.8 (14.8)	130.6 (17.1)	140.5 (20.0)	148.6 (21.1)	116.9 (14.0)	126.1 (18.4)	141.3 (21.2)	153.1 (21.6)
Diastolic blood pressure (mm Hg)	78.6 (9.8)	82.7 (10.9)	85.3 (11.2)	84.4 (10.6)	74.8 (9.4)	79.8 (10.8)	85.1 (11.2)	85.4 (10.9)
Total cholesterol (mg/dl)	199.3 (42.6)	228.6 (45.8)	237.0 (45.8)	232.5 (45.5)	193.4 (36.1)	212.4 (40.4)	246.2 (45.6)	250.9 (47.3)
Total cholesterol (mmol/L)	5.2 (1.1)	5.9 (1.2)	6.1 (1.2)	6.0 (1.2)	5.0 (0.9)	5.5 (1.0)	6.4 (1.2)	6.5 (1.2)
Triglycerides (mg/dl)	131.7 (91.9)	171.2 (120.1)	168.6 (112.6)	151.0 (94.1)	97.7 (51.0)	107.9 (65.8)	135.1 (79.9)	150.9 (85.6)
Glucose (mg/dl)	82.3 (15.6)	89.1 (23.9)	95.5 (32.2)	98.5 (35.7)	80.7 (13.8)	86.8 (19.8)	92.9 (27.7)	98.6 (34.0)
Gamma gt (mg/dl)	18.3 (22.1)	28.5 (40.4)	30.1 (40.9)	26.0 (34.8)	10.3 (11.4)	14.0 (22.1)	17.7 (22.7)	18.5 (22.7)
Regular smoking	30.3%	28.3%	23.1%	14.7%	26.3%	19.8%	9.7%	4.2%

[a]Excluding 2,100 (1.4%) missing values within body mass index and blood pressure and 4,500 (3.1%) missing values within cholesterol, triglyceride, glucose, and gamma-gt (values missing partly due to missing consent of the participants)

[b]Means (SD).

Table 3. Cause of Death by Sex and Age Group at First Examination, VHM&PP, 1985–1999

	Men[a]				*Women*[a]			
	20–34 years	*35–49 years*	*50–64 years*	*≥65 years*	*20–34 years*	*35–49 years*	*50–64 years*	*≥65 years*
Cardiovascular diseases (ICD-9 394-429, 440-456)	9 (7.6%)[b]	104 (25.1%)	356 (33.3%)	561 (41.9%)	7 (9.9%)	31 (12.4%)	125 (22.1%)	707 (45.1%)
Stroke (ICD-9 430-438)	3 (2.5%)	16 (3.9%)	67 (6.3%)	188 (14.0%)	2 (2.8%)	13 (5.2%)	47 (8.3%)	249 (15.9%)
Cancer (ICD-9 140-239)	18 (15.3%)	139 (33.6%)	432 (40.4%)	373 (27.8%)	30 (42.3%)	145 (58.2%)	283 (50.1%)	371 (23.7%)
Other death causes	88 (74.6%)	155 (37.4%)	215 (20.1%)	218 (16.3%)	32 (45.1%)	60 (24.1%)	110 (19.5%)	239 (15.3%)
All-cause mortality	$n = 118$	$n = 414$	$n = 1070$	$n = 1340$	$n = 71$	$n = 249$	$n = 565$	$n = 1566$
All-cause mortality rate	0.45%	1.94%	7.47%	25.60%	0.21%	1.06%	3.34%	18.14%
Age-standardized rate	0.43%	1.81%	7.18%	40.40%	0.20%	1.09%	3.31%	21.13%

[a]5.75 years median survival time from first examination in men; 6.25 years in women.
[b]Absolute (relative) frequency, percentages add to 100% across the age groups.

