International Journal of Epidemiology, 2023, 1–11
https://doi.org/10.1093/ije/dyad011
Original article

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Associations between serum high-density lipoprotein cholesterol levels and cause-specific mortality in a general population of 345 000 men and women aged 20–79 years

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Received 4 July 2022; Editorial decision 3 January 2023; Accepted 31 January 2023

Abstract

Background: Benefits of elevated high-density lipoprotein cholesterol (HDL-C) levels are challenged by reports demonstrating U-shaped relations between HDL-C levels and all-cause mortality; the association with cause-specific mortality is less studied.

Methods: A total of 344 556 individuals (20–79 years, 52 % women) recruited from population-based health screening during 1985–2003 were followed until the end of 2018 for all-cause and cause-specific mortality by serum HDL-C level at inclusion of <30, 30–39, 40–49, 50–59, 60–69, 70–79, 80–89, 90–99 and >99 mg/dl (< 0.78, 0.78–1.01, 1.04–1.27, 1.30–1.53, 1.55–1.79, 1.81–2.04, 2.07–2.31, 2.33–2.56, >2.56 mmol/L). Hazard ratios (HRs) were adjusted for sex, age, calendar period, smoking, total cholesterol, triglycerides, systolic blood pressure, physical activity, educational length, body mass index and ill health.

Results: During a mean follow-up of 22 years, 69 505 individuals died. There were U-shaped associations between HDL-C levels and all-cause, cancer and non-cardiovascular disease/non-cancer mortality (non-CVD/non-cancer), whereas for CVD there was increased risk of death only at lower levels. With HDL-C stratum 50–59 mg/dl (1.30–1.53 mmol/L) as reference, HRs [95% confidence intervals (CIs)] for levels >99 mg/dl (>2.56 mmol/L) were 1.32 (1.21–1.43), 1.05 (0.89–1.24), 1.26 (1.09–1.46) and 1.68 (1.48–1.90) for all–cause, CVD, cancer and non–CVD/non–cancer mortality, respectively. For HDL-C levels <30 mg/dl (0.78 mmol/L), the corresponding HRs (95% CIs) were 1.30 (1.24–1.36), 1.55 (1.44–1.67), 1.14 (1.05–1.23) and 1.19 (1.10–1.29). The mortality from

alcoholic liver disease, cancers of mouth-oesophagus-liver, chronic liver diseases, chronic obstructive pulmonary disease, accidents and diabetes increased distinctly with increasing HDL-C above the reference level. HDL-C levels lower than the reference level were mainly associated with increased mortality of ischaemic heart disease (IHD), other CVDs, stomach cancer and diabetes.

Conclusions: Higher HDL-C levels were associated with increased mortality risk of several diseases which also have been associated with heavy drinking, and lower HDL-C levels were associated with increased mortality from IHD, other CVDs, gastric cancer and diabetes.

Key words: High-density lipoprotein cholesterol (HDL-C), mortality, general population, epidemiology

Key Messages

- U-shaped associations were found between high-density lipoprotein cholesterol (HDL-C) levels and all-cause, cancer and non-cardiovascular disease (CVD)/non-cancer mortality, whereas for CVD there was increased risk of death only at lower HDL-C levels.
- Spline curves showed increasing mortality from alcoholic liver disease and other diagnoses which have been related to heavy drinking with increasing HDL-C levels above a reference set at 50 mg/dl (1.30 mmol/L).
- Below the reference level, an increasing mortality from ischaemic heart disease (IHD), other CVDs, stomach cancer and diabetes was associated with decreasing levels of HDL-C.
- Physicians observing a low HDL-C serum level should be aware of the patient's increased risk of mortality from CVD, stomach cancer and diabetes, whereas a high HDL-C level should increase awareness to exclude the patient's alcohol consumption as a possible underlying cause.

Introduction

The serum concentration of high-density lipoprotein cholesterol (HDL-C) has been considered as a biomarker of risk of cardiovascular disease (CVD) for many years. Since the discovery of the inverse association between the levels of HDL-C and CVD events,[1] several epidemiological studies have demonstrated HDL-C to be a robust, consistent predictor for CVD independent of other risk factors.[2–4] A role of HDL in the reverse transport of cholesterol from macrophages located in vascular atheroma could indicate a causal function of HDL in the protection from atherosclerosis and CVD, as originally proposed by Glomset[5] and as recently summarized by Tall.[6]

In line with this view, several clinical studies have investigated treatments to enhance HDL-C levels, most recently with inhibitors of cholesteryl ester transfer protein (CETP), which would reduce the transfer of cholesteryl esters from HDL-C to low-density lipoprotein and other pro-atherogenic lipoprotein particles. Although elevations of the levels of HDL-C were obtained by such treatment in patients with either recent acute coronary syndrome or at high risk for vascular outcomes, no reduction in vascular event rates were obtained in most studies[7–10] except one.[11] Furthermore, a Mendelian randomization study failed to find a relationship between a single nucleotide polymorphism (SNP) that exclusively increased HDL-C levels and risk of myocardial infarction.[12] A recent review has discussed the incoherence of evidence associating HDL-C levels with CVD risk.[13]

Beyond CVD there is emerging evidence that HDL-particles may be involved in a series of biological processes with antioxidative, anti-thrombotic, anti-inflammatory and complex regulatory functions.[13,14] This suggests that HDL-C could be related to disease processes also outside the cardiovascular domain. An association between higher HDL-C levels and risk of certain cancers,[15–19] and findings of higher HDL-C levels in populations of exceptional longevity have called for further studies of the association with vascular and non-vascular diseases of elderly.[20]

An assumption of beneficial associations of high HDL-C, however, was weakened by prospective cohort studies[21,22] and a recent pooled analysis of 39 such studies[23] reporting a U-shaped association between HDL-C levels and all-cause mortality. Two of these studies also found increased CVD-mortality risk at higher HDL-C levels, questioning the role of elevated HDL-C as a CVD

protective biomarker. There are, however, some uncertainties related to those studies[21–23] which mostly included people in their late 50s or middle 60s with observation periods shorter than 10 years. Studies of associations between mortality risks and HDL-C levels in younger general populations with an extended observation period appear, however, to be lacking.

