**Supplementary Appendix**

**U-shaped relationship of high-density lipoprotein and risk of infectious disease: two prospective population-based cohort studies**Christian M. Madsen, Anette Varbo, and Børge G. Nordestgaard

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**Methods** *Study cohorts*

Studies were approved by local institutional reviews boards and Danish ethical committees (KF-100-2039/91and H-KF-01-144/01). Informed consent was obtained from all individuals and the studies were conducted in accordance with the Declaration of Helsinki.

*The Copenhagen General Population Study*

The primary study cohort was comprised of 97,166 individuals from the prospective Copenhagen General Population Study1 with baseline measurements of HDL cholesterol. It was initiated in 2003 and recruitment is ongoing. White individuals of Danish descent are invited from the area around Copenhagen using information from the Danish Civil Registration System. Individuals answer a questionnaire regarding health and lifestyle which is reviewed together with an investigator. In addition, a physical examination is conducted and blood is drawn for biochemical measurements.

*The Copenhagen City Heart Study*

9,387 individuals from the 1991-1994 examination of the Copenhagen City Heart Study with baseline measurements of HDL cholesterol were included as an independent cohort for confirmation of the results obtained in the Copenhagen General Population Study.2 Individuals in the Copenhagen City Heart Study were recruited from a geographically separate region of Copenhagen and no individuals were included in both studies. Recruitment and examinations were similar to those of the Copenhagen General Population Study.

*Endpoints*

Infectious disease endpoints were based on data from the national Danish Patient Registry which records all hospital contacts in Denmark.3 We only included infectious events listed as the primary cause of admission until end of follow-up November 8th 2014. Infectious diseases were grouped based on International Classification of Diseases codes as shown in Supplementary Table S1 and as done previously.4, 5

Infectious diseases were also further grouped according to likely etiology into bacterial (gastroenteritis, bacterial pneumonia, skin infection, urinary tract infection, sepsis, endocarditis, bacterial meningitis, tuberculosis) and viral (hepatitis, viral meningitis, influenza and viral lower respiratory tract infections, HIV/AIDS). The use of the national Danish Patient Registry for classification of infectious disease has previously been validated.6 For the endpoint infectious disease related death, data was retrieved from the national Danish Register of Causes of Death7 and the cause of death was classified as infectious disease related if one of the three first ranked causes of death was an infectious disease. Information on death or emigration was retrieved from the Danish Civil Registration System. Due to the completeness of the Danish registries, not a single individual was lost to follow-up.

*Laboratory analyses and genotyping*HDL cholesterol, LDL cholesterol, triglycerides, apolipoprotein A1, blood leukocytes and plasma C-reactive protein (CRP) were all measured nonfasting. HDL cholesterol and triglycerides were measured using colorimetric assays (Konelab and Roche), and LDL cholesterol was calculated using the Friedewald equation when triglycerides were below 4 mmol/L (354 mg/dL) or otherwise measured directly (Konelab). Apolipoprotein A1 was measured using an immunoturbidimetric assay (Konelab). CRP was measured using high-sensitivity nephelometry or turbidimetry assays.

Genotyping was done using TaqMan-based assays. For genetic analyses we included two common genetic variants in genes encoding two proteins with known importance for HDL metabolism and concentrations of HDL cholesterol – hepatic lipase (LIPC) 2480C>T (rs1800588) and cholesteryl-ester transfer protein (CETP) Taq1bG>A (rs708272). Information on genotype was available in 104,867 and 100,686 individuals from the Copenhagen General Population Study and Copenhagen City Heart study combined, on the *LIPC* and *CETP* variant respectively. A total of 100,115 individuals had information on both variants.  
  
*Covariates*  
Covariates for adjustment were chosen based on known association with HDL cholesterol and risk of infectious disease. Body mass index was measured weight in kilograms divided by measured height in meters squared. Body mass index was included as a continuous variable. Alcohol intake, smoking, physical activity, and lipid-lowering therapy were self-reported. Alcohol was included as a continuous variable in the form of average weekly consumption in units (1 unit~12g). Smoking was current, former, or never smokers. Physical activity was weekly physical activity in leisure time in the categories passive, light activity 2–4h/week, light/moderate activity >4 h/week, and very active >4 h/week. Lipid-lowering therapy was self-reported at baseline and was mainly statins. Information on a diagnosis of ischemic heart disease(ICD8:410-414, ICD10:I20-I25) before baseline examination was collected and verified from 1977 through 2014 by reviewing all hospital admissions and diagnoses entered in the national Danish Patient Registry and all causes of death entered in the national Danish Causes of Death Registry. Diabetes mellitus was self-reported disease, nonfasting plasma glucose >11.0 mmol/L, medication prescribed for diabetes, and/or hospitalization due to diabetes(ICD8:249,250; ICD10:E10,E11,E13,E14) before baseline examination. Kidney function was included as the estimated glomerular filtration rate (eGFR) using plasma creatinine measurements at baseline and the CKD-EPI formula.8

*Statistical Analyses*

Statistical analyses were performed using Stata 13.1 and P-values are two-sided. For baseline characteristics, Pearsons’s chi-square test was used for categorical variables, and Wilcoxon rank-sum test or Kruskal-Wallis test for continuous variables which were given as median (interquartile range). Only for adjustment in the few individuals with missing information on certain covariates (Supplementary Tables S2 and S3), we used multiple imputations with chained equations to fill out the missing values.

The associations between HDL cholesterol and plasma CRP and blood leukocytes at baseline were assessed using heteroscedasticity robust simple linear regression. The linearity assumption was tested visually using a lowess smoother. Normality of residuals was visually tested using a histogram of residuals and homoscedasticity was visually tested using a plot of residuals versus predicted values. CRP was log base 2 transformed to avoid violation of the mentioned assumptions; hence change in CRP per change in HDL cholesterol is given as percent change as opposed to absolute values as for blood leukocytes. For analyses on blood leukocytes we excluded individuals with leukocytes > 20mmol/L with possible malignant haematogical disease. The associations between HDL and CRP and leukocytes were also assessed visually using Kernel-weighted local polynomial smoothing.

Associations between risk of infectious disease and HDL cholesterol, apolipoprotein A1 and triglycerides on a continuous scale were examined using restricted cubic splines, with knots at equally spaced percentiles9, which were used in multiple events Cox proportional hazards regression. The number of knots was chosen as the number that gave the best fit as assessed by the lowest value of the Akaike information criterion. If results were similar (within 2 units of the best fit), the model with fewest knots were chosen to avoid overfitting. These analyses were used to help define meaningful reference groups using categories of HDL cholesterol, with the category having the lowest risk as the reference group. First, individuals were stratified into four clinically relevant HDL cholesterol groups with 0.5mmol/L (19mg/dL) intervals, with the group with highest HDL cholesterol as reference and lowest risk. Second, to capture extreme values, individuals were also stratified into 11 groups with 0.2mmol/L (8mg/dL) intervals, with the group with HDL cholesterol of 2.2-2.3mmol/L (85-93mg/dL) as reference and lowest risk. Analyses were made based on the concentration in mmol/L and later converted to mg/dL by multiplying with 38.6 and rounding to nearest 1mg/dL.