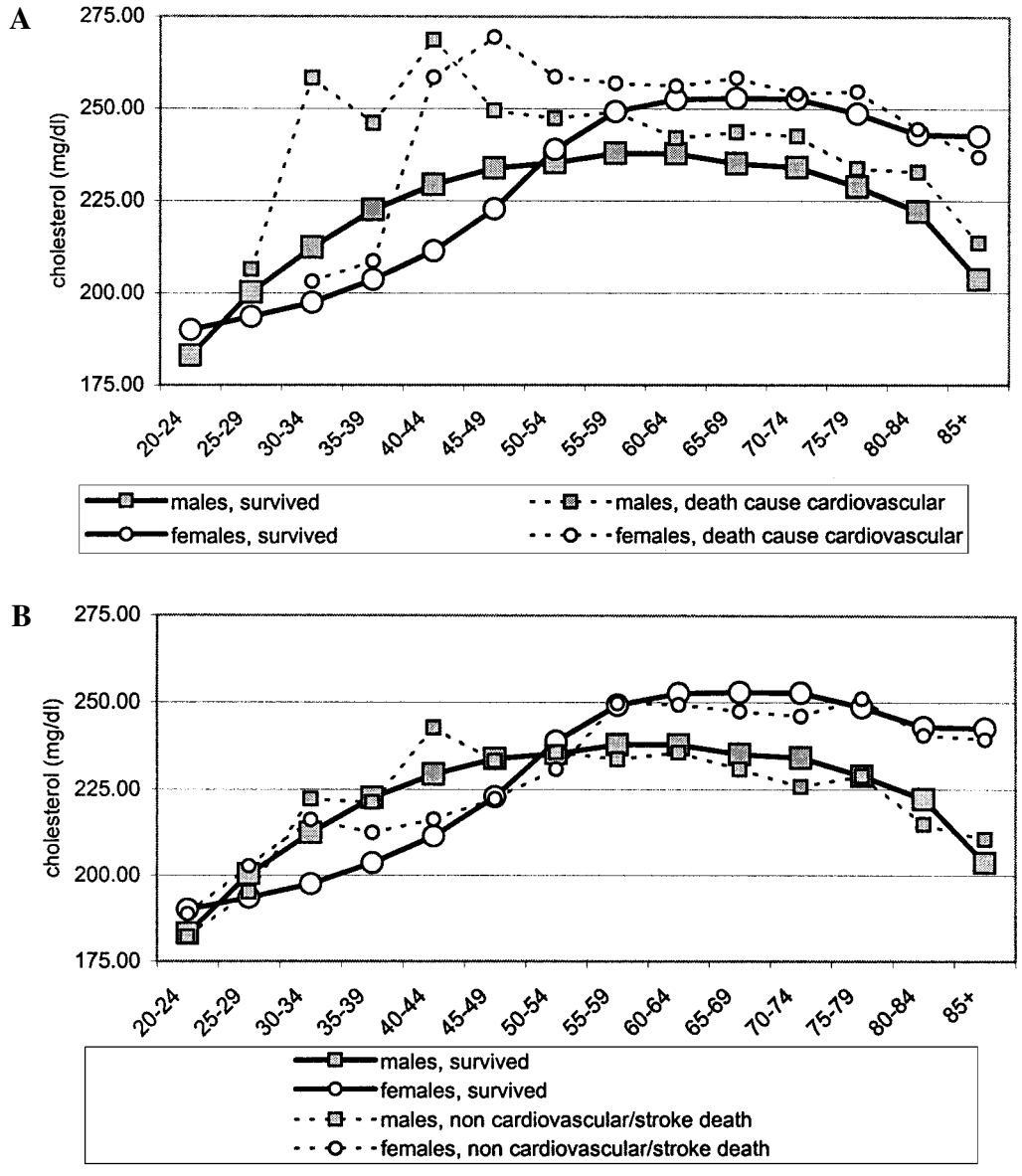

FIG. 1. a and 1b. Mean levels of cholesterol by age at first examination and death from **(A)** cardiovascular and **(B)** noncardiovascular disease for men and women, VHM&PP, 1985–1999.

women then having higher average levels up to the late 80s. The contrast in patterns is striking, as is the precision at which the crossover point occurs, consistent with the onset of menopause. In Figure 1A, mean levels of cholesterol are shown for male and female survivors and for males and females who died of cardiovascular disease during the follow-up period (median survival time was 6 years). In both sexes, mean cholesterol level is considerably higher among younger participants dying of cardiovascular disease. However, there is a lag effect of about 10 years for women compared with men, and at all ages there is a greater gap between male survivors and victims of cardiovascular disease than is the case for women. Average cholesterol level is considerably higher in women than men from the mid-50s onward, irrespective of disease outcome. Figure 1B presents patterns for survivors and those who died of other diseases, showing no relationship with average cholesterol level.