The objective of our study was to gain more information on which cause-specific mortalities were associated with higher or lower HDL-C levels, to widen the knowledge base for the association of HDL-C serum levels with mortality risks. This was done prospectively for a mean follow-up period of 22.1 years in about 345 000 subjects recruited from the general Norwegian population with a mean age of 46 [standard deviation (SD) = 11] years. The individuals were screened for several health conditions and biomarker measurements, including HDL-C levels at baseline. All causes of death were based on quality-controlled death certificates collected from a national cause of death registry.

Methods

Study population

We combined data from three cohorts: the Norwegian Counties Study (1977–87), the Age 40 Program (1985–99) and the Cohort of Norway (CONOR)(1994–2003).[24–26] A total of 360 396 men and women aged 20 to 79 years, mean age 45.5 years, participated in these three cohorts with participation rates of 80%, 69% and 62%, respectively. We excluded 15 840 subjects with missing information in one or more of the covariates, leaving 344 556 subjects (166 050 men and 178 506 women) on whom our analyses are based.

Baseline measurements

At each screening site, participants' height and weight were measured to the nearest kilogram and centimetre. Blood pressure was measured three times with a Dinamap device, except for 43 194 participants who were measured twice with a sphygmomanometer in 1977–83. We used the mean of the second and third registration and the second registration, respectively. A non-fasting blood sample was drawn and serum analysed for total cholesterol, triglycerides and HDL cholesterol, which were analysed by standard laboratory methods at the time of screening.[27,28] HDL-C was measured enzymatically from the cholesterol remaining in the supernatant after precipitation of low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL) particles by heparin-manganese reagent. All analyses were done at Oslo Hospital, except for $n = 8500$ analysed by the Institute of Medical Biology, University of Tromsø. Both laboratories used the same HDL-C method. The participants answered a questionnaire at home which was checked for inconsistencies at the screening site. Smoking habits were recorded as: never-smoker, ex-smoker and 1–9, 10–19 and 20+ cigarettes/day. This variable, smoking, was entered as a factor variable in the analyses with never smoker as reference category. Two non-overlapping questions on leisure time physical activity were used during the first and last part of the screening period: one with the alternatives: no, <1 hour, 1–2 hours, 3+ hours/week hard physical activity ($n = 167\,959$), the other with the alternatives: sedentary, moderate, intermediate, hard physical activity during leisure time ($n = 176\,597$). We categorized as physically active those who reported at least 1 h hard physical activity in a week, or those who reported at least moderate activity during leisure time. Information on educational duration came from linkage to Statistics Norway. The questionnaires can be found at: [https://www.fhi.no/div/helseundersokelser/landsomfattende-helseundersokelser-lhu/]. Nine categories of educational duration, <7 years, 7–9, 10, 11–12, 13–14, 15–16, 17–18, >18, where years were categorized as <11, 12–16, 17+ years of education. This variable was entered as a factor variable in the analyses with <11 years as reference category. We defined persons with ill health as those with a history of cancer at baseline, based on information from linkage to the Cancer Registry of Norway or self-reported history of heart infarction, angina pectoris, stroke or diabetes. Altogether 24 663 persons had ill health and this variable was associated with HDL-C and any death, and was therefore included in the multivariable analyses together with other potential confounders. We did additional analyses excluding the first 5 years of follow-up and those with ill health. We defined four periods based on the year of screening: 1977–83, 1984–88, 1989–99, 2000–03. The two first periods are the second and third wave of Norwegian counties study, the third is the Age 40 programme and CONOR, and the fourth is CONOR. Period is entered as a factor variable in the analyses with 1977–83 as reference category. Age was categorized in 5-year age spans and was also entered as a factor variable in the analyses with age 40–44 as reference category.

Outcome

The participants accrued person-years from date of participation to date of death, date of emigration or 31 December 31 2018, whichever came first. The total number of person-years in the study was 7 626 853. The Norwegian Cause of Death Registry provided outcome data on causes of death using the eighth, ninth and tenth revisions of the

International Classification of Diseases (ICD). The primary outcomes were cardiovascular death; cancer death and other (non-CVD/non-cancer) deaths, which encompassed all other causes including external ones. We also performed analyses for outcomes of several subgroups of the three primary outcomes (Supplementary Table S1, available as Supplementary data at *IJE* online).

Statistical analysis

Less than 5% had missing values in one or more variables and we did complete case analyses. We used the margins procedure in STATA to adjust mean values for sex, age at start of follow-up, and period. Margins are statistics from predictions of a previously fit model at fixed values of covariates. We used linear regression and specified the mean values.[29] We estimated absolute mortality rates by the direct method using an internal standard, adjusting for sex, age in 5-years age spans, and the four periods. The direct method produces a weighted average of stratum-specific rates. We used a Cox proportional hazards model, with follow-up time as time axis, to adjust for several potential confounders. We graphed restricted cubic splines with 95% confidence bands, using mkspline with four knots.[29] All tests were two-sided with a significance level of 0.05.

Results

The baseline characteristics of our sample and distribution of subjects by calendar period of examination and age, sex, education and ill health are presented (Table 1; Supplementary Table S2, available as Supplementary data at *IJE* online). The percentage of men decreased with increasing HDL-C levels. The participants' cholesterol levels and educational duration increased in strata with higher HDL-C values, whereas ill health, body mass index (BMI) and triglyceride levels showed the opposite trend. The triglyceride levels were distinctly higher at the lower HDL levels. The prevalence of never- and ex-smokers was lowest at lower levels, whereas number of cigarettes was highest at lower levels of HDL-C. A weak inverted-U-shape relationship was found for the percentage of subjects who were physically active.

During the study period, 69 505 participants (39 448 men, 30 057 women) died. The mean period between screening and death from all-cause, CVD, cancer and other causes was 16.9, 16.2, 16.8 and 17.5 years for men, and 18.3, 18.4, 16.9, and 19.8 years for women, respectively.