To allow for repeated infectious disease events for each individual, multiple events Cox proportional hazards regression using the approach described by Andersen-Gill10 with robust standard errors was used as the primary analysis. Age was used as time scale, and analyses were conducted with delayed entry (left truncation), and censoring at death or emigration(0.4%). Individuals with a diagnosis of human immunodeficiency virus, hepatitis or tuberculosis before study entry could not contribute with an event prospectively within the respective disease category, as these diseases are considered chronic. They could however contribute with events in other infectious disease categories, so no individuals were excluded from the prospective analyses due to prior infectious disease history. Conventional single event Cox proportional hazards regressions were carried out as sensitivity analyses and was used for analyses of infectious disease related death. Proportional hazard assumptions were assessed graphically using Schoenfeld residuals with no major violations detected. Infectious disease events were also analyzed prospectively as a count variable using negative binomial regression to allow for overdispersion. To account for competing risk of death and emigration, risk of infectious disease was analyzed using Fine and Gray competing risk regression with death and emigration as competing event. We used logistic regression to determine the association between HDL cholesterol and risk of infectious disease in a cross-sectional setting. For sensitivity analysis, infectious disease events were included from 1977 (registry start) or from the age of 18 years, whichever came last.

For genetic analyses, genotypes were combined into an unweighted allele score of HDL cholesterol increasing alleles. The number of double homozygotes was limited (N=869) so individuals with 3 or 4 HDL cholesterol increasing alleles were combined into one group. As genotypes are present from birth we included infectious disease events from birth or 1977 (registry start), whichever came last. Multiple events Cox proportional hazards regression adjusted for age and sex was used for the genetic analyses. As the association between HDL cholesterol and risk of infectious disease does not appear to be linear, the effect of the allele score has to be interpreted with caution and as a population-averaged effect. Analyses were also done in two strata divided by the median of HDL cholesterol after removing the effects of the genotypes on the concentration of HDL cholesterol.11 This was done by regressing HDL cholesterol on the genotypes using simple linear regression and subsequently stratifying based on the residual variation.

Risk estimates and confidence intervals were corrected for regression dilution bias using a nonparametric method,12 as done previously.2 This was done using measurements of HDL cholesterol, apolipoprotein A1, and triglycerides from 4,162 individuals from the Copenhagen City Heart Study who attended both the 1991-94 examination and the 2001-03 examination. Regression dilution ratios of 0.73, 0.68, 0.53, and 0.60 were calculated for HDL cholesterol, apolipoprotein A1, triglycerides, and LDL cholesterol respectively.

Population-attributable risks of infectious disease for HDL cholesterol <1.2mmol/L(<46mg/dL) and ≥2.4mmol/L(≥93mg/dL) were calculated as: [f(RR − 1)]/[1 + f(RR − 1)] × 100%, where f is the prevalence of the exposure and RR is the multifactorially adjusted hazard ratio.

P-values are for linear trend and were estimated by assigning the groups continuous numbers (0, 1, 2, 3 etc.) and including them as a continuous variable in the regression analyses. We tested for interactions by incorporating two-factor interaction terms between HDL cholesterol and included covariates in categories or as continuous variables as indicated. P-values for interaction were obtained using the Wald test.

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| --- | --- | --- | --- | --- |
| **Table S1. Categorization of infectious disease endpoints based on the International Classification of Diseases version 8 (ICD-8) and 10 (ICD-10).** | | | | |
| **Infectious disease subgroup** |  | **ICD-8 codes** |  | **ICD-10 codes** |
|  |  |  |  |  |
| Gastroenteritis |  | 003xx-005xx, 008xx-009xx |  | A020, A022-A029, A03-A05, A08-A09 |
| Bacterial pneumonia |  | 481xx-486xx |  | A481, J13-J16, J170, J18 |
| Skin infection |  | 03599, 680xx-684xx, 68501, 68509, 68600, 68608, 68609, 68690, 68691, 68692, 68695, 68696, 68699 |  | A46, L00-L08, L303, L308F |
| Urinary tract infection |  | 5900x, 5901x, 59099, 59500-59502, 59508, 59509, 59906 |  | N109A-N109C, N110-N118B, N118D, N119, N12, N300, N308A-N308C, N309, N390 |
| Sepsis |  | 03610, 038xx |  | A021, A282B, A327, A392-A394, A40-A41, A427, A483, A499A, R572 |
| Other infections: |  |  |  |  |
|  |  |  |  |  |
| Endocarditis |  | 421xx |  | I33, I38, I398 |
| Bacterial meningitis |  | 02701, 320xx, 03609 |  | A390, G00-G01, G039, G042 |
| Mycoses |  | 110xx-112xx, 114xx-117xx |  | B35-B49 |
| Hepatitis |  | 070xx |  | B15-B19, Z225 |
| Imported & parasitic infections |  | 000xx-002xx, 006xx-007xx, 060xx-061xx, 084xx-087xx, 129xx-130xx, 13600, 13603 |  | A00-A01, A06-A07, A90-A96, B50-B64 |
| Viral meningitis |  | 045xx, 05403, 07929 |  | A87, B003, B004A, G020 |
| Influenza and viral lower respiratory tract infections |  | 470xx-472xx, 48099 |  | J09-J101C, J12, J171 |
| HIV/AIDS |  | 07983 |  | B20-B24, F024, Z21 |
| Tuberculosis |  | 010xx, 011xx, 01200, 01208, 01209, 0121x-0129x, 013xx-018xx |  | A15-A19, N330, N740-N741 |
| Parasitic worm diseases |  | 120xx-128xx |  | B65-B83, N308J |
| Pertussis |  | 03309, 03319 |  | A37 |

**Table S2. Number of individuals with missing and imputed covariates in the Copenhagen General Population Study.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Covariate** | **Complete** | **Imputed** | **Total** |
| Age | 97,166 | 0 | 97,166 |
| Sex | 97,166 | 0 | 97,166 |
| Body mass index | 97,011 | 155 (0.2%) | 97,166 |
| Diabetes mellitus | 96,849 | 317 (0.3%) | 97,166 |
| Ischemic heart disease | 97,166 | 0 | 97,166 |
| Smoking habits | 96,826 | 340 (0.3%) | 97,166 |
| Alcohol intake | 92,563 | 4,603 (4.7%) | 97,166 |
| Lipid-lowering therapy | 96,831 | 335 (0.3%) | 97,166 |
| Physical activity leisure time | 96,349 | 817 (0.8%) | 97,166 |
| Birth year | 97,166 | 0 | 97,166 |
| LDL cholesterol | 96,849 | 317 (0.3%) | 97,166 |
| Triglycerides | 97,154 | 12 (0.0%) | 97,166 |
| eGFR | 96,986 | 180 (0.2%) | 97,166 |
| Plasma CRP | 97,068 | 98 (0.1%) | 97,166 |

eGFR=estimated glomerular filtration rate. CRP=C-reactive protein.

**Table S3. Number of individuals with missing and imputed covariates in the Copenhagen City Heart Study.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Covariate** | **Complete** | **Imputed** | **Total** |
| Age | 9,387 | 0 | 9,387 |
| Sex | 9,387 | 0 | 9,387 |
| Body mass index | 9,133 | 254 (2.7%) | 9,387 |
| Diabetes mellitus | 9,386 | 1 (0.0%) | 9,387 |
| Ischaemic heart disease | 9,387 | 0 | 9,387 |
| Smoking habits | 9,353 | 34 (0.4%) | 9,387 |
| Alcohol intake | 9,298 | 89 (0.9%) | 9,387 |
| Lipid-lowering therapy | 9,303 | 84 (0.9%) | 9,387 |
| Physical activity leisure time | 9,299 | 88 (0.9%) | 9,387 |
| Birth year | 9,387 | 0 | 9,387 |
| LDL cholesterol | 9,294 | 93 (1.0%) | 9,387 |
| Triglycerides | 9,305 | 82 (0.9%) | 9,387 |
| eGFR | 8,833 | 554 (5.9%) | 9,387 |
| CRP | 8,412 | 975 (10.4%) | 9,387 |

eGFR=estimated glomerular filtration rate. CRP=C-reactive protein.