In Tables 4A and 4B, Cox proportional hazard regression analyses for men and women are reported in relation to all-cause mortality in three cohort age bands. These highlight contrasting patterns in risk factor profiles between men and women. As might be expected, smoking status is predictive of mortality at all ages and in both

Table 4a. Cox Proportional Hazard Regression Analyses for Men at First Examination in Relation to All-Cause Mortality, VHM&PP, 1985–1999

	Cox models (based on measurements at first examination)		
Men[a]	*Up to 49 (mean 34.2) years* n = *46,227, 504 deaths* *Hazard ratio (95% CI),* p-*value*	*50–64 (mean 56.7) years* n = *13,697, 992 deaths* *Hazard ratio (95% CI),* p-*value*	*≥65 (mean 72.0) years* n = *4,931, 1,227 deaths* *Hazard ratio (95% CI),* p-*value*
Age (years)	1.088 (1.075–1.102), <0.001	1.091 (1.074–1.108), <0.001	1.097 (1.086–1.108), <0.001
Systolic blood pressure (mm Hg)	1.014 (1.009–1.019), <0.001	1.005 (1.002–1.008), =0.001	1.004 (1.001–1.007), 0.003
Body mass index <22.9 kg/m^2	1.451 (1.156–1.821), 0.001	1.612 (1.353–1.921), <0.001	1.212 (1.047–1.402), 0.01
Body mass index medium quartiles (kg/m^2)	Referent	Referent	Referent
Body mass index >27.4 kg/m^2	0.95 (0.765–1.179), 0.64	1.161 (1.006–1.340), 0.04	0.976 (0.852–1.118), 0.725
Cholesterol <187 mg/dl	1.278 (1.005–1.626), 0.046	1.283 (1.058–1.555), 0.011	1.257 (1.074–1.471), 0.004
Cholesterol medium quartiles (mg/dl)	Referent	Referent	Referent
Cholesterol >248 mg/dl	1.242 (1.01–1.526), 0.04	1.042 (0.908–1.196), 0.561	1.005 (0.884–1.143), 0.939
Triglyceride >200 mg/dl	1.063 (0.862–1.311), 0.567	0.943 (0.812–1.096), 0.446	1.089 (0.94–1.263), 0.256
Glucose >100 mg/dl	1.163 (0.948–1.425), 0.147	1.225 (1.093–0.373), <0.001	1.225 (1.066–0.408), 0.004
Gamma-gt >28 mg/dl	1.664 (1.367–2.026), <0.001	1.653 (1.448–1.887), <0.001	1.477 (1.302–1.675), <0.001
Current smoking	1.694 (1.416–2.025), <0.001	1.815 (1.593–2.067), <0.001	1.420 (1.233–1.636), <0.001

[a]Excluding participants with missing values: 5.75 years median survival time from first examination to death; 9.25 years for men alive.

TABLE 4B. COX PROPORTIONAL HAZARD REGRESSION ANALYSES FOR WOMEN AT FIRST EXAMINATION IN RELATION TO ALL-CAUSE MORTALITY, VHM&PP, 1985–1999

	Cox models (based on measurements at first examination)		
Women[a]	*Up to 49 (mean 33.3) years* n = *54,445, 309 deaths* *Hazard ratio (95% CI),* p-*value*	*50–64 (mean 56.9 years)* n = *16,118, 520 deaths* *Hazard ratio (95% CI),* p-*value*	*≥65 (mean 72.3) years* n = *8,010, 1,404 deaths* *Hazard ratio (95% CI),* p-*value*
Age (years)	1.079 (1.062–1.097), <0.001	1.11 (.087–1.134), <0.001	1.117 (1.106–1.127), <0.001
Systolic blood pressure (mm Hg)	1.011 (1.005–1.017), <0.001	1.005 (1.001–1.009), 0.018	1.003 (1.001–1.005), 0.016
Body mass index <21 kg/m^2	1.155 (0.854–1.561), 0.350	1.346 (0.977–1,853), 0.069	1.244 (1.06–1.46), 0.008
Body mass index medium quartiles (kg/m^2)	Referent	Referent	Referent
Body mass index >26.7 kg/m^2	1.167 (0.887–1.534), 0.269	0.998 (0.828–1.204), 0.984	0.985 (0.877–1.106), 0.798
Cholesterol <184 mg/dl	0.904 (0.672–1.217), 0.904	1.722 (1.26–2.354), <0.001	1.477 (1.214–1.797), <0.001
Cholesterol medium quartiles (mg/dl)	Referent	Referent	Referent
Cholesterol >244 mg/dl	1.201 (0.909–1.586), 0.19	0.842 (0.7–1.012), 0.068	0.943 (0.843–1.055), 0.308
Triglyceride >200 mg/dl	1.367 (0.954–1.954), 0.089	1.365 (1.091–1.708), 0.006	1.214 (1.068–1.380), 0.003
Glucose >100 mg/dl	1.181 (0.909–1.533), 0.2130	1.204 (1.003–1.445), 0.046	1.172 (1.053–1.305), 0.004
Gamma-gt >28 mg/dl	2.417 (1.767–3.308), <0.001	1.557 (1.251–1.938), <0.001	1.391 (1.207–1.604), <0.001
Current smoking	1.999 (1.580–2.530), <0.001	1.67 (1.308–2.131), <0.001	1.494 (1.165–1.916), 0.002