There were U-shaped associations between HDL-C levels and fully adjusted hazard ratios of all-cause mortality and non-CVD/non-cancer mortality (Figure 1). The mortality HRs of cancer and CVD were increased at lower HDL-C levels, but the U-shape was less pronounced for

Table 1 Baseline characteristics by serum high-density lipoprotein cholesterol - level, sex, age, and period adjusted

	High-density lipoprotein (HDL) cholesterol (mg/dl)[a]								
	<30	30–39	40–49	50–59	60-69	70-79	80-89	90-99	100+
Men and women (*n*)	9001	59 457	96 671	89 783	53 133	22 580	9081	3080	1770
Age	45	45	45	45	46	47	49	51	53
Survey year (mean)	1993	1994	1994	1994	1995	1995	1996	1996	1996
Male (%)	82	73	58	41	29	22	20	20	24
Age-, sex- and period-adjusted									
Cholesterol (mmol/l)	5.7	5.8	5.7	5.7	5.8	5.9	6.0	6.2	6.5
Triglycerides (mmol/l)	3.5	2.5	1.8	1.5	1.3	1.1	1.1	1.0	1.1
Systolic bp (mmHg)	132	132	132	131	131	131	131	132	134
Physical active (%)	84	86	89	91	92	93	93	93	92
BMI (kg/m^2)	28	27	26	25	24	24	24	23	23
Educational duration									
<= 10 yrs	55	53	51	48	45	43	42	42	42
11–16 yrs	43	44	46	48	50	51	51	51	51
17+ yrs	3	3	4	4	5	6	7	7	8
Smoking									
Never	23	25	26	28	30	31	31	31	31
Ex	34	35	37	40	42	44	45	44	39
1–9 cigarettes/d	11	10	10	10	9	8	8	7	9
10–19 cigarettes/d	24	23	21	18	15	13	12	13	14
20+ cigarettes/d	9	7	6	5	5	4	4	5	7
Ill health (%)	12	9	8	6	6	5	5	5	4

BMI, body mass index; bp, blood pressure; y, years; d, day.
[a]To convert to mmol/L, multiply by 0.0259.

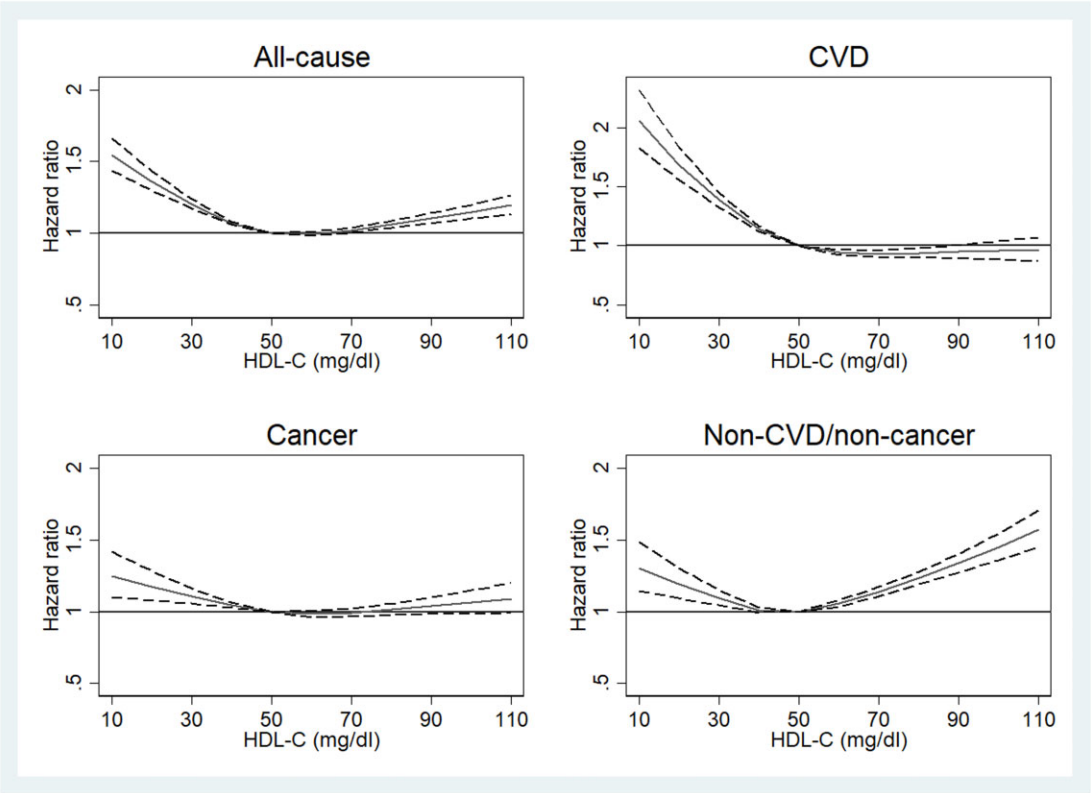

Figure 1 High-density lipoprotein cholesterol (HDL-C) and mortality hazard ratios. Mortality hazard ratios for men and women combined with 95% confidence bands adjusted for sex, age, calendar period, smoking, total cholesterol, triglycerides, systolic blood pressure, body mass index, educational duration, physical activity and illness. CVD, cardiovascular disease. To convert high-density lipoprotein cholesterol (HDL-C) concentrations to mmol/L, multiply by 0.0259. Note: not common scale on Y-axes

cancer and hardly present for CVD. The number of deaths, absolute mortality rates, and age- and period-adjusted (both categorical) and multivariate-adjusted hazard ratios (HR) for all-cause mortality and mortality in the main disease groups in various HDL cohorts are presented (Table 2). The reference group is 50–59 mg/dl (1.30–1.53 mmol/L) HDL-C. The mean HDL-C value for the whole study population was 52 mg/dl (1.35 mmol/L) and the most abundant HDL-C stratum among men was 40–49 mg/dl (1.04–1.27 mmol/L), 50–59 mg/dl (1.30–1.53 mmol/L) among women. We performed a gender-specific analysis of HRs (Supplementary Table S3 and Supplementary Figure S1, available as Supplementary data at *IJE* online) and found approximately the same shape of associations in men and women.

We did a sensitivity analysis where we studied the association between quintiles of HDL-C/total cholesterol ratio and mortality, stratified by total cholesterol level below and above the mean level of 215.4 mg/dl (5.57 mmol/l). The associations were U-shaped for all-cause, cancer and non-CVD/non-cancer mortality with a turning point at quintile 3 (0.213–0.254). For CVD and IHD, the mortality decreased with increasing quintile, more steeply below than above the turning point.

HDL-C levels higher than reference were mainly associated with increased mortality risk (with HR above 1.5, 95% CI above 1.0) for alcoholic liver disease, upper digestive cancers (cancer of mouth-oesophagus-liver), digestive diseases (mostly chronic liver diseases), respiratory diseases [mostly chronic obstructive pulmonary disease (COPD), accidents and endocrine disorders (mostly diabetes)]. Alcoholic liver disease showed by far the steepest linear gradient with increasing HDL-C levels of these specific causes (Figure 2; Supplementary Table S4, available as Supplementary data at *IJE* online). Low HDL-C levels were mainly associated with increased mortality risk of IHD, other CVDs (mostly heart failure, arrhythmias and aortic aneurysm), stomach cancer and endocrine diseases (mostly diabetes).