**Table S4. Baseline characteristics of individuals in the Copenhagen General Population Study by infectious disease status.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **No infectious disease during follow-up** | **Infectious disease**  **during follow-up** | **P-value** |
| Participants | 88,684 (91%) | 8,482 (9%) | Not applicable |
| Men | 39,320 (44%) | 4,339 (51%) | <0.001 |
| Age, years | 57 (48-66) | 67 (57-76) | <0.001 |
| Body mass index, kg/m2 | 25.5 (23.2-28.4) | 26.3 (23.6-29.3) | <0.001 |
| Current smokers | 15,177 (17%) | 2,103 (25%) | <0.001 |
| High alcohol intake\* | 34,857 (41%) | 3,361 (43%) | 0.003 |
| Physical inactivity\*\* | 42,516 (48%) | 4,866 (59%) | <0.001 |
| Diabetes mellitus | 3,350 (4%) | 776 (9%) | <0.001 |
| Ischemic heart disease | 4,482 (5%) | 1,129 (13%) | <0.001 |
| Lipid-lowering therapy | 9,904 (11%) | 1,567 (19%) | <0.001 |
| HDL cholesterol |  |  |  |
| mmol/L | 1.6 (1.3-1.9) | 1.5 (1.2-1.9) | <0.001 |
| mg/dL | 61 (48-75) | 59 (47-74) | <0.001 |
| Apolipoprotein A1, mg/dL | 159 (141-179) | 156 (138-178) | <0.001 |
| LDL cholesterol |  |  |  |
| mmol/L | 3.2 (2.6-3.9) | 3.1 (2.4-3.8) | <0.001 |
| mg/dL | 124 (100-150) | 120 (93-147) | <0.001 |
| Triglycerides |  |  |  |
| mmol/L | 1.4 (1.0-2.0) | 1.5 (1.1-2.2) | <0.001 |
| mg/dL | 121 (85-181) | 133 (93-198) | <0.001 |
| eGFR, mL/min/1.73m2 | 80 (70-91) | 73 (61-85) | <0.001 |
| CRP, mg/L | 1.4 (1.0-2.2) | 1.9 (1.2-3.6) | <0.001 |

Values are median (interquartile range) or number of individuals (%). P-values are from Pearson’s chi-square test for categorical variables and Wilcoxon rank-sum test for continuous variables. The number of individuals varies slightly according to availability of the variables (data is without imputation). \* >7 units per week for women and >14 units per week for men (1 unit~ 12g of alcohol). \*\* ≤4 hours physical activity in leisure time per week. eGFR=estimated glomerular filtration rate. CRP=C-reactive protein.

**Table S5. Baseline characteristics of individuals in the Copenhagen General Population Study by 0.5 mmol/L (19 mg/dL) groups of HDL cholesterol.**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **HDL cholesterol, mmol/L (mg/dL)** | | | | |  | |
|  | **<1.0 (<39)** | **1.0-1.4 (39-58)** | **1.5-1.9 (58-77)** | **≥2.0 (≥77)** | **P-value** | |
| Participants | 9,101 | 34,229 | 32,219 | 21,617 |  | |
| Men | 7,117 (78%) | 20,015 (58%) | 11,866 (37%) | 4,661 (22%) | <0.001 | |
| Age, years | 55 (46-65) | 56 (47-66) | 58 (48-67) | 61 (52-69) | <0.001 | |
| Body mass index, kg/m2 | 28.4 (25.8-31.4) | 26.7 (24.3-29.5) | 25.0 (22.9-27.6) | 23.8 (21.9-26.2) | <0.001 | |
| Current smokers | 2,306 (25%) | 6,857 (20%) | 5,068 (16%) | 3,049 (14%) | <0.001 | |
| High alcohol intake\* | 2,155 (25%) | 10,926 (34%) | 13,509 (44%) | 11,628 (56%) | <0.001 | |
| Physical inactivity\*\* | 5,239 (58%) | 17,468 (51%) | 14,987 (47%) | 9,688 (45%) | <0.001 | |
| Diabetes mellitus | 828 (9%) | 1,707 (5%) | 1,009 (3%) | 582 (3%) | <0.001 | |
| Ischemic heart disease | 791 (9%) | 2,326 (7%) | 1,580 (5%) | 914 (4%) | <0.001 | |
| Lipid-lowering therapy | 1,333 (15%) | 4,352 (13%) | 3,530 (11%) | 2,256 (10%) | <0.001 | |
| HDL cholesterol |  |  |  |  |  | |
| mmol/L | 0.9 (0.8-0.9) | 1.3 (1.1-1.4) | 1.7 (1.6-1.8) | 2.3 (2.1-2.5) | <0.001 | |
| mg/dL | 34 (30-36) | 49 (44-54) | 66 (62-71) | 88 (82-98) | <0.001 | |
| Apolipoprotein A1, mg/dL | 127 (116-140) | 144 (133-156) | 164 (153-177) | 193 (178-211) | <0.001 | |
| LDL cholesterol |  |  |  |  |  | |
| mmol/L | 3.2 (2.6-3.9) | 3.3 (2.7-4.0) | 3.2 (2.6-3.8) | 3.0 (2.4-3.6) | <0.001 | |
| mg/dL | 124 (100-151) | 127 (104-154) | 124 (100-147) | 116 (93-139) | <0.001 | |
| Triglycerides |  |  |  |  |  | |
| mmol/L | 2.6 (1.8-3.7) | 1.7 (1.2-2.4) | 1.3 (0.9-1.7) | 1.0 (0.8-1.3) | <0.001 | |
| mg/dL | 232 (162-328) | 152 (108-213) | 111 (81-151) | 87 (67-117) | <0.001 | |
| eGFR, mL/min/1.73m2 | 85 (74-95) | 82 (71-92) | 79 (69-90) | 76 (66-86) | <0.001 | |
| CRP, mg/L | 1.8 (1.2-3.2) | 1.5 (1.1-2.5) | 1.3 (0.9-2.1) | 1.3 (0.8-1.9) | <0.001 | |