[a]Excluding participants with missing values: 6.25 years median survival time from first examination to death; 9.77 years for women alive.

sexes, as is level of systolic blood pressure. In men, a low cholesterol level is significantly predictive of risk at all ages, including the youngest age group screened, <50 years of age, although the latter is of borderline significance. As well as other expected predictors, a low BMI is also consistently significant in men. In women, a low cholesterol level is even more markedly predictive among those >50 years, but there is no significant impact on mortality of either low cholesterol level or BMI in women <50 years.

In Table 5, adjusted hazard ratios (HR) for low and high cholesterol values at first examination in relation to different causes of death are given. These reveal a higher risk of death from coronary heart diseases with elevated cholesterol levels (compared with medium quartiles) in young men (HR = 2.31, $p < 0.001$) and women (HR = 3.17, $p = 0.018$). Average cholesterol level was also consistently predictive of risk in men at all ages but not among women from 50 years onward. Low cholesterol level was predictive for death of "other cardiovascular diseases" (more chronic patterns, such as heart failure) in women >65 years of age (HR = 1.96, $p = 0.004$).

In men, low cholesterol level appeared to be associated with increased risk of death from cancer in all age groups. However, only in the ≥65 years group was this statistically significant ($p = 0.014$). In women, low cholesterol level was significantly predictive for death of cancer in the age group 50–64 ($p = 0.004$). In the oldest age group, there was a borderline significant protective effect of elevated cholesterol >244 mg/dl.

No significant association of cholesterol and death through stroke could be detected. For "other causes of death," there were strong effects of low cholesterol in women >50 years of age. Between 50 and 65, the HR was 2.826 ($p < 0.001$), and >65 years, the risk was increased by 1.818 ($p = 0.017$). In men, the HR with lower cholesterol was increased in the 50–64 years age group by 1.51 ($p = 0.035$). Exploratory analyses revealed that low cholesterol levels predict liver disease, gastrointestinal cancers in both men and women, and death through suicide or mental diseases in men.

Finally, GEE models that take account of the repeated measures (more than 450,000) were used to examine the relationship between risk factors and subsequent mortality for both men and women in the different age categories. In relation to all-cause mortality, these produced essentially similar results as the Cox models, high cholesterol level being significant in men <50 ($p = 0.005$). Low cholesterol level was significantly predictive in men and women of 50–64 years (both $p < 0.001$) as well as in men of ≥65 years ($p = 0.048$) and in women ≥65 years of age ($p < 0.001$). However, the relationship between low cholesterol level and all-cause mortality in men up to 49 years was no longer significant ($p = 0.129$). Regarding mortality through coronary heart disease, there was only one difference between the results of the two multivariate models. For women <50 years of age, having a low cholesterol level (<184 mg/dl) was a significant protective factor ($p = 0.009$), in contrast to young men, where this association was insignificant.

Findings from GEE and Cox models were almost the same when eliminating deaths that occurred within 1 year of the examination (between 3% and 7% depending on age and sex group). The estimates for cholesterol also remained stable when sociodemographic variables were added to the models. In this population, total mortality risk increased in blue collar male workers up to the age of 64 ($p < 0.001$) and in women up to the age of 50 ($p < 0.001$). Participants who were married had a lower risk ($p < 0.001$), but there were no significant interactions with cholesterol levels.