To evaluate reverse causality, the HRs when the participants reported illness at inclusion or died during the first 5 years of the follow-up period were excluded, resulting in only minor changes of the HRs for all-cause mortality and the three major groups (Table 3). The most marked trend

Table 2 Mortality rates[a] and hazard ratios (HR) with 95% confidence intervals (95% CI). Men and women 20–79 years, combined

	High-density lipoprotein (HDL) cholesterol (mg/dl[b])								
	<30	**30–39**	40–49	50–59	60–69	70–79	80–89	90–99	100+
Person-years	196 461	1 312 086	2 165 999	2 000 464	1 175 150	490 198	190 016	62 509	33 970
All-cause									
n deaths	2548	14 117	19 417	16 476	9478	4122	1974	789	584
Rate[c]	1323	1044	917	860	869	914	1021	1113	1326
HR[c]	1.53	1.23	1.08	Ref	0.98	0.98	1.04	1.07	1.32
HR[d]	1.29	1.11	1.03	Ref	1.02	1.05	1.10	1.10	1.31
95% CI	1.23–1.35	1.08–1.14	1.01–1.05		1.00–1.05	1.02–1.09	1.05–1.15	1.02–1.18	1.20–1.42
CVD									
n deaths	1006	5171	6225	4926	2617	1132	519	207	145
Rate[c]	471	367	294	261	243	259	276	298	315
HR[c]	1.91	1.44	1.14	Ref	0.91	0.91	0.90	0.91	1.05
HR[d]	1.54	1.26	1.08	Ref	0.97	1.00	0.98	0.94	1.04
95% CI	1.43–1.66	1.21–1.31	1.04–1.12		0.92–1.01	0.93–1.06	0.89–1.07	0.82–1.09	0.88–1.23
Cancer									
n deaths	771	4708	6943	5994	3363	1447	642	236	182
Rate[c]	439	355	326	309	304	314	296	330	471
HR[c]	1.29	1.14	1.05	Ref	0.95	0.96	0.97	0.95	1.24
HR[d]	1.13	1.06	1.02	Ref	0.99	1.02	1.03	0.98	1.25
95% CI	1.04–1.23	1.01–1.10	0.98–1.05		0.95–1.04	0.96–1.08	0.94–1.11	0.86–1.12	1.08–1.45
Non-CVD/non-cancer									
n deaths	771	4238	6249	5556	3498	1543	813	346	257
Rate[c]	413	323	297	290	322	342	449	485	541
HR[c]	1.43	1.12	1.04	Ref	1.06	1.06	1.22	1.33	1.66
HR[d]	1.18	1.01	1.00	Ref	1.11	1.15	1.30	1.37	1.66
95% CI	1.09–1.28	0.96–1.05	0.96–1.03		1.06–1.16	1.08–1.21	1.20–1.40	1.23–1.53	1.46–1.88

CVD, cardiovascular disease.
[a]Deaths per 100 000 person years.
[b]To convert to mmol/L, multiply by 0.0259.
[c]Rate or Hazard ratio adjusted for sex, age and calendar period.
[d]Hazard ratio adjusted for sex, age, calendar period, smoking, total cholesterol, triglycerides, systolic blood pressure, physical activity, educational duration, body mass index and ill health.

was a reduction of HRs observed for non-CVD/non-cancer mortality associated with high HDL-C levels. An analysis of two cause-specific mortalities (alcoholic liver disease and digestive diseases) showed that both increased markedly with increasing HDL-C levels, but revealed no clear changes of HRs when deaths during the first 5 years were excluded.

Discussion

This prospective population-based study of 344 556 participants revealed mostly U-shaped associations between the HDL-C strata at screening and the risk of all-cause mortality and specific mortality of CVD, cancer and other causes during an observation period of about 22 years. For all-cause deaths this was in accordance with other large studies.[21–23] We found that the increased mortality risks associated with higher or lower HDL-C levels were related to certain subgroups within the three main outcomes. The most pronounced increases of risks at higher HDL-C levels were associated with alcoholic liver disease, cancers of mouth-esophagus-liver, chronic liver diseases, COPD, accidents and diabetes. At lower HDL-C levels, the most marked increases of HRs were related to IHD, heart failure, arrythmias, aortic aneurysm, stomach cancer and diabetes. The cause-specific mortalities increasing with higher HDL-C levels have in common that they are over-represented among heavy drinkers.[30–34]

Epidemiological studies have suggested that there is a relationship between the magnitude of alcohol intake and the concentration of HDL-C in blood at a population level.[35–39] A significant dose-response between alcohol consumption and HDL-C has also been found in experimental studies.[40,41] Alcohol-induced increases in HDL-C levels would be assumed to add to individual levels of HDL-C otherwise governed by genetic factors[42] and to