Values are median (interquartile range) or number of individuals (%). P-values are from Pearson’s chi-square test for categorical variables and   
Kruskal-Wallis test for continuous variables. The number of individuals varies slightly according to availability of the variables (data is without   
imputation). \* >7 units per week for women and >14 units per week for men (1 unit~ 12g of alcohol). \*\* ≤4 hours physical activity in leisure   
time per week. eGFR=estimated glomerular filtration rate. CRP=C-reactive protein.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **HDL Cholesterol, mmol/L (mg/dL)** | | | | | | | | | | |  |
|  | **<0.8 (31)** | **0.8-0.9 (31-39)** | **1.0-1.1 (39-46)** | **1.2-1.3 (46-54)** | **1.4-1.5 (54-62)** | **1.6-1.7 (62-69)** | **1.8-1.9 (69-77)** | **2.0-2.1 (77-85)** | **2.2-2.3 (85-93)** | **2.4-2.5 (93-100)** | **≥2.6 (≥100)** | **P-value** |
| Participants | 2,500 | 6,601 | 11,559 | 15,711 | 14,631 | 14,367 | 10,180 | 8,257 | 5,443 | 3,748 | 4,169 |  |
| Men | 2,047 (82%) | 5,070 (77%) | 7,853 (68%) | 8,816 (56%) | 6,691 (46%) | 5,420 (38%) | 3,101 (30%) | 2,100 (25%) | 1,160 (21%) | 707 (19%) | 694 (17%) | <0.001 |
| Age, years | 54 (45-65) | 55 (46-65) | 56 (46-65) | 57 (47-67) | 57 (47-67) | 58 (48-67) | 59 (49-68) | 60 (50-68) | 61 (52-69) | 62 (52-69) | 63 (55-71) | <0.001 |
| Body mass index, kg/m2 | 28.9 (26.4-32.1) | 28.1 (25.7-31.1) | 27.3 (25.0-30.1) | 26.5 (24.1-29.3) | 25.8 (23.5-28.5) | 25.0 (23.0-27.6) | 24.5 (22.5-27.0) | 24.2 (22.2-26.6) | 23.9 (22.0-26.2) | 23.7 (21.8-26.0) | 23.2 (21.3-25.5) | <0.001 |
| Current smokers | 693 (28%) | 1,613 (25%) | 2,597 (23%) | 3,020 (19%) | 2,529 (17%) | 2,289 (16%) | 1,490 (15%) | 1,204 (15%) | 703 (13%) | 521 (14%) | 621 (15%) | <0.001 |
| High alcohol intake\* | 533 (23%) | 1,622 (26%) | 3,338 (31%) | 5,092 (34%) | 5,450 (39%) | 5,989 (44%) | 4,566 (47%) | 3,997 (50%) | 2,902 (55%) | 2,115 (58%) | 2,614 (65%) | <0.001 |
| Physical inactivity\*\* | 1,518 (61%) | 3,721 (57%) | 6,131 (54%) | 7,927 (51%) | 7,081 (49%) | 6,717 (47%) | 4,599 (46%) | 3,728 (45%) | 2,396 (44%) | 1,698 (46%) | 1,866 (45%) | <0.001 |
| Diabetes mellitus | 275 (11%) | 553 (8%) | 735 (6%) | 700 (4%) | 535 (4%) | 462 (3%) | 284 (3%) | 220 (3%) | 144 (3%) | 94 (3%) | 124 (3%) | <0.001 |
| Ischemic heart disease | 257 (10%) | 534 (8%) | 922 (8%) | 1,009 (6%) | 794 (5%) | 713 (5%) | 468 (5%) | 353 (4%) | 226 (4%) | 175 (5%) | 160 (4%) | <0.001 |
| Lipid-lowering therapy | 387 (16%) | 946 (14%) | 1,596 (14%) | 1,935 (12%) | 1,686 (12%) | 1,614 (11%) | 1,051 (10%) | 770 (9%) | 578 (11%) | 413 (11%) | 495 (12%) | <0.001 |
| HDL cholesterol |  |  |  |  |  |  |  |  |  |  |  |  |
| mmol/L | 0.7 (0.6-0.8) | 0.9 (0.9-1.0) | 1.1 (1.0-1.1) | 1.3 (1.3-1.4) | 1.5 (1.5-1.5) | 1.7 (1.6-1.8) | 1.9 (1.9-1.9) | 2.1 (2.0-2.1) | 2.3 (2.2-2.3) | 2.5 (2.4-2.5) | 2.8 (2.7-3.0) | <0.001 |
| mg/dL | 28 (25-29) | 35 (33-37) | 42 (41-44) | 50 (48-52) | 58 (56-60) | 66 (63-68) | 73 (71-75) | 81 (79-83) | 88 (86-90) | 96 (94-98) | 107 (103-116) | <0.001 |
| Apolipoprotein A1, mg/dL | 121 (109-133) | 129 (119-141) | 137 (126-148) | 145 (135-157) | 154 (143-166) | 163 (152-175) | 172 (161-184) | 181 (169-194) | 190 (179-204) | 201 (189-216) | 221 (205-241) | <0.001 |
| LDL cholesterol |  |  |  |  |  |  |  |  |  |  |  |  |
| mmol/L | 3.0 (2.4-3.7) | 3.3 (2.6-4.0) | 3.4 (2.7-4.0) | 3.3 (2.7-4.0) | 3.2 (2.6-3.9) | 3.2 (2.6-3.8) | 3.1 (2.5-3.8) | 3.1 (2.5-3.7) | 3.0 (2.4-3.6) | 3.0 (2.4-3.6) | 2.9 (2.3-3.5) | <0.001 |
| mg/dL | 117 (93-143) | 127 (100-154) | 130 (104-154) | 127 (104-154) | 125 (101-151) | 124 (100-147) | 120 (97-146) | 120 (97-143) | 116 (93-139) | 116 (93-139) | 112 (89-135) | <0.001 |
| Triglycerides |  |  |  |  |  |  |  |  |  |  |  |  |
| mmol/L | 3.1 (2.2-4.5) | 2.5 (1.8-3.5) | 2.0 (1.4-2.8) | 1.7 (1.2-2.3) | 1.4 (1.0-2.0) | 1.3 (0.9-1.7) | 1.1 (0.9-1.5) | 1.1 (0.8-1.4) | 1.0 (0.8-1.3) | 0.9 (0.7-1.3) | 0.9 (0.7-1.1) | <0.001 |
| mg/dL | 275 (193-398) | 218 (155-306) | 176 (125-245) | 147 (105-204) | 127 (91-175) | 111 (82-152) | 101 (75-137) | 94 (72-127) | 88 (68-116) | 83 (65-111) | 77 (60-102) | <0.001 |
| eGFR, mL/min/1.73m2 | 87 (75-96) | 84 (73-94) | 83 (72-93) | 81 (71-92) | 81 (70-91) | 79 (69-90) | 78 (68-88) | 77 (67-87) | 76 (66-87) | 75 (65-86) | 73 (64-83) | <0.001 |
| CRP, mg/L | 1.9 (1.3-3.5) | 1.7 (1.2-3.1) | 1.6 (1.1-2.8) | 1.5 (1.0-2.5) | 1.4 (1.0-2.3) | 1.4 (0.9-2.1) | 1.3 (0.9-1.9) | 1.3 (0.9-1.9) | 1.3 (0.8-1.8) | 1.2 (0.8-1.7) | 1.3 (0.8-1.8) | <0.001 |

**Table S6. Baseline characteristics of individuals in the Copenhagen General Population Study by 0.2 mmol/L (8 mg/dL) groups of HDL cholesterol.**

Values are median (interquartile range) or number of individuals (%). P-values are from Pearson’s chi-square test for categorical variables and Kruskal-Wallis test for continuous variables. The number of individuals varies slightly according to availability of the variables (data is without imputation). \* >7 units per week for women and >14 units per week for men (1 unit~ 12g of alcohol). \*\* ≤4 hours physical activity in leisure time per week. eGFR=estimated glomerular filtration rate. CRP=C-reactive protein.

