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Cohort study of serum total cholesterol and in-hospital incidence of infectious diseases

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SUMMARY

A multiethnic cohort of adult members of the Kaiser Permanente Medical Care Program (55300 men and 65271 women) was followed for 15 years (1979–93) to assess the association between total cholesterol and risk of infections (other than respiratory and HIV) diagnosed in the in-patient setting. Using multivariate Cox regression, total cholesterol was inversely and significantly related to urinary tract, venereal, musculo-skeletal, and all infections among men; and to urinary tract, all genito-urinary, septicaemia or bacteraemia, miscellaneous viral site unspecified, and all infections among women. The reduction of risk of all infections associated with a 1 S.D. increase in total cholesterol was 8% in both men (95% CI, 4–12%) and women (95% CI, 5–11%). For urinary tract infections among men, as for septicaemia or bacteraemia and nervous system infections among women, the risk relation was restricted to persons aged 55–89 years. Nervous system infections were positively related to total cholesterol among women aged 25–54. In both genders, the significant inverse association with all infections persisted after excluding the first 5 years of follow-up. Collectively, these data are suggestive of an inverse association, although not entirely consistent, between total cholesterol and incidence of infections either requiring hospitalization or acquired in the hospital. Further research is needed to elucidate whether these associations are biologically plausible or represent uncontrolled confounding by unmeasured risk factors.

INTRODUCTION

Earlier epidemiological studies have found that subjects with either high or low blood cholesterol levels experience elevated total mortality rates, whereas individuals with intermediate levels experience the least mortality [1–4]. While the consequences of hypercholesterolaemia are well understood (i.e. increased risk of coronary disease and thromboembolic stroke) [5, 6], the nature and implications of associations between low blood cholesterol and non-cardiovascular causes of death represent a complex problem and continue to be an area of intense scrutiny [1–7]. Increased non-cardiovascular mortality at low levels of blood cholesterol include some cancers, haemorrhagic stroke, some respiratory diseases, digestive diseases, suicide and heterogeneous residual causes including those of infectious aetiology.

Two lines of evidence have recently stimulated an interest in a possible role of lipids in immune processes and thus in infection. First, animal experiments have shown that lipoproteins may protect against the lethal effect of endotoxins [8]. Second, pre-epidemic low

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levels of serum cholesterol have been found to predict HIV-infection and risk of death from AIDS in two separate US populations [9, 10]. However, no epidemiological studies have explicitly investigated the association of serum cholesterol level with infectious diseases other than those of the respiratory system and HIV/AIDS.

Thus, our primary aim was to examine the association between total cholesterol level and subsequent risk of developing specific common infectious diseases in the context of hospitalizations in a large health maintenance organization.

METHODS

Cohort description

The Kaiser Permanente Medical Care Program of Northern California is a pre-paid health plan that provides health coverage to over one third of the greater San Francisco–Oakland area population. A full description of the Program is available elsewhere [11, 12]. Kaiser Permanente members are ethnically diverse, but not strictly representative of the Bay Area population in that they have, on average, higher educational attainment than those not in the health plan. In the present study, the baseline examination consisted of Multiphasic Health Checkups (MHC) undertaken in Kaiser Permanente Medical Centers between 1979 and 1985. For participants with repeated MHC, we used data from the first available MHC.

At the MHC, members filled in questionnaires detailing personal and demographic data (age, sex, race, education level, marital status), past medical history, reproductive history (pregnancy and menopausal status), and health behaviours (smoking and alcohol consumption). Pre-existing or current medical conditions were ascertained by the questions 'has a doctor ever said you had any of the diseases listed below?' and 'Do you now have any of the following problems?', followed by 'No', 'Yes', or 'Currently under treatment' response options. A 'Yes' or 'Currently under treatment' response was considered a positive history of each disease. A validation study of self-reported data *vs*. medical chart review on liver disease and venereal diseases yielded sensitivity and specificity ranging between 76 and 86% [13]. Unexplained weight loss (as a Yes/No item) was also queried in the medical history questionnaire. No information on time period or magnitude of unexplained weight loss was obtained. Based on answers to the alcohol questionnaire, we classified persons as abstainers (participants who responded that they never or almost never consumed alcoholic beverages in the past year), former drinkers, and current drinkers. Current drinkers were further classified by the average number of drinks per day consumed during the past year (i.e. special occasion only, < 1/day, 1–2/day, 3–5/day, 6–8/day, $\geqslant 9$/day).

Weight, height, systolic and diastolic blood pressure, blood glucose and leucocyte count were measured according to standardized laboratory procedures [12]. Body mass index was computed as weight (kg) divided by height (m^2). Total serum cholesterol was measured at the Kaiser Permanente Regional Laboratory (Berkeley, CA) according to enzymatic methods and calibration standards reference to the Abell–Kendall method [13]. Quarterly peer review evaluation was performed using specimens provided by the American College of Pathologists, and all measurements were within the acceptable limits of ± 2 S.D. of the group mean. Furthermore, prior to analysis, all the cholesterol values were corrected for measurement deviation as previously described [14].