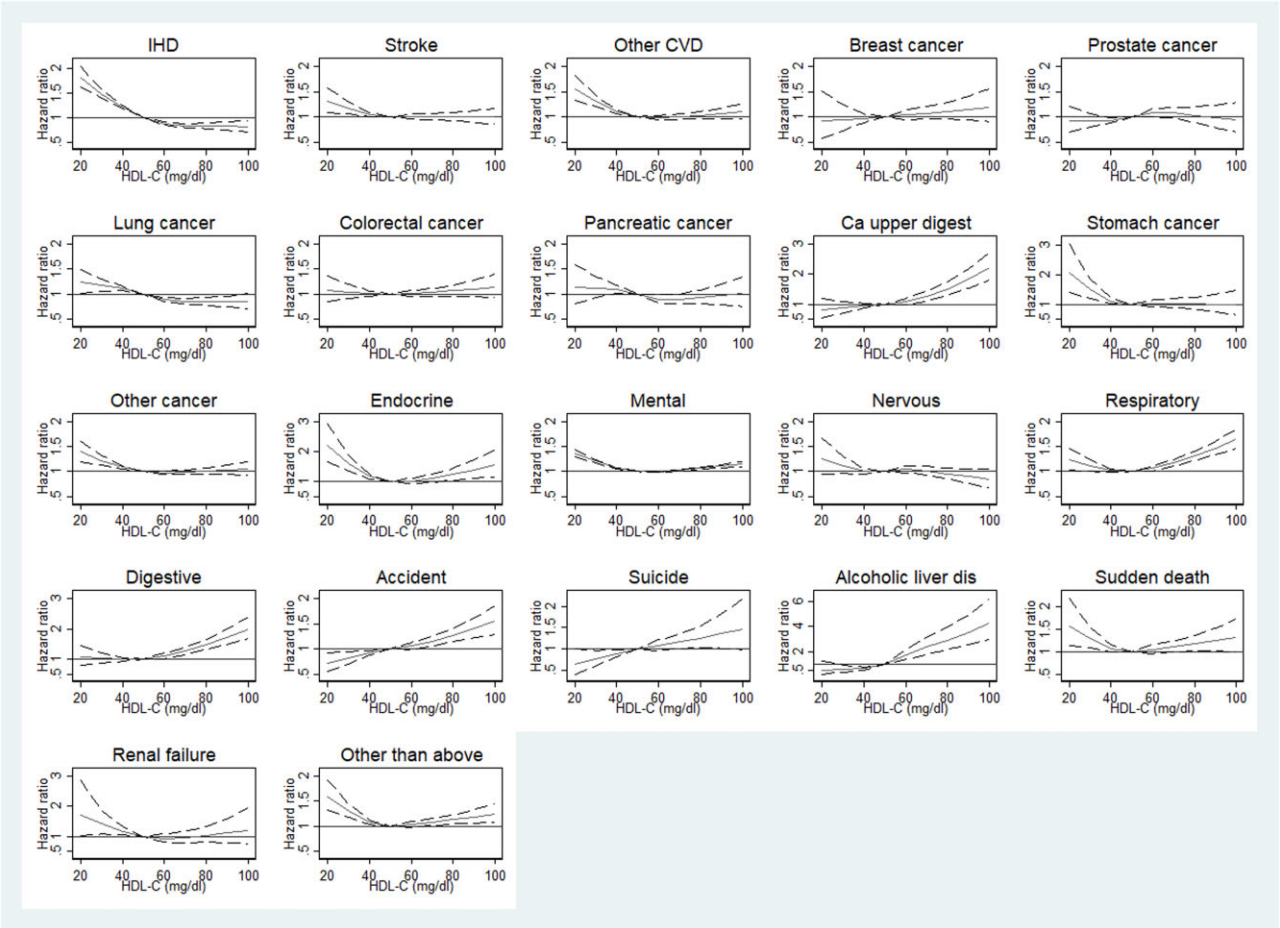

Figure 2 High-density lipoprotein cholesterol (HDL-C) and specific mortality hazard ratios. Mortality hazard ratios for men and women combined with 95% confidence bands adjusted for sex, age, calendar period, smoking, total cholesterol, triglycerides, systolic blood pressure, body mass index, educational duration, physical activity and illness. IHD, ischaemic heart disease; CVD, cardiovascular disease; Ca, cancer. To convert high-density lipoprotein cholesterol (HDL-C) concentrations to mmol/L, multiply by 0.0259. Note: not common scale on Y-axes

some extent by other factors. Although this presumably reduces the value of HDL-C measured at one time point as a perfect quantitative biomarker of alcohol intake, a recent study in a population partly overlapping our study population, found a close relation between the number of daily drinks reported and the HDL-C levels measured.[43] This indicates that people with increased alcohol intake will be over-represented in the higher HDL-C strata, and further suggests that increased mortality risk of alcohol-related conditions in the high HDLC-group in our study could be due to an over-representation of heavy drinkers in this group. Also, in the study of Ko *et al.*,[21] heavy drinking was observed frequently among subjects with very high HDL-C levels.

Our findings can certainly not exclude explanations other than heavy drinking for the association between higher HDL-C levels and the increased cause-specific mortality risks observed, but such links have not to our knowledge been published. It should also be noted that CVD mortality HRs at HDL-C levels above 50–59 mg/dl were not increased in the our study. At higher HDL-C levels (above 59 mg/dl, 1.53 mmol/L) we found the mortality of IHD to be slightly reduced, but unchanged from the reference level for stroke and other CVD.

A large collaborative meta-analysis of almost 900 000 individuals[44] found a similar inverse association between HDL-C levels up to 70 mg/dl (1.81 mmol/L) and IHD mortality, and not for stroke mortality. For higher HDL-C levels, one study, collapsing all HDL-C levels above 70 mg/dl (1.81 mmol/L) into one group, reported reduced IHD but unchanged CVD mortality.[2] Analysis of eight pooled individual studies revealed an inverse association of HDL-C levels up to approximately 100 mg/dl (2.59 mmol/L) for coronary heart disease mortality, but not for CVD mortality.[23] It has been discussed whether the inverse relation between IHD and HDL-C levels could have a threshold at levels higher than 90–100 mg/dl (2.33–2.59 mmol/L), or even be associated with increased risk for coronary heart

Table 3 Hazard ratios (HR) with 95% confidence intervals (95% CI). Men (M) and women (W) 20–79 years. Total population (All) and excluding 28 597 individuals with illness and first 5 years of follow-up (-5+ill)

	High-density lipoprotein (HDL) cholesterol (mg/dl[a])								
M and W	<30	30–39	40–49	50–59	60–69	70–79	80–89	90–99	100+
All-cause									
HR[b] (All)	1.30	1.11	1.03	Ref	1.02	1.05	1.11	1.10	1.32
HR[b] (-5+ill)	1.24	1.10	1.03	Ref	1.01	1.04	1.08	1.09	1.29
95% CI	1.17–1.31	1.07–1.13	1.00–1.05		0.98–1.04	1.00–1.08	1.02–1.14	1.00–1.19	1.17–1.43
CVD									
HR[b]	1.55	1.26	1.08	Ref	0.97	1.00	0.99	0.95	1.05
HR[b] (-5+ill)	1.43	1.23	1.07	Ref	0.97	1.01	1.01	1.01	1.10
95% CI	1.30–1.57	1.17–1.30	1.02–1.12		0.92–1.03	0.93–1.09	0.91–1.13	0.85–1.19	0.91–1.35
Cancer									
HR[b]	1.14	1.06	1.02	Ref	0.99	1.02	1.03	0.99	1.26
HR[b] (-5+ill)	1.13	1.08	1.03	Ref	0.98	0.99	0.99	0.98	1.30
95% CI	1.03–1.24	1.03–1.134	0.99–1.07		0.93–1.03	0.92–1.06	0.90–1.09	0.84–1.15	1.09–1.54
Non-CVD/ non- cancer									
HR[b]	1.19	1.01	1.00	Ref	1.11	1.15	1.31	1.38	1.68
HR[b] (-5+ill)	1.15	1.00	0.99	Ref	1.09	1.13	1.25	1.29	1.50
95% CI	1.05–1.27	0.95–1.05	0.95–1.03		1.04–1.14	1.06–1.21	1.15–1.36	1.13–1.47	1.29–1.76

CVD, cardiovascular disease.