**Table S7. Baseline characteristics of individuals in the Copenhagen General Population Study by percentiles of HDL cholesterol.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **HDL cholesterol, percentiles** | | | | |  |
|  | **1-5** | **6-40** | **41-60** | **61-95** | **96-100** | **P-value** |
| Participants | 5,160 | 34,404 | 19,301 | 33,525 | 4,776 |  |
| Men | 4,134 (80%) | 21,198 (62%) | 8,261 (43%) | 9,257 (28%) | 809 (17%) | <0.001 |
| Age, years | 54 (45-65) | 56 (47-66) | 57 (48-67) | 60 (50-68) | 63 (55-71) | <0.001 |
| Body mass index, kg/m2 | 28.7 (26.1-31.7) | 26.9 (24.5-29.7) | 25.5 (23.3-28.1) | 24.3 (22.3-26.8) | 23.3 (21.3-25.5) | <0.001 |
| Current smokers | 1,365 (27%) | 7,129 (21%) | 3,219 (17%) | 4,861 (15%) | 706 (15%) | <0.001 |
| High alcohol intake\* | 1,130 (23%) | 10,586 (33%) | 7,526 (41%) | 15,989 (50%) | 2,987 (64%) | <0.001 |
| Physical inactivity\*\* | 3,051 (60%) | 17,809 (52%) | 9,268 (48%) | 15,127 (45%) | 2,127 (45%) | <0.001 |
| Diabetes mellitus | 504 (10%) | 1,877 (5%) | 673 (3%) | 934 (3%) | 138 (3%) | <0.001 |
| Ischemic heart disease | 476 (9%) | 2,438 (7%) | 1,007 (5%) | 1,505 (4%) | 185 (4%) | <0.001 |
| Lipid-lowering therapy | 794 (15%) | 4,452 (13%) | 2,183 (11%) | 3,482 (10%) | 560 (12%) | <0.001 |
| HDL cholesterol |  |  |  |  |  |  |
| mmol/L | 0.8 (0.7-0.9) | 1.2 (1.1-1.3) | 1.6 (1.5-1.6) | 2.0 (1.8-2.2) | 2.8 (2.7-3.0) | <0.001 |
| mg/dL | 31 (28-33) | 47 (42-51) | 61 (58-63) | 77 (71-85) | 106 (102-114) | <0.001 |
| Apolipoprotein A1, mg/dL | 124 (113-136) | 141 (130-154) | 157 (147-169) | 178 (165-193) | 219 (203-239) | <0.001 |
| LDL cholesterol |  |  |  |  |  |  |
| mmol/L | 3.2 (2.5-3.8) | 3.3 (2.7-4.0) | 3.2 (2.6-3.9) | 3.1 (2.5-3.7) | 2.9 (2.3-3.5) | <0.001 |
| mg/dL | 123 (97-147) | 128 (104-154) | 124 (100-151) | 120 (97-143) | 112 (89-135) | <0.001 |
| Triglycerides |  |  |  |  |  |  |
| mmol/L | 2.8 (2.0-4.0) | 1.8 (1.3-2.6) | 1.4 (1.0-1.9) | 1.1 (0.8-1.5) | 0.9 (0.7-1.1) | <0.001 |
| mg/dL | 250 (173-357) | 161 (113-227) | 120 (88-165) | 96 (73-130) | 78 (61-102) | <0.001 |
| eGFR, mL/min/1.73m2 | 86 (74-96) | 82 (71-93) | 80 (70-91) | 77 (67-88) | 73 (64-84) | <0.001 |
| CRP, mg/L | 1.9 (1.2-3.4) | 1.5 (1.1-2.6) | 1.4 (1.0-2.3) | 1.3 (0.9-1.9) | 1.2 (0.8-1.8) | <0.001 |

Values are median (interquartile range) or number of individuals (%). P-values are from Pearson’s chi-square test for categorical variables and Kruskal-Wallis test for   
continuous variables. The number of individuals varies slightly according to availability of the variables (data is without imputation). \* >7 units per week for women   
and >14 units per week for men (1 unit~ 12g of alcohol). \*\* ≤4 hours physical activity in leisure time per week. eGFR=estimated glomerular filtration rate.   
CRP=C-reactive protein.

**Table S8.** **Baseline characteristics of individuals in the Copenhagen City Heart Study** **by infectious disease status.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **No infectious disease during follow-up** | **Infectious disease**  **during follow-up** | **P-value** |
| Participants | 6,483 | 2,904 | Not applicable |
| Men | 2,825 (44%) | 1,296 (45%) | 0.34 |
| Age, years | 58 (44-69) | 66 (56-72) | <0.001 |
| Body mass index, kg/m2 | 24.7 (22.4-27.8) | 25.6 (23.0-28.7) | <0.001 |
| Current smokers | 3,116 (48%) | 1,492 (52%) | 0.003 |
| High alcohol intake\* | 2,034 (32%) | 849 (30%) | 0.04 |
| Physical inactivity\*\* | 4,167 (65%) | 1,975 (69%) | <0.001 |
| Diabetes mellitus | 249 (4%) | 180 (6%) | <0.001 |
| Ischemic heart disease | 280 (4%) | 202 (7%) | <0.001 |
| Lipid-lowering therapy | 62 (1%) | 29 (1%) | 0.84 |
| HDL cholesterol |  |  |  |
| mmol/L | 1.5 (1.2-1.9) | 1.5 (1.2-1.9) | 0.96 |
| mg/dL | 58 (46-73) | 58 (46-73) | 0.96 |
| Apolipoprotein A1, mg/dL | 139 (121-159) | 141 (122-141) | 0.002 |
| LDL cholesterol, mmol/L |  |  |  |
| mmol/L | 3.6 (2.9-4.4) | 3.8 (3.0-4.6) | <0.001 |
| mg/dL | 141 (113-171) | 146 (118-176) | <0.001 |
| Triglycerides, mmol/L |  |  |  |
| mmol/L | 1.5 (1.1-2.2) | 1.6 (1.2-2.4) | <0.001 |
| mg/dL | 133 (94-192) | 142 (103-210) | <0.001 |
| eGFR, mL/min/1.73m2 | 71 (61-82) | 66 (57-77) | <0.001 |
| CRP, mg/L | 1.7 (1.2-2.8) | 2.0 (1.4-3.6) | <0.001 |

Values are median (interquartile range) or number of individuals (%). P-values are from Pearson’s chi-square test for categorical variables and Wilcoxon rank-sum test for continuous variables. The number of individuals varies slightly according to availability of the variables (data is without imputation). \* >7 units per week for women and >14 units per week for men (1 unit~ 12g of alcohol). \*\* ≤4 hours physical activity in leisure time per week. eGFR=estimated glomerular filtration rate. CRP=C-reactive protein.

**Table S9. Baseline characteristics of individuals in the Copenhagen City Heart Study by 0.5 mmol/L (19 mg/dL) groups of HDL cholesterol.**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **HDL cholesterol, mmol/L (mg/dL)** | | | | |  | |
|  | **<1.0 (<39)** | **1.0-1.4 (39-58)** | **1.5-1.9 (58-77)** | **≥2.0 (≥77)** | **P-value** | |
| Participants | 662 | 3,523 | 3,316 | 1,886 |  | |
| Men | 503 (76%) | 2,068 (59%) | 1,153 (35%) | 397 (21%) | <0.001 | |
| Age, years | 61 (49-70) | 60 (48-70) | 60 (47-70) | 63 (52-72) | <0.001 | |
| Body mass index, kg/m2 | 27.9 (25.2-30.9) | 26.1 (23.6-29.1) | 24.5 (22.1-27.3) | 23.4 (21.3-26.0) | <0.001 | |
| Current smokers | 372 (56%) | 1,804 (51%) | 1,595 (48%) | 837 (45%) | <0.001 | |
| High alcohol intake\* | 124 (19%) | 891 (26%) | 1,072 (33%) | 796 (43%) | <0.001 | |
| Physical inactivity\*\* | 193 (29%) | 1,175 (34%) | 1,176 (36%) | 613 (33%) | 0.008 | |
| Diabetes mellitus | 81 (12%) | 209 (6%) | 100 (3%) | 39 (2%) | <0.001 | |
| Ischemic heart disease | 75 (11%) | 205 (6%) | 147 (4%) | 55 (3%) | <0.001 | |
| Lipid-lowering therapy | 15 (2%) | 36 (1%) | 32 (1%) | 8 (<1%) | <0.001 | |
| HDL cholesterol |  |  |  |  |  | |
| mmol/L | 0.9 (0.8-0.9) | 1.2 (1.1-1.3) | 1.7 (1.6-1.8) | 2.2 (2.1-2.5) | <0.001 | |
| mg/dL | 35 (31-35) | 46 (42-50) | 66 (62-69) | 85 (81-97) | <0.001 | |
| Apolipoprotein A1, mg/dL | 100 (92-107) | 123 (113-133) | 147 (137-158) | 178 (165-193) | <0.001 | |
| LDL cholesterol |  |  |  |  |  | |
| mmol/L | 3.6 (2.9-4.4) | 3.9 (3.1-4.6) | 3.7 (3.0-4.5) | 3.4 (2.7-4.2) | <0.001 | |
| mg/dL | 138 (111-168) | 150 (121-179) | 141 (114-173) | 131 (104-162) | <0.001 | |
| Triglycerides |  |  |  |  |  | |
| mmol/L | 2.8 (1.9-4.2) | 1.9 (1.4-2.6) | 1.4 (1.0-1.9) | 1.1 (0.9-1.5) | <0.001 | |
| mg/dL | 250 (167-374) | 165 (119-233) | 124 (91-167) | 102 (78-134) | <0.001 | |
| eGFR, mL/min/1.73m2 | 70 (60-81) | 71 (60-82) | 70 (60-81) | 68 (59-78) | <0.001 | |
| CRP, mg/L | 2.4 (1.5-4.8) | 1.9 (1.3-3.5) | 1.7 (1.2-2.8) | 1.5 (1.2-2.3) | <0.001 | |