Among 144003 members who had a non-missing serum cholesterol measurement at their first MHC, those aged 24 or younger ($n = 15762$), those aged 90 or older ($n = 59$), as well as women reporting pregnancy at the time of examination ($n = 219$) were excluded. Of the remaining 127963 participants, 7392 were also ineligible because of lack of data on covariates of interest. These exclusions left 55300 men and 65271 women as the sample for statistical analysis. The study was approved by the Institutional Review Boards of the Kaiser Foundation Research Institute and the University of Minnesota.

Hypertension was defined as systolic blood pressure $\geqslant 160$ mmHg and diastolic blood pressure $\geqslant 90$ mmHg or self-reported history of or treatment for hypertension. The following pre-existing (non-mutually exclusive) self-reported history of medical conditions was identified (by questionnaire) at baseline: diabetes (1712 in men; 1750 in women), coronary heart disease (1545 in men; 1135 in women), stroke (386 in men; 360 in women), emphysema (510 in men; 314 in women), asthma (3131 in men; 3579 in women), cancer or tumour ($n = 1274$ in men; 4772 in women), liver disease (2015 in men, 1430 in women), kidney or bladder infections (2348 in men, 10574 in women), thyroid disease (1067 in men; 5580 in women), venereal disease (6167 in men; 2879 in women), and colon-bowel disease ($n = 1282$ in men; $n = 2053$ in

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women). Unexplained weight loss was reported by 1109 men (2%) and by 1116 women (1·7%), respectively.

Ascertainment of study outcome measures

Case identification between the baseline MHC (1979–85) and the end of the study (31 December 1993) consisted of a standardized computerized search for diagnosis codes indicative of infectious diseases among 12 possible discharge diagnosis codes per hospitalization (i.e. primary diagnosis or not), allowing for multiple events per person. For example, a person with three hospitalizations during the follow-up of the study, one for acute appendicitis, another for hepatitis, and another for a kidney infection, contributed three individual events. The same person, however, contributed only one event (the first one, namely the appendicitis) for the 'all infections' outcome.

Combining men and women, and using the entire follow-up, 68·3% had a single event (i.e. hospitalization for infectious disease or infection acquired in the hospital), 18·4% had 2 events, 10·2% had 3 events, 2·5% had 4 events, 0·6% had 5 events or more. The hospital discharge diagnoses were coded according to the *International Classification of Diseases, Ninth Revision* (*ICD-9*) [15]. Outpatient records were not available.

For the purposes of this study, and to facilitate getting enough events to have robust estimates of relative risks, the incidence of infectious diseases were grouped as follows (corresponding ICD-9 rubrics are given in parentheses): (1) intestinal infections (003, 008); (2) viral hepatitis (070); (3) acute appendicitis (540); (4) all digestive-liver infections, including the above three conditions plus diverticulitis (562·01), abscess of intestine (566, 569·5), abscess of liver and portal pyaemia (572·0, 572·1), acute cholecystitis (575·0), and cholangitis (576·1); (5) acute and subacute bacterial endocarditis (421); (6) infections of the kidney (590); (7) urinary tract infections (599); (8) all genito-urinary infections,including infections of the kidney (590), cystitis (595), urinary tract infections (599), inflammatory diseases of the prostate (601), and orchitis and epididymitis (604); (9) venereal diseases (090–099, 131); (10) gynaecological infections, including inflammatory diseases of the ovary, fallopian tube, pelvic cellular tissue, and peritoneum (614–616); (11) musculo-skeletal infections, including pyogenic arthritis (711), infective myositis (728·0), and osteomyelitis, periostitis and other bone infections (730); (12) skin and subcutaneous tissue infections, including herpes zoster (053), herpes simplex (054), dermatophytosis (110), candidiasis (112) and other infections of skin and subcutaneous tissue (680–686); (13) septicaemia or bacteraemia (unspecified) (038, 790·7); (14) gangrene (785·4); (15) central and peripheral nervous system infections, including meningitis (320–321), encephalitis (323), and intracranial and intraspinal abscess (324); (16) endotoxic shock, gram negative (785·59); (17) miscellaneous bacterial infections of unspecified site (041); (18) miscellaneous viral infections of unspecified site (079); and (19) all infections. The incidence of cholera (001), typhoid and paratyphoid fevers (002), zoonotic bacterial diseases (020–027), leprosy (030), tetanus (037), poliomyelitis (045–049), arthropod-borne viral diseases (060–066), infectious mononucleosis (075), rickettsioses and other arthropod-borne diseases (080–088), helminthiasis (120–129), and toxoplasmosis (130) was extremely low in this US urban population (data not shown). Therefore, we were unable to evaluate variations in the risk of these infectious diseases as a function of total cholesterol.

Mortality (both in-hospital and out-of-hospital) through the end of 1993 was ascertained using the California Automated Mortality Linkage System (CAMLIS), which is a probability linkage system based on name, date of birth, race, place of birth and social security number. CAMLIS has been satisfactorily validated against the National Death Index [16].

The associations of total cholesterol with respiratory infections (including upper respiratory infections, influenza, and pneumonia) and with HIV/AIDS among Kaiser members have been reported in previous publications [10, 14].