[a]To convert to mmol/L, multiply by 0.0259.

[b]Hazard ratio adjusted for sex, age, calendar period, smoking, total cholesterol, triglycerides, systolic blood pressure, physical activity, educational duration, body mass index.

disease[45] linked to certain gene variants.[46] We found no increase of CVD or IHD mortality at HDL-C levels above 90 mg/dl (2.33 mmol/L), which is in concert with findings of a lack of relationship between elevated HDL-C levels due to genetic variants of hepatic HDL-receptors and HDL-C levels.[47] Our findings differ from a Danish population study reporting increased CVD mortality (CVD not further specified) for subjects with HDL-C levels above 90–100 mg/dl(2.33–2.59 mmol/L).[48] Our study is in concert with previous meta-analysed[44] and pooled studies,[23] of a possible inverse relation between HDL-C levels and IHD mortality, whereas the relation of high HDL-C levels to other CVD mortalities remains more uncertain. At HDL-C levels below the reference value, CVD mortality increase was most pronounced for IHD and other CVD, but less for stroke, as previously reported.[2,3,21,23,44]

At lower HDL-C concentrations, we found increasing total cancer mortality risk with decreasing HDL levels, as shown previously.[21,23] We could extend previous observations by confining the increased risk mainly to stomach cancer, probably related to previous observations of a close association between low HDL-C levels and lymph node metastasis of gastric cancer[49] and the observation of low HDL-C levels as a negative prognostic factor for gastric cancer.[50] We found increased diabetes mortality among subjects with lower HDL-C levels, which might be related to higher prevalence of diabetes with decreasing HDL-C concentrations.[51] A higher prevalence of metabolic syndrome (and increased risk of diabetes) at low HDL-C levels was indicated by the age-adjusted mean values of triglycerides, BMI, blood pressure and physical activity in our study (Table 1).

Strengths and limitations of the study

Our study recruited a large homogeneous sample from the general population, collected information from general national registries based on quality-controlled death certificates for all deceased and had a long follow-up period (22 years) with observation of close to 7.6 million person-years, with about 70 000 fatalities allowing examination of mortalities of multiple diseases. The study thus might represent a comprehensive basis for conclusions about the associations between HDL-C level and mortality causes; but there are also several limitations. First, the cohorts were established with one set of health information and morphometric data more than 20 years ago without additional measurements during the follow-up period. Thus, we do not know how representative the HDL-C measurements performed were for the total observation period or indeed for the period prior to enrolment into the study. There is relatively sparse information about the stability of

HDL-C levels during the life span, but a weak positive relationship with age has been suggested.[52] Second, lifestyle changes associated with health benefits, such as increased levels of physical activity,[53,54] smoking cessation,[55] and weight reduction,[56] in addition to light to moderate alcohol consumption,[57,58] might increase HDL-C levels. If occurring during the observation period, such changes could have influenced associations between HDL-C levels and cause-specific mortality outcomes. Third, the fasting/feeding state of the participants at the time of sampling for blood lipid measurements was not standardised. However, a recent study has indicated that the differences in feeding status are not critical for measurements of HDL-C.[59] Fourth, the lack of information on alcohol consumption is a drawback. Such information at inclusion and during the follow-up period could have strengthened or weakened our assumption of a link between alcohol intake and HDL-C levels. Fifth, lack of information on the use of statins at inclusion and during the follow-up period could have influenced CVD mortality, but not necessarily HDL-C levels,[60] influencing possible associations of HDL-C levels and CVD mortality. Finally it should be stressed that the observational nature of our data precludes causal deductions. Some of the analyses we have performed reduce the possibility of major reverse causation. The results were adjusted for several possible confounders, but unmeasured and unknown confounders could still have influenced our findings. We are not aware of studies that have applied Mendelian randomization to analyse the U-shaped association with all-cause mortality, but like our findings, one Mendelian randomization study[12] did not report reduced risk of myocardial infarction at higher HDL-C levels.

Conclusions

In this population-based study we found a U-shaped association between all-cause mortality and HDL-C levels. This association was, however, a consequence of different associations between HDL-C and different cause-specific mortalities. High HDL-C levels were associated with increased mortality risk of several diseases which also have been associated with heavy drinking. These associations might be a consequence of an association between alcohol consumption and HDL-C levels. Thus, our report does not support an association of high HDL-C levels with substantially increased mortality risk of diseases and conditions which are not alcohol related. Low HDL-C levels were mainly associated with increased mortality risk of IHD, other CVDs, stomach cancer and diabetes.

Ethics approval

The Regional Committees for Medical and Health Research Ethics (approval number S-06222) and the Norwegian Data Protection Authority approved this study.

Data availability

The individual-level data underlying this article were subject to ethical approval and cannot be shared publicly. One can apply for access to data, and we refer to this website [https://www.fhi.no/en/more/access-to-data/].

Supplementary data

Supplementary data are available at *IJE* online.

Author contributions

J.G.M. and A.T. initiated the study concept and design. A.T. statistically analysed the data and J.G.M. wrote the first draft. J.G.M., P.M., S.E.V., D.A.L., R.S. and A.T. analysed and interpreted the data and contributed to critical revision of the manuscript. All authors have read the final submitted version of the manuscript. A.T. and R.S. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Funding

There was no specific funding for the current work.

Ackowledgements

The access to data from the Norwegian Counties Study, the Age 40 program and the Cohort of Norway is highly appreciated.

Conflict of interest

None declared.