DISCUSSION

The purpose of the present study was to address the independent impact of cholesterol levels on mortality in a healthy population of 149,650 people. To our knowledge, it is probably the largest single prospective database with equivalent numbers of men and women systematically examined using the same protocol, thus offering a clear contrast in the female and male patterns. This allows for precise estimates of the interrelationship between age and sex on both all-cause and disease-specific mortality and with repeated risk factor profiles in the same individuals. Previous reports either were meta-analyses, using different assessment procedures[10] or were not large enough to assess all-cause mortality.[11–19]

An important new finding is the contrast in the predictive value of low cholesterol level between the sexes. Although event rates at follow-up are clearly much lower in the under-50s categories in both sexes, there was a trend of borderline significance between low cholesterol level and mor-

Table 5. Adjusted HR of Cholesterol at First Examination in Relation to Cause-Specific Mortality by Sex and Age Group, VHM&PP, 1985–1999

	Men			*Women*		
	20–49 years	*50–64 years*	*≥65 years*	*20–49 years*	*50–64 years*	*≥65 years*
Coronary heart disease (ICD-9 410-414)						
Cholesterol <187/184 mg/dl[a]	1.74 (0.89–3.43), 0.108[b]	1.09 (0.68–1.73), 0.728	1.19 (0.88–1.63), 0.264	0.31 (0.04–2.50), 0.270	1.18 (0.35–3.97), 0.791	1.437 (0.98–2.10), 0.062
Cholesterol >248/244 mg/dl[c]	2.31 (1.41–3.78), 0.001	1.26 (0.95–1.68), 0.116	1.31 (1.04–1.65), 0.021	3.17 (1.22–8.27), 0.018	1.26 (0.73–2.19), 0.412	1.003 (0.82–1.23), 0.975
Cholesterol per unit mg/dl	1.009 (1.005–1.013), <0.001	1.004 (1.001–1.007), 0.013	1.003 (1–1.005); 0.025	1.015 (1.009–1.021), <0.001	1.004 (0.999–1.009), 0.11	1 (0.998–1.002), 0.762
Stroke (ICD-9 430–438)						
Cholesterol <187/184 mg/dl	0.89 (0.23–3.45), 0.871	0.76 (0.29–1.94), 0.562	1.22 (0.8–1.87), 0.364	1.22 (0.31–4.87), 0.776	1.28 (0.38–4.34), 0.689	1.38 (0.82–2.32), 0.225
Cholesterol >248/244 mg/dl	0.91 (0.29–2.85), 0.873	0.78 (0.44–1.37), 0.38	1.12 (0.8–1.57), 0.518	1.36 (0.28–6.78), 0.7	0.7 (0.36–1.35), 0.287	0.91 (0.66–1.22), 0.539
Other cardiovascular diseases (ICD-9 394-409, 415-429, 440-456)						
Cholesterol <187/184 mg/dl[a]	Insufficient number	1.47 (0.85–2.55), 0.169	0.85 (0.52–1.37), 0.5	Insufficient number	Insufficient number	1.96 (1.24–3.1), 0.004
Cholesterol >248/244 mg/dl[c]	of events	0.93 (0.60–1.42), 0.723	0.81 (0.56–1.18), 0.269	of events	of events	1.04 (0.78–1.39), 0.81
Cancer (ICD-9 140–239)						
Cholesterol <187/184 mg/dl	1.33 (0.86–2.08), 0.203	1.31 (0.97–1.78), 0.08	1.43 (1.08–1.89), 0.014	0.83 (0.55–1.25), 0.366	1.86 (1.22–2.82), 0.004	1.32 (0.88–1.98), 0.18
Cholesterol >248/244 mg/dl	1.11 (0.76–1.61), 0.594	1.12 (0.9–1.36), 0.314	0.97 (0.76–1.24), 0.785	1.02 (0.7–1.51), 0.903	0.8 (0.62–1.04), 0.093	0.8 (0.64–0.99), 0.048
Other death causes						
Cholesterol <187/184 mg/dl	1.14 (0.81–1.6), 0.447	1.51 (1.03–2.21), 0.035	1.19 (0.82–1.73), 0.35	0.94 (0.55–1.6), 0.824	2.83 (1.56–5.13), <0.001	1.82 (1.11–2.98), 0.017
Cholesterol >248/244 mg/dl	1.15 (0.83–1.58), 0.41	0.84 (0.61–1.17), 0.31	0.73 (0.52–1.03), 0.075	1.388 (0.81–2.34), 0.232	0.82 (0.53–1.26), 0.356	1.03 (0.77–1.39), 0.829

[a]187 mg/dl = lower quartile border for men; 184 mg/dl = lower quartile border for women; referent category middle quartiles.