Statistical analysis

Age-adjusted sex-specific incidence rates of hospital-diagnosed common infectious diseases (per 10000 person-years of follow-up) were calculated by categories of total cholesterol at baseline ($< 4{\cdot}14$, 4·14–5·15, 5·16–6·19 and $\geqslant 6{\cdot}20$ mmol/l, respectively) using Poisson regression. Individual follow-up time was estimated as time from the MHC to event, to end of membership, or to closing date (31 December 1993), whichever came first. The median duration of follow-up was 9·9 years (range between < 1 year and up to 15 years).

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To assess graded relationships, each infectious disease outcome was modeled using Cox regression [17] as a function of a continuous total cholesterol and age terms, respectively, and stratifying by sex. To adjust for potential confounding effects, multivariate analysis was then undertaken entering variables for race (black, Asian, and other, relative to white), educational level (college education *vs.* lower than a college education), marital status (married or re-married, separated or divorced, and widowed, relative to never married), menopausal status (among women), cigarette smoking status (former, current, relative to never smokers), alcohol consumption (former, occasional-light-moderate (up to 2 drinks/day), and high ($\geqslant 3$ drinks/day), relative to abstainers), body mass index, systolic blood pressure, leucocyte count, blood glucose, an indicator variable for presence of prevalent disease at baseline (none = 0; one or more = 1), and unexplained weight loss. All these covariates were measured at the time of the MHC.

As an attempt to circumvent the problem of confounding by latent or undiagnosed infectious disease and early mortality by any cause (ascertained by the CAMLIS), the analysis was repeated after excluding events and deaths occurring in the first 5 years of follow-up.

Because low cholesterol has been found to predict non-atherosclerotic disease mortality in middle-aged [2–4] and elderly populations [18, 19], but not in one younger population [20], we assessed whether the interaction between total cholesterol (as a continuous variable) and age (as a categorical variable: 25–54 = 0; 55–89 = 1) improved the fit of the models, respectively. This was done using a likelihood ratio test.

Because of the potential of confounding by co-morbidity (i.e. ailments posing a threat to survival and associated with the cholesterol level), we performed analysis by four strata according to personal history of disease at the time of enrolment: cardiovascular disease (coronary heart disease or stroke), diabetes, any other disease (one or more of the following: emphysema, asthma, cancer or tumour, liver disease, kidney or bladder infection, thyroid disease, venereal disease, colon-bowel disease, or unexplained weight loss), and no history of disease. Finally, we stratified the analysis of all infections into infections 'in first place' (i.e. principal cause of hospitalization, and thus less likely to be affected by co-morbidity), and infections 'not in first place' (i.e. secondary diagnosis, or infections more likely to be related to other contributory illnesses). All statistical analyses were conducted using SAS software (version 6·11, SAS Institute Inc., Cary, NC).

It should be indicated that, given the multiple testing performed in this study, some of the significant associations (i.e. $P < 0{\cdot}05$ or confidence interval not including unity) probably arose by chance.

RESULTS

The average age of the Kaiser Permanente cohort was 43 years, with a S.D. of 14 years (Table 1). The ethnic breakdown was: 60% whites, 25% blacks and 15% Asian and other. Among women, 7% had been widowed (in contrast to less than 2% among men), and 10% had reached menopause. The proportion of current smokers was similar between genders, although men were more likely to be heavy smokers (i.e. > 20 cigarettes/day) than women. More men than women were current alcohol drinkers (87% *vs.* 79%), and more likely to consume $\geqslant 3$ drinks/day (15% *vs.* 5%).

The average concentration of total cholesterol was 5·45 mmol/l (210 mg/dl) in men and 5·41 mmol/l (209 mg/l) in women . There was an increase of total cholesterol as a function of age. The corresponding linear slopes obtained regressing age on total cholesterol were 0·0223 mmol/dl (S.E. = 0·00039 mmol/l] in men, and 0·0430 mmol/l [S.E. = 0·00035 mmol/l] in women, per year respectively, after removing the effects of education, race, smoking, alcohol, body mass index, leucocyte count, medical conditions, and unexplained weight loss at baseline.

The prevalence of hypertension (about 18%) did not differ by sex. By contrast, men showed a higher percentage of personal history of heart disease and venereal diseases, and women showed a higher percentage of personal history of cancer or tumour and of kidney or bladder infections.