References

1. Kannel WB, Dawber TR, Friedman GD, Glennon WE, McNamara PM. Risk factors in coronary heart disease. An evaluation of several serum lipids as predictors of coronary heart disease. *Ann Intern Med* 1964;**61**:888–99.
2. Wilson PFW, Abbott RD, Castelli WP. High density lipoprotein cholesterol and mortality. The Framingham Heart Study. *Arteriosclerosis* 1988;**8**:737–41.
3. Gordon DJ, Probstfield JL, Garrison RJ *et al.* High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. *Circulation* 1989;**79**:8–15.
4. The Emerging Risk Factors Collaboration. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA* 2009;**302**:1993–2000.
5. Glomset JA, Norum KR. The metabolic role of lecithin: cholesterol acyltransferase: perspectives form pathology. *Adv Lipid Res* 1973;**11**:1–65.

6. Tall AR. Plasma high density lipoproteins: therapeutic targeting and links to atherogenic inflammation. *Atherosclerosis* 2018; **276**:39–43.
7. Barter PJ, Caulfield M, Eriksson M *et al.*; ILLUMINATE Investigators. Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med* 2007;**357**:2109–22.
8. Boden WE, Probstfield JL, Anderson T *et al.*; AIM-HIGH Investigators. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med* 2011;**365**: 2255–67.
9. Schwartz GG, Olsson AG, Abt M *et al.*; dal-OUTCOMES Investigators. Effects of dalcetrapib in patients with a recent acute coronary syndrome. *N Engl J Med* 2012;**367**:2089–99.
10. Lincoff AM, Nicholls SJ, Riesmeyer JS *et al.*; ACCELERATE Investigators. Evacetrapib and cardiovascular outcomes in high-risk vascular disease. *N Engl J Med* 2017;**376**:1933–42.
11. Bowman L, Hopewell JC, Chen F *et al.*; HPS3/TIMI55–REVEAL Collaborative Group. Effects of Anacetrapib in patients with atherosclerotic vascular disease. *N Engl J Med* 2017;**377**:1217–27.
12. Voight BF, Peloso GM, Orho-Melander M *et al.* Plasma HDL cholesterol and risk of myocardial infarction: a Mendelian randomisation study. *Lancet* 2012;**380**:572–80.
13. Kajani S, Curley S, McGillicuddy FC, Unravelling HDL. Looking beyond the cholesterol surface to the quality within. *Int J Mol Sci* 2018;**19**:1971.
14. Estrada-Luna D, Ortiz-Rodriguez MA, Medina-Briseno L *et al.* Current therapies focused on high-density lipoproteins associated with cardiovascular disease. *Molecules* 2018;**23**:2730.
15. Mondul AM, Weinstein SJ, Virtamo J, Albanes D. Serum total and HDL cholesterol and risk of prostate cancer. *Cancer Causes Control* 2011;**22**:1545–52.
16. van Duijnhoven FJB, Bueno-De-Mesquita HB, Calligaro M *et al.* Blood lipid and lipoprotein concentrations and colorectal cancer risk in the European Prospective Investigation into Cancer and Nutrition. *Gut* 2011;**60**:1094–102.
17. Pirro M, Ricciuti B, Rader DJ, Catapano AL, Sahebkar A, Banach M. High density lipoprotein cholesterol and cancer: marker or causative? *Prog Lipid Res* 2018;**71**:54–69.
18. Hao B, Bi B, Sang C *et al.* Systematic review and meta-analysis of the prognostic value of serum high-density lipoprotein cholesterol levels for solid tumors. *Nutr Cancer* 2019;**71**:547–56.
19. Brantley KD, Riis AH, Erichsen R, Thorlacius-Ussing O, Møller HJ, Lash TL. The association of serum lipid levels with colorectal cancer recurrence. *Cancer Epidemiol* 2020;**66**:101725.
20. Milman S, Atzmon G, Crandall J, Barzilai N. Phenotypes and genotypes of high density lipoprotein cholesterol in exceptional longevity. *Curr Vasc Pharmacol* 2014;**12**:690–97.
21. Ko DT, Alter DA, Guo H *et al.* High-density lipoprotein cholesterol and cause-specific mortality in individuals without previous cardiovascular conditions: the CANHEART Study. *J Am Coll Cardiol* 2016;**68**:2073–83.
22. Bowe B, Xie Y, Xian H, Balasubramanian S, Zayed MA, Al-Aly Z. High density lipoprotein cholesterol and the risk of all-cause mortality among U.S. Veterans. *Clin J Am Soc Nephrol* 2016;**11**: 1784–93.
23. Zhong G-C, Huang S-Q, Peng Y *et al.* HDL-C is associated with mortality from all causes, cardiovascular disease and cancer in a J-shaped dose-response fashion: a pooled analysis of 37 prospective cohort studies. *Eur J Prev Cardiol* 2020;**27**:1187–203.
24. Bjartveit K, Foss OP, Gjervig T, Lund-Larsen PG. The cardiovascular disease study in Norwegian counties. Background and organization. *Acta Med Scand Suppl* 1979;**634**:1–70.
25. Stensvold I, Tverdal A, Foss OP. The effect of coffee on blood lipids and blood pressure. Results from a Norwegian cross-sectional study, men and women, 40-42 years. *J Clin Epidemiol* 1989;**42**:877–84.
26. Naess Ø, Søgaard AJ, Arnesen E *et al.* Cohort Profile: Cohort of Norway (CONOR). *Int J Epidemiol* 2008;**37**:481–85.
27. Burstein M, Scholnick HR, Morfin R. Rapid method for the isolation of lipoproteins from human serum by precipitation with polyanions. *J Lipid Res* 1970;**11**:583–95.
28. Stensvold I, Urdal P, Thürmer H, Tverdal A, Lund-Larsen PG, Foss OP. High-density lipoprotein cholesterol and coronary, cardiovascular and all-cause mortality among middle-aged Norwegian men and women. *Eur Heart J* 1992;**13**:1155–63.
29. StataCorp. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP, 2014.
30. Rehm J, Room R, Monteiro M *et al.* Alcohol as a risk factor for global burden of disease. *Eur Addict Res* 2003;**9**:157–64.
31. Corrao G, Bagnardi V, Zambon A, La Vecchia C. A meta-analysis of alcohol consumption and the risk of 15 diseases. *Prev Med* 2004;**38**:613–19.
32. Leon DA, Saburova L, Tomkins S *et al.* Hazardous alcohol drinking and premature mortality in Russia: a population based case-control study. *Lancet* 2007;**369**:2001–09.
33. Polsky S, Akturk HK. Alcohol consumption, diabetes risk, and cardiovascular disease within diabetes. *Curr Diab Rep* 2017;**17**: 136.
34. Tabak C, Smit HA, Räsänen L *et al.* Alcohol consumption in relation to 20-year COPD mortality and pulmonary function in middle-aged men from three European countries. *Epidemiology* 2001;**12**:239–45.
35. Wakabayashi I, Araki Y. Influences of gender and age on relationships between alcohol drinking and atherosclerotic risk factors. *Alcohol Clin Exp Res* 2010;**34**(Suppl 1):S54–60.
36. Berger D, Williams EC, Bryson CL, Rubinsky AD, Bradley KA. Alcohol questionnaires and HDL: screening scores as scaled markers of alcohol consumption. *Alcohol* 2013;**47**:439–45.
37. Bradley KA, Rubinsky AD, Lapham GT *et al.* Predictive validity of clinical AUDIT-C alcohol screening scores and changes in scores for three objective alcohol-related outcomes in a Veterans Affairs population. *Addiction* 2016;**111**:1975–84.
38. Würtz P, Cook S, Wang Q *et al.* Metabolic profiling of alcohol consumption in 9778 young adults. *Int J Epidemiol* 2016;**45**: 1493–506.
39. Bell S, Daskalopoulou M, Rapsomaniki E *et al.* Association between clinically recorded alcohol consumption and initial presentation of 12 cardiovascular diseases: population based cohort study using linked health records. *BMJ* 2017;**356**:j909.
40. Rimm EB, Williams P, Fosher K, Criqui M, Stampfer MJ. Moderate alcohol intake and lower risk of coronary heart disease: meta-analysis of effects on lipids and haemostatic factors. *BMJ* 1999;**319**:1523–28.
41. Brien SE, Ronksley PE, Turner BJ, Mukamal KJ, Ghali WA. Effect of alcohol consumption on biological markers associated