Values are median (interquartile range) or number of individuals (%). P-values are from Pearson’s chi-square test for categorical variables and   
Kruskal-Wallis test for continuous variables. The number of individuals varies slightly according to availability of the variables (data is without   
imputation). \* >7 units per week for women and >14 units per week for men (1 unit~ 12g of alcohol). \*\* ≤4 hours physical activity in leisure   
time per week. eGFR=estimated glomerular filtration rate. CRP=C-reactive protein.

**Table S10. Baseline characteristics of individuals in the Copenhagen City Heart Study by 0.2 mmol/L (19 mg/dL) groups of HDL cholesterol.**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **HDL Cholesterol, mmol/L (mg/dL)** | | | | | | | | | | |  |
|  | **<0.8 (31)** | **0.8-0.9 (31-39)** | **1.0-1.1 (39-46)** | **1.2-1.3 (46-54)** | **1.4-1.5 (54-62)** | **1.6-1.7 (62-69)** | **1.8-1.9 (69-77)** | **2.0-2.1 (77-85)** | **2.2-2.3 (85-93)** | **2.4-2.5 (93-100)** | **≥2.6 (≥100)** | **P-value** |
| Participants | 126 | 536 | 1,131 | 1,545 | 1,652 | 1,431 | 1,080 | 740 | 461 | 281 | 404 |  |
| Men | 93 (74%) | 410 (76%) | 763 (67%) | 903 (58%) | 740 (45%) | 517 (36%) | 298 (28%) | 179 (24%) | 94 (20%) | 48 (17%) | 76 (19%) | <0.001 |
| Age, years | 61 (47-69) | 61 (50-70) | 60 (48-70) | 61 (48-70) | 60 (47-70) | 59 (45-70) | 61 (48-71) | 62 (49-72) | 63 (52-72) | 63 (51-71) | 64 (54-72) | <0.001 |
| Body mass index, kg/m2 | 28.4 (25.8-31.4) | 27.8 (25.1-30.8) | 26.5 (24.0-29.7) | 26.1 (23.5-29.0) | 25.4 (22.8-28.4) | 24.4 (22.2-27.0) | 24.2 (21.7-26.9) | 23.7 (21.6-26.4) | 23.5 (21.6-26.3) | 23.0 (20.8-25.5) | 22.8 (20.7-25.1) | <0.001 |
| Current smokers | 71 (57%) | 301 (56%) | 622 (55%) | 770 (50%) | 815 (49%) | 703 (49%) | 489 (45%) | 329 (45%) | 200 (44%) | 124 (44%) | 184 (46%) | <0.001 |
| High alcohol intake\* | 24 (19%) | 100 (19%) | 266 (24%) | 385 (25%) | 486 (30%) | 462 (33%) | 364 (34%) | 274 (37%) | 187 (41%) | 117 (42%) | 218 (54%) | <0.001 |
| Physical inactivity\*\* | 33 (27%) | 160 (30%) | 348 (31%) | 532 (35%) | 570 (35%) | 512 (36%) | 389 (36%) | 251 (34%) | 144 (32%) | 86 (32%) | 132 (33%) | 0.04 |
| Diabetes mellitus | 28 (22%) | 53 (10%) | 89 (8%) | 81 (5%) | 72 (4%) | 42 (3%) | 25 (2%) | 16 (2%) | 7 (2%) | 4 (1%) | 12 (3%) | <0.001 |
| Ischemic heart disease | 16 (13%) | 59 (11%) | 77 (7%) | 87 (6%) | 82 (5%) | 63 (4%) | 43 (4%) | 21 (3%) | 11 (2%) | 8 (3%) | 15 (4%) | <0.001 |
| Lipid-lowering therapy | 4 (3%) | 11 (2%) | 15 (1%) | 13 (1%) | 17 (1%) | 14 (1%) | 9 (1%) | 3 (<1%) | 3 (1%) | 1 (<1%) | 1 (<1%) | 0.02 |
| HDL cholesterol |  |  |  |  |  |  |  |  |  |  |  |  |
| mmol/L | 0.7 (0.6-0.7) | 0.9 (0.8-0.9) | 1.1 (1.0-1.1) | 1.3 (1.2-1.3) | 1.4 (1.4-1.5) | 1.6 (1.6-1.7) | 1.8 (1.8-1.9) | 2.0 (2.0-2.1) | 2.2 (2.2-2.3) | 2.4 (2.4-2.5) | 2.8 (2.7-3.1) | <0.001 |
| mg/dL | 27 (23-27) | 35 (31-35) | 42 (39-42) | 50 (46-50) | 54 (54-58) | 62 (62-66) | 69 (69-73) | 77 (77-81) | 85 (85-89) | 93 (93-97) | 108 (102-120) | <0.001 |
| Apolipoprotein A1, mg/dL | 91 (83-98) | 102 (94-108) | 113 (105-122) | 124 (117-133) | 135 (127-144) | 146 (137-155) | 157 (148-167) | 167 (157-176) | 177 (168-187) | 185 (176-195) | 202 (188-216) | <0.001 |
| LDL cholesterol |  |  |  |  |  |  |  |  |  |  |  |  |
| mmol/L | 3.2 (2.2-3.8) | 3.7 (3.0-4.5) | 3.9 (3.2-4.6) | 3.9 (3.2-4.7) | 3.8 (3.1-4.6) | 3.7 (2.9-4.4) | 3.6 (2.9-4.4) | 3.5 (2.8-4.3) | 3.5 (2.7-4.2) | 3.4 (2.6-4.2) | 3.2 (2.5-3.9) | <0.001 |
| mg/dL | 123 (85-147) | 143 (116-173) | 152 (123-177) | 150 (122-181) | 147 (119-178) | 141 (113-171) | 138 (113-170) | 134 (108-167) | 134 (103-161) | 132 (102-162) | 123 (95-150) | <0.001 |
| Triglycerides |  |  |  |  |  |  |  |  |  |  |  |  |
| mmol/L | 4.1 (2.3-6.6) | 2.6 (1.8-3.9) | 2.2 (1.5-3.1) | 1.9 (1.3-2.6) | 1.5 (1.1-2.1) | 1.4 (1.0-1.9) | 1.3 (1.0-1.7) | 1.2 (0.9-1.6) | 1.1 (0.9-1.6) | 1.1 (0.9-1.5) | 1.1 (0.8-1.3) | <0.001 |
| mg/dL | 363 (202-581) | 234 (163-345) | 191 (134-274) | 164 (119-227) | 137 (100-186) | 125 (90-167) | 118 (87-154) | 108 (81-140) | 102 (78-141) | 99 (75-128) | 94 (73-119) | <0.001 |
| eGFR, mL/min/1.73m2 | 73 (59-85) | 70 (61-80) | 71 (60-83) | 71 (60-81) | 71 (60-82) | 70 (60-82) | 69 (60-80) | 69 (59-80) | 67 (59-77) | 70 (58-80) | 69 (60-78) | 0.009 |
| CRP, mg/L | 3.0 (1.8-5.8) | 2.3 (1.5-4.4) | 2.1 (1.4-3.9) | 1.9 (1.3-3.4) | 1.7 (1.3-3.0) | 1.7 (1.2-2.8) | 1.6 (1.2-2.7) | 1.5 (1.2-2.4) | 1.5 (1.2-2.3) | 1.4 (1.1-2.2) | 1.5 (1.2-2.3) | <0.001 |

Values are median (interquartile range) or number of individuals (%). P-values are from Pearson’s chi-square test for categorical variables and Kruskal-Wallis test for continuous variables. The number of individuals varies slightly according to availability of the variables (data is without imputation). \* >7 units per week for women and >14 units per week for men (1 unit~ 12g of alcohol). \*\* ≤4 hours physical activity in leisure time per week. eGFR=estimated glomerular filtration rate. CRP=C-reactive protein.