The total number of hospital-diagnosed infections with corresponding age-adjusted rates across total cholesterol levels are given in Table 2, separately for men and women. The three most common types of infections were genito-urinary, skin and subcutaneous tissue and digestive-liver among men, and genito-urinary, gynaecological, and of skin and subcutaneous tissue among women. In men, there were inverse significant trends of age-adjusted rates of venereal diseases ($P = 0{\cdot}03$) and of all infections ($P = 0{\cdot}003$)

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Table 1. *Selected baseline characteristics of the cohort. Kaiser Permanente Medical Care Program, N. California Region (1979–85)*

Characteristics	Men ($n = 55300$)	Women ($n = 65271$)
Age (years)	43·3 ± 13·8	42·9 ± 14·2
Partial college or higher education level (%)	68·3	62·6
Race (%)		
White	61·6	57·6
Black	23·2	27·2
Asian	7·4	7·7
Other*	7·8	7·5
Marital status (%)		
Never married	18·9	15·7
Married or remarried	66·4	57·2
Separated or divorced	12·9	9·8
Widowed	1·6	7·1
Unknown	0·2	0·2
Menopausal status (%)		
No	—	89·8
Yes	—	10·2
Smoking status (%)		
Never	41·5	53·6
Former	27·8	17·8
Current	29·4	27·5
< 10 cigarettes/day†	58·5	61·8
10–19 cigarettes/day†	12·0	14·5
20 + cigarettes/day†	29·5	23·7
Unknown	1·4	1·1
Alcohol intake status (%)		
Never	4·8	11·5
Former	3·2	2·0
Current	86·6	79·0
Up to 2 drinks/day‡	84·6	94·7
3 drinks or more/day‡	15·4	5·3
Unknown	5·3	7·5
Body mass index (kg/m^2)	25·4 ± 3·8	24·5 ± 5·2
Serum cholesterol (mmol/l)	5·45 ± 1·16	5·41 ± 1·21
Systolic blood pressure (mmHg)	128·5 ± 17·5	125·2 ± 20·2
Diastolic blood pressure (mmHg)	77·2 ± 10·5	74·7 ± 11·3
Leucocyte count (1000 cells/mm^3)	6·6 ± 3·6	6·8 ± 3·5
Blood glucose (mg/dl)	101·1 ± 29·2	97·0 ± 26·7
Hypertension (%)§	17·7	18·1
Personal history of (%)		
Diabetes	3·1	2·7
Heart disease	2·8	1·7
Stroke	0·7	0·6
Emphysema	0·9	0·5
Asthma	5·7	5·5
Cancer of tumour	2·3	7·3
Liver disease (cirrhosis, hepatitis)	3·6	2·2
Kidney or bladder infections	4·2	16·2
Thyroid disease	1·9	8·5
Venereal disease	11·2	4·4
Colon-bowel disease	2·3	3·1
Unexplained weight loss	2·0	1·7

For continuous variables, values are given as means ± S.D.
* Hispanic non-white, American Indian or Alaskan native.
† % among current smokers.
‡ % among current drinkers.
§ Systolic blood pressure > = 160 mmHg and diastolic blood pressure > = 90 mmHg, or self-reported history of or under treatment for hypertension.

across total cholesterol levels. Also among men, urinary tract infections ($P = 0·08$) displayed a marginally inverse pattern, whereas intestinal infections and gangrene showed borderline significant positive associations (both $P = 0·08$). For most other hospital-based infections (except acute appendicitis, endocarditis, and kidney infections), the age-adjusted rates were highest at the lowest total cholesterol class

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Table 2. *Age-adjusted rates per 10000 person-years of hospital-based incidence of infectious diseases by total cholesterol level and sex. Kaiser Permanent Medical Care Program, N. California Region (1979–93)*

Infections	ICD-9 Code(s)	Total cholesterol (mmol/l)					
		*n**	< 4·14	4·14–5·15	5·16–6·19	6·20+	*P*-linear trend
		Men					
Intestinal	003, 008	83	1·09	1·00	1·13	1·54	0·08
Viral hepatitis	070	33	1·08	0·38	0·62	0·66	0·74
Acute appendicitis	540	266	5·01	5·53	5·26	4·96	0·82
All digestive-liver	003, 008, 070, 540, 562·01, 566 569·5, 572·1, 575, 576·1	576	12·46	11·16	9·42	10·83	0·96
Acute and subacute endocarditis	421	50	0·41	0·70	0·70	0·57	0·81
Kidney	590	78	1·07	1·13	0·97	1·23	0·95
Urinary tract	599	921	6·26	5·44	4·87	4·92	0·08
All genito-urinary	590, 595, 599, 601, 604	1173	9·65	8·47	7·74	8·14	0·13
Venereal diseases	090–099, 131	27	0·65	0·84	0·37	0·27	0·03
Musculo-skeletal	711, 728·0, 730	120	2·21	2·18	1·81	1·72	0·38
Skin and subcutaneous tissue	053, 054, 110, 112, 680–686	781	15·15	12·16	13·04	12·40	0·44
Streptococcal septicaemia or bacteraemia	038, 790·7	465	4·65	4·99	3·81	3·97	0·20
Gangrene	785·4	149	1·42	1·49	1·18	1·75	0·08
Central and peripheral nervous system	320–324	42	1·09	0·76	0·77	0·65	0·31
Endotoxic shock, gram negative	785·59	23	0·32	0·11	0·08	0·14	0·52
Miscellaneous bacterial, unspecified site	041	100	2·13	1·37	1·44	1·16	0·18
Miscellaneous viral, unspecified site	079	63	0·89	0·87	1·21	1·20	0·61
All	All codes above	2888	47·11	40·55	36·69	36·54	0·003
		Women					
Intestinal	003, 008	114	2·18	1·41	1·41	1·30	0·39
Viral hepatitis	070	30	0·65	0·37	0·46	0·43	0·95
Acute appendicitis	540	262	4·52	4·51	4·08	3·70	0·50
All digestive-liver	003, 008, 070, 540, 562·01, 566 569·5, 572·1, 575, 576·1	565	9·79	8·43	8·26	8·18	0·66
Acute and subacute endocarditis	421	22	0·38	0·19	0·26	0·16	0·61
Kidney	590	258	3·96	3·52	3·45	3·62	0·71
Urinary tract	599	1540	9·26	12·25	9·63	9·54	0·05
All genito-urinary	590, 595, 599, 601, 604	2717	43·69	40·33	32·36	32·69	0·0003
Venereal diseases	090–099, 131	53	0·80	0·94	0·90	0·42	0·62
Musculo-skeletal	711, 728·0, 730	70	0·55	0·67	0·96	0·92	0·40
Skin and subcutaneous tissue	053, 054, 110, 112, 680–686	681	10·13	7·58	8·72	8·81	0·44
Streptococcal septicaemia or bacteraemia	038, 790·7	482	3·90	4·18	2·80	2·80	0·004
Gangrene	785·4	91	0·56	0·29	0·69	0·88	0·02
Central and peripheral nervous system	320–324	31	0·15	0·41	0·58	0·53	0·75
Endotoxic shock, gram negative	785·59	28	0·00	0·19	0·39	0·27	0·94
Miscellaneous bacterial, unspecified site	041	107	1·99	1·51	1·07	1·35	0·91
Miscellaneous viral, unspecified site	079	98	2·38	1·80	1·37	0·75	0·006
Gynaecological	614–616	958	13·25	13·50	13·04	14·62	0·47
All	All codes above	4219	70·88	61·62	53·57	53·41	0·0007