[b]HR (95% CI), *p* values for cause-specific survival calculated from Cox proportional hazard regression analyses; coefficients adjusted for age, systolic blood pressure, body mass index, triglycerides, glucose, gamma-gt, and smoking.

[c]248 mg/dl = upper quartile border for men; 244 mg/dl = upper quartile border for women; referent category middle quartiles.

tality from cancer among the younger men, but no such pattern for women. The relationship between low cholesterol level and all-cause mortality[22–29] is confirmed for both men and women of ≥50 years. This contradicts previous assessments that low cholesterol level is just a proxy or marker for frailty occurring with age. The fact that low BMI is important for men but not for premenopausal women suggests that low levels reflect a process of illness in men, and a naturally low cholesterol level in itself is not a risk factor but a physiologically normal state in women. The disease-specific patterns seen for liver disease and some cancers are all in keeping with this conclusion and with the earlier literature. This study appears to be the first to have examined this issue among younger men and women and to show the patterns on such a large scale in middle-aged men and women.

In a definitive state-of-the-art review of the differing mortality experience of men and women from cardiovascular disease, Barrett-Connor[2] emphasizes the likelihood that there are distinct constitutional or biological differences between men and women, as well as gender-related acculturation and lifestyle differences. Improved understanding of the biological determinants, including genotypic programming, will help to elucidate these processes. This dataset provides strong empirical evidence for a significant biological difference between men and women and revisits some of the previous evidence from a current perspective.

Examination of the mean cholesterol levels according to age in relation to both all-cause and cardiovascular disease mortality illustrates strikingly that the expected rise in cholesterol occurs definitively in the decade from 50 years onward and suggests, therefore, that menopausal effect (menopausal status was not directly assessed in the study) has to be the important determinant in cholesterol levels in women. The Renfrew and Paisley study[13] demonstrates that conventional risk factors are predictive of risk of cardiovascular disease, although the level of absolute risk is of a different order, suggesting other factors at play. The analysis of Lawlor et al.,[21] implying that variations in lifestyle risk factors explain the differences in male-female risk ratios in international patterns of coronary heart disease mortality, presents mainly age-standardized data, but this can tend to obscure age-specific differences in risk, especially important with a delayed onset of the disease in women relative to male cohort contemporaries.

Total cholesterol level was not a significant independent predictor in older women, which requires interpretation. This study does not have data available on lipoprotein profiles or hemostatic variables, which is a drawback in addressing the significance of this phenomenon for long-term mortality patterns. However, it is now established in the literature that high-density lipoprotein (HDL) cholesterol patterns are slower to change adversely after menopause in women.[36] It has also been elegantly demonstrated by Meade et al.[8] that it is the interaction between preexisting underlying atheroma and midlife changes in both hemostatic variables and lipoprotein profiles that accounts for the gradual increase in risk for women, in what is a complex multifactorial disease. The dataset provides important information on older participants, both women and men. There are two possible reasons why total cholesterol may not be as important as a risk factor in older people. First, there may be a survivor or attrition effect, with those at highest relative risk succumbing early. In this analysis, mean cholesterol levels in survivors <50 years were considerably lower than in those who developed cardiovascular disease. Second, in a population with lifetime cumulative exposure to atherogenic processes, the disease is very widely established in the population as a whole in old age.

Although its role in the etiology of coronary heart disease is controversial, it is notable too that triglyceride, which may be an especially important risk factor in women,[2] continues to rise with time among women in this dataset, in contrast to the pattern in men. If triglyceride levels constitute an independent risk factor,[37] this may help to explain why women gradually catch up on risk with men. Triglycerides can also impact the coagulation system through their effects on Hageman factor as well as direct effects on factor VII.[38]

There are some limitations to the VHM&PP, primarily because of the mechanism of recruiting the participants. Although the sample is very large and covers a substantial part of the whole population of the region and, hence, is likely to be representative, it is self-selected. Nonetheless, comparisons with the WHO standard population[33] show that the participation profile fits very well with that expected up to the age of 65 years in both men and women. From 65 years on, men

are underrepresented by a factor of 0.63 and women by a factor of 0.86.