**Table S11. Baseline characteristics of individuals in the Copenhagen City Heart Study by percentiles of HDL cholesterol.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **HDL cholesterol, percentiles** | | | | |  |
|  | **1-5** | **6-40** | **41-60** | **61-95** | **96-100** | **P-value** |
| Participants | 662 | 3,523 | 1,605 | 3,193 | 404 |  |
| Men | 503 (76%) | 2,068 (59%) | 656 (41%) | 818 (26%) | 76 (19%) | <0.001 |
| Age, years | 61 (49-70) | 60 (48-70) | 60 (46-70) | 61 (48-71) | 64 (54-72) | <0.001 |
| Body mass index, kg/m2 | 27.9 (25.2-30.9) | 26.1 (23.6-29.1) | 24.8 (22.5-27.8) | 23.9 (21.7-26.5) | 22.8 (20.7-25.1) | <0.001 |
| Current smokers | 372 (56%) | 1,804 (51%) | 799 (50%) | 1,449 (46%) | 184 (46%) | <0.001 |
| High alcohol intake\* | 124 (19%) | 891 (26%) | 509 (32%) | 1,141 (36%) | 218 (54%) | <0.001 |
| Physical inactivity\*\* | 193 (29%) | 1,175 (34%) | 568 (36%) | 1,089 (34%) | 132 (33%) | 0.06 |
| Diabetes mellitus | 81 (12%) | 209 (6%) | 57 (4%) | 70 (2%) | 12 (3%) | <0.001 |
| Ischemic heart disease | 75 (11%) | 205 (6%) | 79 (5%) | 108 (3%) | 15 (4%) | <0.001 |
| Lipid-lowering therapy | 15 (2%) | 36 (1%) | 18 (1%) | 21 (1%) | 1 (<1%) | 0.001 |
| HDL cholesterol |  |  |  |  |  |  |
| mmol/L | 0.9 (0.8-0.9) | 1.2 (1.1-1.3) | 1.5 (1.5-1.6) | 1.9 (1.8-2.1) | 2.8 (2.7-3.1) | <0.001 |
| mg/dL | 35 (31-35) | 46 (42-50) | 58 (58-62) | 73 (69-81) | 108 (102-120) | <0.001 |
| Apolipoprotein A1, mg/dL | 100 (92-107) | 123 (113-133) | 141 (132-150) | 162 (150-175) | 202 (188-216) | <0.001 |
| LDL cholesterol |  |  |  |  |  |  |
| mmol/L | 3.6 (2.9-4.4) | 3.9 (3.1-4.6) | 3.7 (3.0-4.5) | 3.5 (2.8-4.3) | 3.2 (2.5-3.9) | <0.001 |
| mg/dL | 138 (111-168) | 150 (121-179) | 144 (116-175) | 136 (109-168) | 123 (95-150) | <0.001 |
| Triglycerides |  |  |  |  |  |  |
| mmol/L | 2.8 (1.9-4.2) | 1.9 (1.4-2.6) | 1.5 (1.1-2.0) | 1.3 (0.9-1.7) | 1.1 (0.8-1.3) | <0.001 |
| mg/dL | 250 (167-374) | 165 (119-233) | 130 (94-176) | 112 (83-150) | 94 (73-119) | <0.001 |
| eGFR, mL/min/1.73m2 | 70 (60-81) | 71 (60-82) | 71 (60-82) | 69 (59-80) | 69 (60-78) | 0.007 |
| CRP, mg/L | 2.4 (1.5-4.8) | 1.9 (1.3-3.5) | 1.7 (1.2-2.9) | 1.6 (1.2-2.5) | 1.5 (1.2-2.3) | <0.001 |

Values are median (interquartile range) or number of individuals (%). P-values are from Pearson’s chi-square test for categorical variables and Kruskal-Wallis test for   
continuous variables. The number of individuals varies slightly according to availability of the variables (data is without imputation). \* >7 units per week for women   
and >14 units per week for men (1 unit~ 12g of alcohol). \*\* ≤4 hours physical activity in leisure time per week. eGFR=estimated glomerular filtration rate.   
CRP=C-reactive protein.

**Table S12. Baseline characteristics of individuals in the Copenhagen General Population Study and Copenhagen City Heart Study by number of HDL increasing alleles**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **No. of HDL cholesterol increasing alleles** | | | | |  | |
|  | **0** | **1** | **2** | **3-4** | **P-value** | |
| Participants | 19,374 | 41,198 | 30,089 | 9,454 |  | |
| Men | 8,767 (45%) | 18,416 (45%) | 13,579 (45%) | 4,258 (45%) | 0.54 | |
| Age, years | 59 (48-68) | 58 (48-68) | 58 (48-68) | 58 (48-68) | 0.53 | |
| Body mass index, kg/m2 | 25.6 (23.2-28.5) | 25.6 (23.2-28.5) | 25.5 (23.2-28.4) | 25.5 (23.2-28.3) | 0.47 | |
| Current smokers | 3,942 (20%) | 8,402 (20%) | 6,194 (21%) | 1,959 (21%) | 0.81 | |
| High alcohol intake\* | 7,427 (40%) | 15,972 (41%) | 11,595 (40%) | 3,627 (40%) | 0.66 | |
| Physical inactivity\*\* | 9,162 (48%) | 19,661 (48%) | 14,228 (48%) | 4,489 (48%) | 0.65 | |
| Diabetes mellitus | 848 (4%) | 1,681 (4%) | 1,316 (4%) | 395 (4%) | 0.18 | |
| Ischemic heart disease | 1,137 (6%) | 2,296 (6%) | 1,761 (6%) | 524 (6%) | 0.26 | |
| Lipid-lowering therapy | 2,182 (11%) | 4,393 (11%) | 3,245 (11%) | 1,017 (11%) | 0.17 | |
| HDL cholesterol |  |  |  |  |  | |
| mmol/L | 1.5 (1.2-1.8) | 1.5 (1.2-1.9) | 1.6 (1.3-2.0) | 1.7 (1.4-2.1) | <0.001 | |
| mg/dL | 56 (45-69) | 59 (47-73) | 63 (50-78) | 66 (53-81) | <0.001 | |
| Apolipoprotein A1, mg/dL | 151 (135-171) | 156 (138-176) | 161 (142-182) | 165 (146-187) | <0.001 | |
| LDL cholesterol |  |  |  |  |  | |
| mmol/L | 3.3 (2.6-3.9) | 3.2 (2.6-3.9) | 3.2 (2.6-3.9) | 3.2 (2.6-3.9) | <0.001 | |
| mg/dL | 127 (101-151) | 124 (100-151) | 124 (100-151) | 124 (100-151) | <0.001 | |
| Triglycerides |  |  |  |  |  | |
| mmol/L | 1.4 (1.0-2.1) | 1.4 (1.0-2.1) | 1.4 (1.0-2.1) | 1.4 (1.0-2.0) | 0.18 | |
| mg/dL | 125 (87-185) | 124 (86-183) | 123 (86-183) | 125 (88-181) | 0.18 | |
| eGFR, mL/min/1.73m2 | 80 (69-91) | 80 (69-90) | 80 (69-91) | 80 (69-90) | 0.66 | |
| CRP, mg/L | 1.4 (1.0-2.3) | 1.4 (1.0-2.3) | 1.4 (1.0-2.3) | 1.4 (1.0-2.4) | 0.95 | |

Values are median (interquartile range) or number of individuals (%). P-values are from Pearson’s chi-square test for categorical variables and   
Kruskal-Wallis test for continuous variables. The number of individuals varies slightly according to availability of the variables (data is without   
imputation). \* >7 units per week for women and >14 units per week for men (1 unit~ 12g of alcohol). \*\* ≤4 hours physical activity in leisure   
time per week. eGFR=estimated glomerular filtration rate. CRP=C-reactive protein.