* Number of infections. For all infections, only first occurrence of infection is counted.

(< 4·14 mmol/l), but they were not part of any discernible linear trends.

In women, there were inverse associations of total cholesterol with all genito-urinary infections ($P = 0·0003$), septicaemia or bacteraemia ($P = 0·004$), miscellaneous viral infections of unspecified site ($P = 0·006$), and all infections ($P = 0·0007$). By contrast, age-adjusted incidence of gangrene was positively

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Table 3. *Age-adjusted and multivariate-adjusted relative risks of hospital-based incidence of infectious diseases per 1 S.D. increase in total cholesterol level (1·19 mmol/l), by sex. Kaiser Permanente Medical Care Program, N. California Region (1979–93)*

	Men		Women	
Infections	Age-adjusted	Multivariate-adjusted*	Age-adjusted	Multivariate-adjusted
Intestinal	1·20 (0·97–1·48)	1·18 (0·96–1·46)	0·91 (0·74–1·12)	0·93 (0·75–1·13)
Viral hepatitis	0·94 (0·64–1·36)	0·93 (0·64–1·35)	1·01 (0·68–1·50)	1·04 (0·70–1·54)
Acute appendicitis	0·98 (0·86–1·12)	0·95 (0·83–1·09)	0·95 (0·83–1·09)	0·94 (0·82–1·09)
All digestive-liver	0·99 (0·91–1·09)	0·95 (0·87–1·04)	0·98 (0·89–1·08)	0·96 (0·87–1·05)
Acute and subacute endocarditis	0·96 (0·71–1·31)	0·96 (0·70–1·30)	0·89 (0·56–1·40)	0·84 (0·53–1·36)
Kidney	0·99 (0·78–1·26)	0·95 (0·75–1·21)	0·97 (0·85–1·11)	0·93 (0·81–1·06)
Urinary tract	0·94 (0·87–1·01)	0·92 (0·86–0·99)	0·95 (0·90–1·00)	0·93 (0·88–0·98)
All genito-urinary	0·95 (0·89–1·01)	0·94 (0·88–1·00)	0·92 (0·88–0·96)	0·91 (0·87–0·95)
Venereal diseases	0·61 (0·39–0·97)	0·66 (0·42–1·03)	0·92 (0·66–1·28)	0·89 (0·65–1·23)
Musculo-skeletal	0·91 (0·75–1·11)	0·82 (0·68–0·99)	1·10 (0·87–1·41)	1·02 (0·80–1·29)
Skin and subcutaneous tissue	0·97 (0·89–1·05)	0·93 (0·86–1·00)	1·03 (0·95–1·12)	0·98 (0·91–1·07)
Streptococcal septicaemia or bacteraemia	0·93 (0·84–1·03)	0·92 (0·83–1·02)	0·86 (0·78–0·95)	0·84 (0·76–0·93)
Gangrene	1·15 (0·98–1·36)	0·98 (0·85–1·14)	1·25 (1·03–1·51)	1·10 (0·92–1·33)
Central and peripheral nervous system	0·84 (0·59–1·18)	0·90 (0·64–1·27)	1·22 (0·87–1·73)	1·10 (0·78–1·57)
Endotoxic shock, gram negative	0·96 (0·71–1·30)	0·84 (0·53–1·32)	9·89 (0·56–1·40)	0·96 (0·65–1·39)
Miscellaneous bacteria, unspecified site	0·86 (0·69–1·07)	0·83 (0·67–1·03)	0·99 (0·80–1·21)	0·96 (0·78–1·18)
Miscellaneous viral, unspecified site	1·07 (0·82–1·38)	1·04 (0·80–1·36)	0·72 (0·56–0·91)	0·70 (0·56–0·89)
Gynaecological	—	—	1·03 (0·95–1·11)	1·00 (0·93–1·08)
All	0·94 (0·90–0·98)	0·92 (0·88–0·96)	0·94 (0·91–0·97)	0·92 (0·89–0·95)