In conclusion, this large-scale population-based study clearly demonstrates the contrasting patterns of cholesterol level in relation to risk, particularly among those less well studied previously, that is, women of all ages and younger people of both sexes. The role of high cholesterol in predicting risk of premature heart disease could be confirmed in men of all ages and in women under the age of 50, as could low cholesterol in those >50 years of both sexes and in men, but not women, <50 years. Our analysis provides comprehensive empirical support for the proposition that the differences in risk between men and women have a constitutional basis, in addition to expected environmental influences.

ACKNOWLEDGMENTS

We thank Prof. Weiland, University of Ulm, and Prof. Leslie Daly, University College Dublin, for their helpful critical comments on earlier drafts of this paper.

REFERENCES

1. Wingard DL, Suarez L, Barrett-Connor E. The sex differential in mortality from all causes and ischemic heart disease. Am J Epidemiol 1983;117:165.
2. Barrett-Connor E. Sex differences in coronary heart disease. Why are women so superior? The 1995 Ancel Keys Lecture. Circulation 1997;95:252.
3. Grundy SM, D'Agostino Sr RB, Mosca L, et al. Cardiovascular risk assessment based on U.S. cohort studies: Findings from a National Heart, Lung, and Blood institute workshop. Circulation 2001;104:491.
4. Stamler J, Dyer AR, Shekelle RB, Neaton J, Stamler R. Relationship of baseline major risk factors to coronary and all-cause mortality, and to longevity: Findings from long-term follow-up of Chicago cohorts. Cardiology 1993;82:191.
5. Anderson KM, Castelli WP, Levy D. Cholesterol and mortality. 30 years of follow-up from the Framingham study. JAMA 1987;257:2176.
6. Jacobs D, Blackburn H, Higgins M, et al. Report of the Conference on Low Blood Cholesterol: Mortality associations. Circulation 1992;86:1046.
7. Menotti A, Mulder I, Nissinen A, et al. Cardiovascular risk factors and 10-year all-cause mortality in elderly European male populations: The FINE study. Finland, Italy, Netherlands, Elderly. Eur Heart J 2001;22:573.
8. Meade TW, Dyer S, Howarth DJ, Imeson JD, Stirling Y. Antithrombin-III and procoagulant activity—Sex differences and effects of the menopause. Br J Haematol 1990;74:77.
9. Lowe LP, Greenland P, Ruth KJ, Dyer AR, Stamler R, Stamler J. Impact of major cardiovascular disease risk factors, particularly in combination, on 22-year mortality in women and men. Arch Intern Med 1998;158:2007.
10. Stamler J, Stamler R, Neaton JD, et al. 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 1999;282:2012.
11. Boniface DR, Tefft ME. Dietary fats and 16-year coronary heart disease mortality in a cohort of men and women in Great Britain. Eur J Clin Nutr 2002;56:786.
12. Dorn JM, Winkelstein W, Trevisan M. Body mass index in a general population sample of men and women—The Buffalo Health Study. Am J Epidemiol 1997;146:919.
13. Isles CG, Hole DJ, Hawthorne VM, Lever AF. Relation between coronary risk and coronary mortality in women of the Renfrew and Paisley survey: Comparison with men. Lancet 1992;339:702.
14. Houterman S, Vershuren WMM, Hofman A, Witterman JCM. Serum cholesterol is a risk factor for myocardial infarction in elderly men and women: The Rotterdam Study. J Intern Med 1999;246:25.
15. Jonsdottir LS, Sigfusson N, Guonason V, Sigvaldason H, Trorgeirsson G. Do lipids, blood pressure, diabetes and smoking confer equal risk of myocardial infarction in women as in men? The Reykjavik Study. J Cardiovasc Risk 2002;9:67.
16. Jousilahti P, Vartiainen E, Tuomilehto J, Puska P. Sex, age, cardiovascular risk factors, and coronary heart disease—A prospective follow-up study of 14,789 middle-aged men and women in Finland. Circulation 1999;99:1165.
17. Murabito JM, Evans JC, Nieto K, Larson MG, Levy D, Wilson PWF. Prevalence and clinical correlates of peripheral arterial disease in the Framingham Offspring Study. Am Heart J 2002;143:961.
18. Prescott E, Hippe M, Schnohr P, Hein HO, Vestbo J. Smoking and risk of myocardial infarction in women and men: Longitudinal population study. Br Med J 1998;316:1043.
19. Wilson PWF, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation 1998;97:1837.
20. Ecological analysis of the association between mortality and major risk factors of cardiovascular disease. The World Health Organization MONICA Project. Int J Epidemiol 1994;23:505.
21. Lawlor DA, Ebrahim S, Davey-Smith G. Sex matters: secular and geographical trends in sex differences in coronary heart disease mortality. Br Med J 2001;323:541.