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**Figure S1.** **Association between HDL cholesterol, plasma C-reactive protein and blood leukocytes at baseline in the Copenhagen General Population Study.**Upper panel is simple linear regression with CRP log base 2 tranformed and leukocytes untransformed. Lower panel is from Kernel-weighted local polynomial smoothing. The shaded grey areas indicate the 95% confidence intervals.

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*The figure continues on the next page*

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**Figure S2. HDL cholesterol in 0.2 mmol/L (8mg/dL) categories and risk of infectious disease in subgroups of diagnoses in 97,166 individuals from the Copenhagen General Population Study.**Hazard ratios were from multiple event Cox proportional hazards regression. Multifactorial adjustment was for age, sex, body mass index, smoking, alcohol intake, physical activity in leisure time, diabetes mellitus, ischemic heart disease, lipid-lowering therapy, eGFR, LDL cholesterol, and triglycerides.

**Figure S3.** **HDL cholesterol on a continuous scale and risk of bacterial and viral infectious disease in 97,166 individuals from the Copenhagen General Population Study.**Analyses were conducted using restricted cubic splines, with hazard ratios and 95% confidence intervals from multiple event Cox proportional hazards regression. The values of HDL cholesterol with the lowest hazard ratio were chosen as reference. Multifactorial adjustment was for age, sex, body mass index, smoking, alcohol intake, physical activity in leisure time, diabetes mellitus, ischemic heart disease, lipid-lowering therapy, eGFR, LDL, and triglycerides. The light green areas indicate the distribution of concentrations of HDL cholesterol.

 **Figure S4. HDL cholesterol and risk of any infectious disease with further adjustment for plasma C-reactive protein and blood leukocytes in 97,166 individuals from the Copenhagen General Population Study.**Individuals are in the top part divided into 0.5 mmol/L (19mg/dL) intervals, and in the bottom part into 0.2 mmol/L (8mg/dL) intervals of HDL cholesterol. Hazard ratios were from multiple event Cox proportional hazards regression. Multifactorial adjustment was for age, sex, body mass index, smoking, alcohol intake, physical activity in leisure time, diabetes mellitus, ischemic heart disease, lipid-lowering therapy, LDL cholesterol and triglycerides. Left panel shows results for further adjustment for CRP and right panel for further adjustment for leukocytes.



**Figure S5. HDL cholesterol on a continuous scale and risk of any infectious disease in 97,166 women and men from the Copenhagen General Population Study.**Analyses were conducted using restricted cubic splines, with hazard ratios and 95% confidence intervals from multiple event Cox proportional hazards regression. The values of HDL cholesterol with the lowest hazard ratio were chosen as reference. Multifactorial adjustment was for age, body mass index, smoking, alcohol intake, physical activity in leisure time, diabetes mellitus, ischemic heart disease, lipid-lowering therapy, eGFR, LDL cholesterol, and triglycerides. The light green areas indicate the distribution of concentrations of HDL cholesterol.

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**Figure S6. HDL cholesterol and risk of any infectious disease using complete case analysis of 90,675 individuals from the Copenhagen General Population Study**Individuals are in the top part divided into 0.5 mmol/L (19mg/dL) intervals, and in the bottom part into 0.2 mmol/L (8mg/dL) intervals of HDL cholesterol. Hazard ratios were from multiple event Cox proportional hazards regression. Multifactorial adjustment was for age, sex, body mass index, smoking, alcohol intake, physical activity in leisure time, diabetes mellitus, ischemic heart disease, lipid-lowering therapy, eGFR, LDL cholesterol and triglycerides.

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**Figure S7. HDL cholesterol and risk of any infectious disease using single event Cox proportional hazards regression in 97,166 individuals from the Copenhagen General Population Study**Individuals are in the top part divided into 0.5 mmol/L (19mg/dL) intervals, and in the bottom part into 0.2 mmol/L (8mg/dL) intervals of HDL cholesterol. Hazard ratios were from single event Cox proportional hazards regression. Multifactorial adjustment was for age, sex, body mass index, smoking, alcohol intake, physical activity in leisure time, diabetes mellitus, ischemic heart disease, lipid-lowering therapy, eGFR, LDL cholesterol and triglycerides.

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**Figure S8. HDL cholesterol and risk of any infectious disease using competing risk regression in 97,166 individuals from the Copenhagen General Population Study**Individuals are in the top part divided into 0.5 mmol/L (19mg/dL) intervals, and in the bottom part into 0.2 mmol/L (8mg/dL) intervals of HDL cholesterol. Subhazard ratios were from Fine and Gray competing risk regression with death and emigration as competing events. Multifactorial adjustment was for age, sex, body mass index, smoking, alcohol intake, physical activity in leisure time, diabetes mellitus, ischemic heart disease, lipid-lowering therapy, eGFR, LDL cholesterol and triglycerides.

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**Figure S9. HDL cholesterol and risk of any infectious disease using negative binomial regression in 97,166 individuals from the Copenhagen General Population Study**Individuals are in the top part divided into 0.5 mmol/L (19mg/dL) intervals, and in the bottom part into 0.2 mmol/L (8mg/dL) intervals of HDL cholesterol. Incidence rate ratios were from prospective negative binomial regression. Multifactorial adjustment was for age, sex, body mass index, smoking, alcohol intake, physical activity in leisure time, diabetes mellitus, ischemic heart disease, lipid-lowering therapy, eGFR, LDL cholesterol, and triglycerides.

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**Figure S10. HDL cholesterol and risk of any infectious disease using logistic regression in 97,166 individuals from the Copenhagen General Population Study**Individuals are in the top part divided into 0.5 mmol/L (19mg/dL) intervals, and in the bottom part into 0.2 mmol/L (8mg/dL) intervals of HDL cholesterol. Odds ratios were from cross-sectional logistic regression. For this analysis infectious disease events were included from 1977 (start of the registry) or from the age of 18 years, whichever came last. Multifactorial adjustment was for age, sex, body mass index, smoking, alcohol intake, physical activity in leisure time, diabetes mellitus, ischemic heart disease, lipid-lowering therapy, eGFR, LDL cholesterol and triglycerides.

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**Figure S11. Genetic variants in *LIPC* and *CETP* and risk of any infectious disease in 104,867 and 100,686 individuals from the Copenhagen General Population Study and Copenhagen City Heart Study combined.**Lower panel shows the mean (±SEM) concentration of HDL cholesterol for the carrier status of the two variants in the genes encoding hepatic lipase (LIPC) and cholesteryl-ester transfer protein (CETP), with the percent change in HDL cholesterol compared to noncarriers. Upper panel shows the risk of any infectious disease with hazard ratios from multiple event Cox proportional hazards regression adjusted for age and sex. For this analysis infectious disease events were included from 1977 (start of the registry) or from birth, whichever came last.