* Age, race, education level, marital status, menopausal status (among women), smoking status, alcohol consumption, body mass index, systolic blood pressure, blood glucose, leucocyte count, medical conditions at baseline (none *vs.* one or more), and unexplained weight loss. Medical conditions include self-reported personal history of diabetes, heart disease, stroke, emphysema, asthma, cancer or tumour, liver disease, kidney or bladder infection, thyroid disease, venereal disease or colon-bowel disease at baseline. Codes and total number of events are displayed in Table 2. Estimates based on complete follow-up.

related to total cholesterol among women ($P = 0{\cdot}02$). Rates of other infections, with the exception of venereal, gynaecological, of the central and peripheral nervous system, and endotoxic shock were elevated in the lowest total cholesterol class, but these elevated rates were not part of any discernible linear trends.

Sex-specific Cox proportional hazards estimates of relative risks are given in Table 3. Among men, in age-adjusted analysis using all follow-up data, a 1 S.D. increase in total cholesterol was associated with a 39% (95% confidence interval, 3–61%) reduction in risk of venereal diseases, and with a 6% (95% confidence interval, 2–10%) reduction of the risk of all infections. The 27 venereal diseases among men encompassed 18 mentions of syphilis (3 congenital, 3 early, 8 neurosyphilis and 4 other forms of syphilis), 6 mentions of gonococcal infections, 1 mention of trichomoniases and 2 mentions of other venereal diseases. A 1 S.D. increase in total cholesterol among men was related to nonsignificant reductions in risk of other types of infections in the range 1–16%, and to a nonsignificant increase of the risk of intestinal infections, gangrene and miscellaneous viral infections of unknown site. In multivariate analysis, there were significantly reduced risk of urinary tract infections (8%), musculo-skeletal (18%), and all infections (8%) per 1 S.D. increase in total cholesterol. There were also borderline reductions of risk with increasing total cholesterol level for all genito-urinary and for skin and subcutaneous tissue infections. After adjustment for covariates, the marginal positive association of serum cholesterol with the risk of gangrene virtually disappeared.

Among women, the age-adjusted analysis using complete follow-up indicated significant inverse risk relationships between total cholesterol and all genito-

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Table 4. *Sex- and age-specific relative risks of hospital-based incidence of infectious diseases per 1 S.D. increase in total cholesterol level (1·19 mmol/l) for outcomes where a sex by total cholesterol interaction significantly improved the fit of the model. Kaiser Permanente Medical Care Program, N. California Region (1979–93)*

Infections	25–54	55–89
	Men	
Urinary tract		
At risk	41974	13326
*n**	147	774
Relative risk (95% CI)	1·00 (0·85–1·19)	0·91 (0·84–0·99)
	Women	
Streptococcal septicaemia or bacteraemia		
At risk	49590	15681
*n**	127	355
Relative risk (95% CI)	0·99 (0·82–1·20)	0·80 (0·72–0·90)
Central and peripheral nervous system		
n	21	10
Relative risk (95% CI)	1·53 (1·06–2·21)	0·41 (0·20–0·83)

Entries are relative risks and 95% confidence intervals adjusted for age, race, education level, marital status, menopausal status (among women), smoking status, alcohol consumption, body mass index, systolic blood pressure, blood glucose, leucocyte count, medical conditions at baseline (none *vs.* one or more), and unexplained weight loss. Estimates based on complete follow-up.

* Number of events.

urinary infections (8% reduction of risk per S.D. increase), septicaemia or bacteraemia (14% reduction of risk per S.D. increase), miscellaneous viral infections of unspecified site (28% reduction of risk per S.D. increase), and all infections (6% reduction of risk per S.D. increase). Conversely, a significantly increased risk of gangrene (25% increase of risk per S.D. increase in total cholesterol) was observed. In the multivariate setting, all the above associations among women persisted, with the exception of attenuation of the risk of gangrene (which became not statistically significant).

Exclusion of the first 5 years of follow-up to rule out influence of early events or impending death did not appreciable alter the risk relations in either gender (data not shown).

Supplemental multivariate analysis by percentile of total cholesterol distribution revealed that the risk of all infections was 1·4 fold higher (95% confidence interval, 1·2–1·6) in the first (lower) quintile when compared to persons in the fifth (upper) quintile in both men and women. This excess risk associated with the first quintile was somewhat attenuated in men (R.R. = 1·2, 95% confidence interval, 1·0–1·4) and did not change in women when events in the first 5 years and those with unexplained weight loss at baseline were excluded from the analysis. Further adjustment for amount of cigarettes smoked had a trivial impact on the results (data not shown).