22. Epstein FH. Relationship between low cholesterol and disease. Evidence from epidemiological studies and preventive trials. Ann NY Acad Sci 1995;748:482.
23. Muldoon MF, Manuck SB, Matthews KA. Lowering cholesterol concentrations and mortality: A quantitative review of primary prevention trials. Br Med J 1990;301:309.
24. Muldoon MF, Manuck SB, Mendelsohn AB, Kaplan JR, Belle SH. Cholesterol reduction and non-illness mortality: Meta-analysis of randomised clinical trials. Br Med J 2001;322:11.
25. Wannamethee G, Shaper AG, Whincup PH, Walker M. Low serum total cholesterol concentrations and mortality in middle aged British men. Br Med J 1995; 311:409.
26. Song YM, Sung J, Kim JS. Which cholesterol level is related to the lowest mortality in a population with low mean cholesterol level: A 6.4-year follow-up study of 482,472 Korean men. Am J Epidemiol 2000; 151:739.
27. Horwich TB, Hamilton MA, Maclellan WR, Fonarow GC. Low serum total cholesterol is associated with marked increase in mortality in advanced heart failure. J Card Fail 2002;8:216.
28. Schatz IJ, Masaki K, Yano K, Chen R, Rodriguez BL, Curb JD. Cholesterol and all-cause mortality in elderly people from the Honolulu Heart Program: A cohort study. Lancet 2001;358:351.
29. Iso H, Sato H, Chambless L, et al. Collaborative overview (meta-analysis) of prospective observational studies of the associations of usual blood pressure and usual cholesterol levels with common causes of death: Protocol for the second cycle of the Prospective Studies Collaboration. J Cardiovasc Risk 1999;6: 315.
30. Ulmer H, Kelleher C, Diem G, Concin H. Long-term tracking of cardiovascular risk factors among men and women in a large population-based health system: The Vorarlberg Health Monitoring & Promotion Programme. Eur Heart J 2003;24:1004.
31. Ulmer H, Bachmann J, Huber K, Concin H, Bischof HP. Follow-up studies of routine health screening in Vorarlberg 1986–1994. Wien Klin Wochenschr 1997; 109:160.
32. Ulmer H, Diem G, Bischof HP, Ruttmann E, Concin H. Recent trends and sociodemographic distribution of cardiovascular risk factors: Results from two population surveys in the Austrian WHO CINDI demonstration area. Wien Klin Wochenschr 2001;113:573.
33. Ahmad OE, Boschi-Pinto C, Lopez AD, Murray CJL, Lozano R, Inoue M. Age standardization of rates: A new WHO standard. Geneva: World Health Organization GPE Discussion Paper Series 2000:31.
34. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. Biometrics 1986; 42:121.
35. Stata Corporation. Stata Statistical Software: Release 7 Special Edition. College Station, TX, 2001.
36. Kuller LH, Gutai JP, Meilahn EN, Matthews KA, Plantinga P. Relationship of endogenous sex hormones to lipids and apoproteins in postmenopausal women. Arteriosclerosis 1990;10:1058.
37. Gaziano JM, Hennekens CH, O'Donnell CJ, Breslow JL, Buring JE. Fasting triglycerides, high-density lipoprotein and risk of myocardial infarction. Circulation 1997;96:2520.
38. Kelleher CC, Mitropoulos KA, Imeson J, et al. Hageman factor and risk of myocardial infarction in middle-aged men. Atherosclerosis 1992;97:67.

Address reprint requests to:
Hanno Ulmer, Ph.D.
Department of Biostatistics and Documentation
Leopold Franzens University of Innsbruck
Schoepfstrasse 41
A-6020 Innsbruck
Austria

E-mail: Hanno.Ulmer@uibk.ac.at