with risk of coronary heart disease: systematic review and meta-analysis of interventional studies. *BMJ* 2011;**342**:d636.
42. Boes E, Coassin S, Kollerits B, Heid IM, Kronenberg F. Genetic-epidemiological evidence on genes associated with HDL cholesterol levels: a systematic in-depth review. *Exp Gerontol* 2009; **44**:136–60.
43. Tverdal A, Høiseth G, Magnus P *et al.* Alcohol consumption, HDL-cholesterol and incidence of colon and rectal cancer: a prospective cohort study including 250,010 participants. *Alcohol Alcohol* 2021;**56**:718–25.
44. Lewington S, Whitlock G, Clarke R *et al.*; Prospective Studies Collaboration. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. *Lancet* 2007;**370**:1829–39.
45. Wilkins T, Ning H, Stone NJ *et al.* Coronary heart disease risks associated with high levels of HDL cholesterol. *J Am Heart Assoc* 2014;**3**:e000519.
46. Zanoni P, Khetarpal SA, Larach DB *et al.*; Global Lipids Genetics Consortium. Rare variant in scavenger receptor BI raises HDL cholesterol and increases risk of coronary heart disease. *Science* 2016;**351**:1166–71.
47. Helgadottir A, Sulem P, Thorgeirsson G *et al.* Rare SCARB1 mutations associate with high-density lipoprotein cholesterol but not with coronary artery disease. *Eur Heart J* 2018;**39**:2172–78.
48. Madsen CM, Varbo A, Nordestgaard BC. Extreme high high-density lipoprotein cholesterol is paradoxically associated with high mortality in men and women: two prospective cohort studies. *Eur Heart J* 2017;**38**:2478–86.
49. Guo E, Chen L, Xie Q, Chen J, Tang Z, Wu Y. Serum HDL-C as a potential biomarker for nodal stages in gastric cancer. *Ann Surg Oncol* 2007;**14**:2528–34.
50. Tamura T, Inagawa S, Hisakura K, Enomoto T, Ohkohchi N. Evaluation of serum high-density lipoprotein cholesterol levels as a prognostic factor in gastric cancer patients. *J Gastroenterol Hepatol* 2012;**27**:1635–40.
51. Prospective Studies Collaboration and Asia Pacific Cohort Studies Collaboration. Sex-specific relevance of diabetes to occlusive vascular and other mortality: a collaborative meta-analysis of individual data from 980 793 adults from 68 prospective studies. *Lancet Diabetes Endocrinol* 2018;**6**:538–46.
52. Jeffs JAR, Godsland IF, Johnston DG. Less than 50% of variation in HDL cholesterol between and within individuals is explained by established predictors. *Atherosclerosis* 2006;**184**: 178–87.
53. Hartung GH, Foreyt JP, Mitchell RE, Vlasek I, Gotto AM. Relation of diet to high-density-lipoprotein cholesterol in middle-aged marathon runners, joggers, and inactive men. *N Engl J Med* 1980;**302**:357–61.
54. Kokkinos PE, Fernhall B. Physical activity and high density lipoprotein cholesterol levels: what is the relationship? *Sports Med* 1999;**28**:307–14.
55. Gepner AD, Piper ME, Johnson HM, Fiore MC, Baker TB, Stein JH. Effects of smoking and smoking cessation on lipids and lipoproteins: outcomes from a randomized clinical trial. *Am Heart J* 2011;**161**:145–51.
56. Hasan B, Nayfeh T, Alzuabi M *et al.* Weight loss and serum lipids in overweight and obese adults: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2020;**105**:dgaa673.
57. Tolstrup JS, Grønbaek M, Nordestgaard BG. Alcohol intake, myocardial infarction, biochemical risk factors, and alcohol dehydrogenase genotypes. *Circ Cardiovasc Genet* 2009;**2**:507–14.
58. Vu KN, Ballantyne CM, Hoogeveen RC *et al.* Causal role of alcohol consumption in an improved lipid profile: the Atherosclerosis Risk in Communities (ARIC) Study. *PLoS One* 2016;**11**:e0148765.
59. Cartier L_J, Collins C, Lagacé M, Douville P. Comparison of fasting and non-fasting lipid profiles in a large cohort of patients presenting at a community hospital. *Clin Biochem* 2018;**52**: 61–66.
60. Jia J, Zhang L, Wang L, Ji C, Xia R, Yang Y. A systematic review and meta-analysis on the efficacy of statins in the treatment of atherosclerosis. *Ann Palliat Med* 2021;**10**:6793–803.