Results of the assessment of effect modification by age are presented in Table 4. Among men, an age by total cholesterol interaction term significantly improved the fit of the model for urinary tract infections ($P = 0{\cdot}004$). The pattern of age interaction was such that the inverse association between total cholesterol and hospital incidence of urinary tract infections applied to men aged 55 and older, but not to younger men. Among women, an age by total cholesterol interaction term significantly improved the prediction of septicaemia or bacteraemia ($P = 0{\cdot}003$), and the prediction of infections of the central and peripheral nervous system ($P = 0{\cdot}001$). The reduction of risk of streptococcal septicaemia or bacteraemia and of central and peripheral nervous system infections per 1 S.D. increase in total cholesterol was seen only among women over age 54. Contrary to expectation, a 53% increased risk of infections of the central and peripheral nervous system per 1 S.D. increase in total

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Table 5. *Sex-specific relative risks of hospital-based incidence of all infections per 1 S.D. increase in total cholesterol level (1·19 mmol/l), stratifying by self-reported personal history of disease and by position of the ICD-9 code in the discharge diagnostic list. Kaiser Permanente Medical Care Program, N. California Region (1979–93)*

	Men	Women
Self-reported personal history		
Cardiovascular disease*		
At risk	1850	1432
n‡	271	248
Relative risk (95% CI)§	0·92 (0·81–1·04)	0·96 (0·85–1·08)
Diabetes		
At risk	1526	1598
n	272	259
Relative risk (95% CI)	1·02 (0·92–1·13)	0·91 (0·81–1·02)
Other diseases†		
At risk	14290	23143
n	730	1559
Relative risk (95% CI)	0·93 (0·86–1·01)	0·94 (0·89–0·99)
None		
At risk	37634	39098
n	1615	2153
Relative risk (95% CI)	0·88 (0·83–0·93)	0·90 (0·85–0·94)
ICD-9 code position		
Any infection in first place		
n	1663	1906
Relative risk (95% CI)	0·91 (0·86–0·96)	0·93 (0·89–0·98)
Any infection not in first place		
n	1225	2312
Relative risk (95% CI)	0·93 (0·87–0·99)	0·90 (0·86–0·94)

* Coronary heart disease or stroke.
† One or more of the following: emphysema, asthma, cancer or tumour, liver disease, kidney or bladder infection, thyroid disease, venereal disease, colon-bowel disease, or unexplained weight loss.
‡ Number of events.
§ Relative risks and 95% confidence intervals adjusted for age, race, education level, marital status, menopausal status (among women), smoking status, alcohol consumption, body mass index, systolic blood pressure, blood glucose and leucocyte count.
All estimates are based on complete follow-up.

cholesterol was observed among women aged 25–54. Risk estimates for other infectious disease outcomes (including all infections) did not significantly differ by age.

The analysis by strata of self-reported history of medical conditions revealed a rather consistent pattern of risk across conditions (Table 5). The only exceptions were the lack of an association among diabetic men and among women with a history of cardiovascular disease. As shown in Table 5, the inverse association between total cholesterol and all infections was present both when the infection was the first problem on admission or not. Thus, the relative position of the ICD-9 code did not seem to influence the results.

DISCUSSION

The findings of this epidemiologic study suggest a weak inverse relationship between total cholesterol level and the incidence of some, but not all, infections diagnosed in the hospital, whether acquired before or after admission. In multivariate analysis, statistically significant inverse associations were noted for urinary

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tract infections, venereal diseases, musculo-skeletal infections, and for all infections among men, and for urinary tract infections, all genito-urinary infections, septicaemia or bacteraemia, miscellaneous viral infections of unspecified site, and for all infections among women. The estimated reduction of risk of all infections associated with a 1 S.D. increase in total cholesterol was about 8% in both men and women.

It should also be noted that some infectious disease outcomes showed nonsignificant positive associations with the level of total cholesterol, namely intestinal infections among men, and gangrene and central and peripheral nervous system infections among women. The positive association between total cholesterol and gangrene was not unexpected, given the known links between dyslipaemia and peripheral vascular disease, and the interplay between diabetes, peripheral vascular disease and gangrene.

Examination of effect modification by age indicated that several infectious diseases (urinary tract infections among men; and streptococcal septicaemia or bacteraemia, and central and peripheral nervous system infections among women) were inversely related to total cholesterol only among participants aged 55 and above.

Another observation of interest was that total cholesterol was unrelated to infections among diabetic men and among women reporting cardiovascular disease at baseline. These conditions are usually associated with perturbed lipoprotein profiles, making this observation difficult to evaluate.

Several non-mutually exclusive explanations for the inverse associations between total cholesterol and infections seem possible. First, although caution should be exercised in claiming biological plausibility, low total cholesterol level (as such or as a surrogate of low levels of other aspects of the lipoproteins) may be a contributory factor of infections or a determinant of the severity of the infectious condition. Second, the apparent associations may be spurious, or due to confounding by unmeasured characteristics. Third, low cholesterol may be a consequence of disease rather than an aetiological factor (i.e. reverse causality explanation). Another potential source of reverse causality is the increased likelihood of hospitalization for other reasons.

How could total cholesterol be involved or aggravate infectious disease risk? Recent studies have shown that alterations in lipid metabolism occur in response to infections and inflammation, which are mediated by cytokines [21–23]. These changes in lipid metabolism represent part of the acute phase response, and it is believed that the acute phase response is beneficial to the host [24]. There are a number of different potential mechanisms by which increased lipid levels could be beneficial. First, an increase in serum lipid levels may result in enhanced delivery of lipids to cells that are activated during the immune response and for the cells involved in tissue repair. Second, although this mechanism may not be relevant for all the infectious examined in our study, experiments have demonstrated that all classes of lipoproteins bind endotoxins [25]. Moreover, this binding could protect the animal from the toxic effects of lipopolysaccharide including mortality [26, 27]. Hypolipidaemia has been shown to increase an animal's susceptibility to endotoxic shock syndrome [8]. Third, cholesterol protects rat myocardial cells from the cytotoxic injury caused by streptolysis O [28] and lipid extracts suppressed the antistreptolysis O response in the skin [29]. Fourth, lipoproteins also bind a variety of viruses blocking their cytopathic effects [30, 31]. Lastly, specifically high density lipoprotein induce the lysis of the parasite *Trypanosoma bruceii* [32]. Thus, it has been postulated that lipoproteins play a role in protecting animals from the toxic effect of a variety of harmful microorganisms. The finding of interaction between total cholesterol and age in increasing the risk of several infections favours the idea that these proposed pathophysiological mechanisms may be more important among older than among younger persons.

A second plausible explanation of the inverse association between total cholesterol and several infections in the present analysis is confounding by unmeasured biological or lifestyle factors. Candidates for confounders are variables associated both with the disease and the risk factor of interest. For example, lipid-soluble vitamins such as vitamin E [33], carotenoids [34], and vitamin A [35], which are correlated with total cholesterol, have been shown to be needed to maintain the immune response in humans, particularly among the elderly [36–40]. Polyunsaturated fatty acids (particularly γ-linolenic acid, the most abundant n-6 PUFA in the diet), which influence serum lipids [41, 42], crucially modifies parameters on immune function [43], and has a bactericidal effect [44]. Zinc deficiency, associated to malabsorption syndromes, chronic renal disease, and alcohol abuse [45] (conditions likely to be related to low total cholesterol levels), results in selective decrease in the number of $T4^+$ and $CD8^+CD73^+$ cytolytic cells, as well

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as decreases in serum thymulin activity, production of interleukin-2, and T-lymphocyte proliferation [46]. For venereal diseases among men, sexual preference and sexual risk behaviour may be confounders of the association if those at heightened risk of contracting venereal diseases have also low cholesterol level. There are two relevant observations in this regard: first, data indicating that homosexual men weigh less than heterosexual men [47] and, second, the well established link between body weight and total cholesterol [48].

A third interpretation is that low cholesterol is the consequence of infection, as opposed to being a pre-existing risk factor. Reduced total cholesterol has been observed after severe infection [49–53] and following minor illness [54], an effect mediated by release of acute phase reactants [55, 56]. However, reverse causality seems unlikely to explain the observed inverse associations between total cholesterol and several infectious disease outcomes reported here, since they persisted after eliminating events in the first 5 years of follow-up, and were present regardless of being the primary cause of hospitalization or not. These findings are consistent with the argument raised by of Allison and colleagues and the exclusion of subjects who die during the first k years of follow-up does not necessarily lead to a reduction of bias in the estimated effect of a risk factor on mortality, when this relation is confounded by the presence of occult disease [57].

The strengths of this study include its large sample size, and the ability to focus on the most severe types of infection, namely those requiring hospitalization. However, there are also some limitations to bear in mind. First, we did not elucidate the relative importance of cholesterol subfractions, apolipoproteins, or fat-soluble vitamins. Second, the infections were ascertained in the hospital setting, and thus may not be generalized to the out-patient setting or to infections occurring in community dwellers. Third, although every effort was made to identify and control for pre-existing illness, the presence of unidentified comorbid conditions altering immune responsiveness and lipid levels may be an important source of residual confounding of the risk relations between total cholesterol and infectious disease. Fourth, we did not examine specific infecting pathogens, but rather clinical entities more readily identifiable through hospital discharge diagnostic codes. Finally, the continuous exposure to total cholesterol was based on a single determination, a circumstance that may introduce unpredictable bias in multivariate estimates of risk [58].

On the balance, these data support a weak but statistically significant inverse association between total cholesterol and incidence of some infectious diseases diagnosed in the hospital setting. Additional research is needed on the role of lipoprotein subfractions, apolipoproteins, fat-soluble vitamins, acute phase reactants and comorbidity in the association between lipids and infection. Moreover, the inverse relationship between total cholesterol and infectious diseases should be investigated among ambulatory patients and in the context of minor infections.

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